Please note that all redactions in this document have been made under Section 40 of the FOI Act.

1. Title Page

Clinical Study Report: Fluoxetine Versus Placebo in Childhood/Adolescent Depression

Fluoxetine Hydrochloride (LY110140)
Major Depressive Disorder

A multicenter, double-blind, randomized, parallel-group study over a total of 51 weeks comparing the efficacy and safety of fluoxetine 20 mg/day and placebo for the acute treatment (9 weeks), fluoxetine 20 to 60 mg/day and placebo for the subchronic treatment (up to 19 weeks), and fluoxetine 20 to 60 mg/day and placebo for the long-term relapse prevention (an additional 32 weeks) of major depressive disorder in children and adolescents. The relapse prevention phase is ongoing and these data will be presented in a future clinical study report.

Eli Lilly and Company
Protocol B1Y-MC-HCJE
Phase 3
First patient enrolled (assigned to therapy): 27 April 1998
Last patient completed Study Period V: 16 December 1999
Final Analysis of Study Periods I-V (Data Cut-Off Date): 16 December 1999
Date report approved by Lilly Medical: 6 August 2000

Name and affiliation of coordinating investigator

Eli Lilly and Company

Eli Lilly and Company

This study was performed in compliance with the principles of good clinical practice (GCP). The information contained in this clinical study report is confidential and the information contained within it may not be reproduced or otherwise disseminated without the approval of Eli Lilly and Company or its subsidiaries.

2. Synopsis

Name of company: Eli Lilly and Company	Summary table referring to Part of the dossier,	(For National Authority use only)
Name of finished product: Prozac®	Volume: Page:	
Name of active ingredient: Fluoxetine hydrochloride		

Clinical Study Synopsis: Study B1Y-MC-HCJE

Title:	Fluoxetine Versus Placebo in Childhood/Adolescent Depression
Investigators:	This multicenter study included 19 principal investigators, 15 of whom randomized patients.
Study Centers:	There were 20 study centers, 16 of which randomized patients.
Dates of Study:	Study Periods I-V: April 1998 through December 1999 Study Period VI: Ongoing
Clinical Phase:	Phase 3
Objectives:	To compare the efficacy and safety of fluoxetine 20 mg/day and placebo in the acute treatment (up to 9 weeks) of major depressive disorder (MDD) in children and adolescents. To compare the efficacy and safety of fluoxetine 20 mg/day with fluoxetine 40 or 60 mg/day in the treatment of MDD in children and adolescents who did not respond to acute treatment with fluoxetine 20 mg/day (up to 10 weeks). To compare the efficacy and safety of fluoxetine 20 to 60 mg/day and placebo in the treatment of MDD in children and adolescents following subchronic treatment (up to 19 weeks).
Methodology:	Multicenter, double-blind, randomized, parallel-group, placebo-controlled study.
Number of Subjects:	Fluoxetine: Male 55, Female 54, Total 109; Placebo: Male 56, Female 54, Total 110. Children (8 to <13): Fluoxetine 61, Placebo 61, Total 122; Adolescents (13 to <18): Fluoxetine 48, Placebo 49, Total 97.

Diagnosis and Inclusion Criteria:	Outpatients with a primary diagnosis of nonpsychotic MDD (single or recurrent episode) according to the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV), aged 8 to <18 years, and were willing and able to provide informed consent (parent and patient). Diagnosis of MDD was dependent on evaluation of the Missouri Assessment of Genetics Interview for Children (MAGIC) or Diagnostic Interview for Children and Adolescents (DICA). Patients were required to have a Children's Depression Rating Scale-Revised (CDRS-R) score >40 and a rating of at least moderate on the Clinical Global Impression of Severity (CGI-Severity) scale at study entry.
Dosage and Administration:	Test Product Fluoxetine hydrochloride: 10 to 60 mg, given once daily CT07620, CT12697: fluoxetine capsules, 10 mg CT09678, CT10738: fluoxetine capsules, 20 mg CT09679, CT10799: placebo capsules Expiration dates: 1 September 2000, 31 October 2000
Duration of Treatment:	Fluoxetine: acute treatment phase (9 weeks), subchronic treatment phase (19 weeks), and relapse prevention phase (32 weeks). Total duration of treatment is 51 weeks. Placebo: acute treatment phase (9 weeks), subchronic treatment phase (19 weeks), and relapse prevention phase (32 weeks). Total duration of treatment is 51 weeks.
Criteria for Evaluation of Acute and Subchronic Phases	Efficacy: Primary efficacy analysis was response on the CDRS-R. Secondary analyses included evaluation of CDRS-R, Clinical Global Impression of Improvement (CGI-Improvement), CGI-Severity, Beck Depression Inventory (BDI), Children's Depression Inventory (CDI), Montgomery-Asberg Depression Rating Scale (MADRS), Hamilton Anxiety Rating Scale (HAMA), Global Assessment of Functioning (GAF) Current Functioning, and the Affective Disorders module of the Kiddie Schedule for Affective Disorders and Schizophrenia–Present and Lifetime (K-SADS-PL). Safety: Safety was evaluated through the reporting of concomitant medications, vital signs, routine laboratory testing, electrocardiograms (ECGs), and adverse event data (solicited and non-solicited).

Statistical Methods:	For analyses of continuous data, treatment groups were compared using last-observation-carried-forward (LOCF) with Type III sums of squares from an analysis of variance (ANOVA) with treatment in the model. For analyses of categorical data, Fisher's exact test was used.
Publications Based on the Study:	None at this time.

Summary and Conclusions

This double-blind, placebo-controlled study of the efficacy of fluoxetine versus placebo in the treatment of MDD in children and adolescents consisted of three study phases. Results from the 9-week acute treatment phase (Study Periods III through IV) and the 19-week subchronic treatment phase (Study Periods III through V) are presented in this report. The 32-week relapse prevention phase (Study Period VI) is ongoing and these results will be presented in a future report.

Two hundred nineteen patients were randomized to treatment in this study, with 109 patients receiving fluoxetine and 110 patients receiving placebo. One hundred fifty-eight (72%) patients completed acute treatment (90, 83% fluoxetine-treated; 68, 62% placebo-treated). Seventy-five (34%) patients completed subchronic treatment (40, 37% fluoxetine-treated; 35, 32% placebo-treated). The treatment groups were balanced with respect to demographic characteristics and psychiatric evaluations at baseline.

Fluoxetine 20 mg/day was effective in the treatment of MDD in this pediatric population when patients were treated acutely. Sixty-five percent of fluoxetine-treated patients met response criteria as compared with 54% of placebo-treated patients. Although numerically greater for fluoxetine-treated patients, these findings were not statistically significant ($p=.093$). Statistically significantly more fluoxetine-treated patients had decreases in CDRS-R total score of 20%, 40%, 50%, and 60% from baseline as compared with placebo-treated patients. Statistical significance was also achieved in favor of fluoxetine treatment for CDRS-R total score mean change (-22 fluoxetine, -15 placebo; $p<.001$). Remission ($p<.01$) and recovery ($p<.01$) analyses for CDRS-R also demonstrated the effectiveness of fluoxetine treatment as compared with placebo treatment. In addition, endpoint ($p=.025$) and response ($p=.028$) analyses of CGI-Improvement scores demonstrated the superiority of fluoxetine treatment over placebo treatment.

Analyses of the efficacy variables that demonstrated statistical superiority of fluoxetine treatment over placebo treatment during the acute treatment phase are summarized below:

Efficacy Variable Analyzed	p-Value
Response, at least a 20% reduction in CDRS-R Total score from baseline (at endpoint)	.002
Response, at least a 40% reduction in CDRS-R Total score from baseline (at endpoint)	.002
Remission, CDRS-R endpoint score ≤28	<.01
Recovery, CDRS-R score ≤28 and CGI-Improvement score of 1 or 2 at endpoint	<.01
Mean change from baseline to endpoint in CDRS-R Total score	<.001
Mean change from baseline to endpoint in CDRS-R Mood subtotal score	.002
Mean change from baseline to endpoint in CDRS-R Somatic subtotal score	.004
Mean change from baseline to endpoint in CDRS-R Behavior subtotal score	<.001
Mean change from baseline to endpoint in CDRS-R Subjective subtotal score	.026
Endpoint analysis of CGI-Improvement score	.025
Response, CGI-Improvement score of 1 or 2 at endpoint	.028
Mean change from baseline to endpoint in CGI-Severity score	<.001
Mean change from baseline to endpoint in MADRS score	.023

Dose titration to fluoxetine 40 mg/day, then 60 mg/day, was effective in the treatment of pediatric patients who did not respond to fluoxetine 20 mg/day. Twice as many patients treated at the higher dose levels demonstrated response on the CDRS-R as compared with patients who remained on fluoxetine 20 mg/day (71% fluoxetine 40 or 60 mg, 36% fluoxetine 20 mg; p=.128). Patients receiving fluoxetine 40 or 60 mg/day also demonstrated greater mean change in CDRS-R total score (-9.4 fluoxetine 40 or 60 mg, -1.5 fluoxetine 20 mg; p=.099). Statistical significance was not achieved on any of these measures; however, the sample sizes were small (n=29). The magnitude of the observed changes indicate that these data are clinically relevant and support dose escalation to achieve efficacy in children and adolescents who do not respond to acute treatment with fluoxetine 20 mg/day.

Fluoxetine 20 to 60 mg/day was also found to be effective in the treatment of MDD in this pediatric population when patients were treated subchronically, as supported by the observed response rates on the CDRS-R total score (75% fluoxetine, 60% placebo; p=.026) and CDRS-R total score mean change (-23 fluoxetine, -19 placebo; p=.021). The analysis of mean change in CGI-Severity scores also supports the effectiveness of fluoxetine 20 to 60 mg/day in the treatment of MDD during the subchronic treatment phase (p=.025). The analyses comparing patients who received fluoxetine 20 to 60 mg/day versus patients receiving placebo during the subchronic treatment phase include nonresponders who were maintained on 20 mg/day, making it difficult to fully evaluate the impact of longer-term treatment. In spite of this limitation, these data support the efficacy of fluoxetine 20 to 60 mg/day in the subchronic treatment of MDD in children and adolescents.

Analyses of the efficacy variables that demonstrated statistical superiority of fluoxetine treatment over placebo treatment during the subchronic treatment phase are summarized below:

Efficacy Variable Analyzed	p-Value
Response, at least a 30% reduction in CDRS-R Total score from baseline (at endpoint)	.026
Mean change from baseline to endpoint in CDRS-R Total score	.021
Mean change from baseline to endpoint in CDRS-R Behavior subtotal score	.011
Mean change from baseline to endpoint in CGI-Severity score	.025

Pharmacokinetic results showed that observed fluoxetine plasma concentrations in children were 2-fold higher than those in adolescents, and observed norfluoxetine plasma concentrations in children were 1.5-fold higher than in those in adolescents. Differences between fluoxetine and norfluoxetine plasma concentrations in children and adolescents can be attributed to body weight.

A total of nine serious adverse events occurred during Study Periods I through V; three of these occurred prior to randomization. Six serious advents occurred following randomization (two in fluoxetine-treated patients, four in placebo-treated patients). Twenty-three patients (1 not randomized, 11 fluoxetine-treated, 11 placebo-treated) discontinued due to an adverse event during Study Periods I through V. No statistically significant differences were observed between treatment groups in discontinuations due to adverse events during either acute or subchronic treatment, and no event that led to discontinuation occurred in more than 1 fluoxetine-treated patient.

Headache was the only non-solicited adverse event reported by more fluoxetine-treated patients than placebo-treated patients (p=.017 and .014 for the acute treatment phase and subchronic treatment phase, respectively). All other reported adverse events occurred in comparable numbers of fluoxetine-treated and placebo-treated patients.

Fluoxetine-treated patients demonstrated a statistically significantly greater decrease in alkaline phosphatase levels as compared with placebo-treated patients. No fluoxetine-treated patients had a decrease in alkaline phosphatase that was outside normal range. Lesser increases in both weight and height were also observed in fluoxetine-treated patients during subchronic treatment.

Two independent, blinded analyses of ECG interval changes did not reveal clinically significant changes in any ECG parameter.

Subgroup analyses of efficacy and safety endpoints indicated that there were no differences in the effectiveness or safety profile for subgroups based on age category, gender, or family history of depression.

The results of this study support the efficacy and safety of acute treatment with fluoxetine 20 mg/day, titration to fluoxetine 40 and 60 mg/day in acute treatment nonresponders, and subchronic treatment with fluoxetine 20 to 60 mg/day in children and adolescents diagnosed with MDD.

3. Table of Contents for the Clinical Study Report

Table of Contents

Section		Page
1.	Title Page	1
2.	Synopsis	2
3.	Table of Contents for the Clinical Study Report	7
4.	List of Abbreviations and Definitions of Terms	40
5.	Ethics	47
5.1.	Ethical Review	47
5.2.	Ethical Conduct of the Study	47
5.3.	Patient Information and Consent	47
6.	Investigators and Study Administrative Structure	48
7.	Introduction	50
8.	Study Objectives	52
8.1.	Primary Objective	52
8.2.	Secondary Objectives	52
9.	Investigational Plan	54
9.1.	Overall Study Design and Plan: Description	54
9.1.1.	Study Period I: Diagnostic Evaluation Period	55
9.1.2.	Study Period II: Placebo Washout Period	57
9.1.3.	Study Period III: Adaptation Period	57
9.1.4.	Study Period IV: Fixed-Dose Period	57
9.1.5.	Study Period V: Double-Blind Nonresponder Rerandomization Period	58
9.1.6.	Study Period VI: Relapse Prevention Period	58
9.2.	Discussion of Study Design, Including the Choice of Control Groups	59
9.3.	Selection of Study Population	59
9.3.1.	Inclusion Criteria	59
9.3.2.	Exclusion Criteria	60
9.3.3.	Removal of Patients from Therapy or Assessment	62
9.4.	Treatments	62
9.4.1.	Treatments Administered	62
9.4.1.1.	Study Period I: Diagnostic Evaluation Period	62
9.4.1.2.	Study Period II: Placebo Washout Period	62
9.4.1.3.	Study Period III: Adaptation Period	62
9.4.1.4.	Study Period IV: Fixed-Dose Period	63

Table of Contents

Section		Page
9.4.1.5.	Study Period V: Double-Blind Nonresponder Rerandomization Period	63
9.4.1.6.	Study Period VI: Relapse Prevention Period	64
9.4.2.	Identity of Investigational Products	64
9.4.3.	Method of Assigning Patients to Treatment Groups	64
9.4.4.	Selection of Doses in the Study	65
9.4.5.	Selection and Timing of Dose for Each Patient	65
9.4.6.	Blinding	65
9.4.7.	Prior and Concomitant Therapy	67
9.4.7.1.	Excluded Medications	67
9.4.7.2.	Permitted Medications	68
9.4.8.	Treatment Compliance	68
9.5.	Efficacy and Safety Variables	68
9.5.1.	Efficacy and Safety Measurements Assessed and Schedule of Events	68
9.5.2.	Appropriateness of Measurements	75
9.5.3.	Primary Efficacy Variable	75
9.5.4.	Drug Concentration Measurements	75
9.6.	Data Quality Assurance	75
9.7.	Statistical Methods Planned in the Protocol and Determination of Sample Size	76
9.7.1.	Statistical and Analytical Plans	76
9.7.1.1.	General Considerations	76
9.7.1.2.	Data Analyzed	76
9.7.1.3.	Patient Disposition	77
9.7.1.4.	Patient Characteristics	77
9.7.1.5.	Efficacy Analyses	77
9.7.1.6.	Safety Analyses	80
9.7.1.7.	Subgroup Analyses	82
9.7.1.8.	Interim Analyses	82
9.7.2.	Determination of Sample Size	83
9.7.3.	Pharmacokinetic Methods	83
9.7.3.1.	Biological Sampling	83
9.7.3.2.	Bioanalytical Methods	83
9.7.3.3.	Dataset for Pharmacokinetic Analyses	84
9.7.3.4.	Pharmacokinetic Data Analysis: Descriptive Statistics and Data Visualization	85
9.8.	Changes in the Conduct of the Study or Planned Analyses	85

Table of Contents

Section	Page
9.8.1. Changes in the Conduct of the Study	85
9.8.2. Changes in the Planned Analyses	86
10. Study Patients	88
10.1. Disposition of Patients	88
10.1.1. Early Discontinuation of Patients	89
10.1.2. Patient Allocation	94
10.2. Significant Protocol Violations	96
11. Efficacy Evaluation	97
11.1. Data Sets Analyzed	97
11.2. Demographic and Other Baseline Characteristics	99
11.2.1. Patient Characteristics	99
11.2.2. Psychiatric History	102
11.2.3. Previous Treatment	104
11.2.4. Concomitant Medication	105
11.3. Measurements of Treatment Compliance	115
11.4. Efficacy Results and Tabulations of Individual Patient Data	117
11.4.1. Analysis of Efficacy	117
11.4.1.1. Acute Treatment Phase (Study Periods III through IV)	117
11.4.1.2. Analyses of Patients Not Responding to Acute Treatment (Study Period V)	118
11.4.1.3. Subchronic Treatment Phase (Study Periods III through V)	118
11.4.1.4. Additional Analyses	118
11.4.1.5. Baseline Variability	119
11.4.2. Acute Treatment Phase (Study Periods III-IV)	121
11.4.2.1. Analysis of Primary Endpoint: Patients Meeting Criteria for CDRS-R Total Response	121
11.4.2.2. Additional Analyses of CDRS-R	123
11.4.2.2.1. Remission	123
11.4.2.2.2. Mean Change from Baseline to Endpoint	124
11.4.2.2.3. By-Visit Analyses	127
11.4.2.3. Secondary Efficacy Measures	128
11.4.2.4. Subgroup Analyses	131
11.4.2.4.1. CDRS-R Total Response	131
11.4.2.4.2. CDRS-R Total Score	134

Table of Contents

Section **Page**

11.4.2.4.3. CGI-Improvement Score 136
11.4.2.5. Additional Secondary Efficacy Endpoints 138
11.4.3. Analysis of Patients Not Responding to Acute Treatment (Study Period V) 140
11.4.4. Statistical/Analytical Issues 143
11.4.4.1. Adjustments for Covariates 143
11.4.4.2. Handling of Dropouts or Missing Data 144
11.4.4.3. Interim Analyses and Data Monitoring 144
11.4.4.4. Multicenter Studies 144
11.4.4.5. Multiple Comparisons/Multiplicity 144
11.4.4.6. Use of an “Efficacy Subset” of Patients 145
11.4.5. Tabulation of Individual Response Data 145
11.4.6. By-Patient Displays 145
11.4.7. Efficacy Conclusions 145
11.5. Pharmacokinetic Results 149
11.5.1. Patient Demographics 149
11.5.2. Plasma Sample Collection 150
11.5.3. Observed Concentrations 151
11.5.4. Discussion 156
11.5.5. Conclusions 157

12. Safety Evaluation 158
12.1. Extent of Exposure 158
12.2. Adverse Events 160
12.2.1. Brief Summary of Adverse Events 161
12.2.2. Display and Analysis of Adverse Events 162
12.2.2.1. Acute Treatment Phase (Study Periods III-IV) 162
12.2.2.1.1. Non-Solicited Events 162
12.2.2.1.2. Solicited Events 166
12.2.2.2. Subchronic Treatment Phase (Study Periods III-V) 169
12.2.2.2.1. Non-Solicited Adverse Events 169
12.2.2.2.2. Solicited Events 173
12.2.2.3. Adverse Events in Nonresponders Following Rerandomization 177
12.2.2.3.1. Non-Solicited Events 177
12.2.2.3.2. Solicited Events 178
12.2.3. Listing of Adverse Events by Patient 179

Table of Contents

Section	Page
12.3. Deaths, Serious Adverse Events, and Nonserious Clinically Significant Adverse Events	180
12.3.1. Deaths	180
12.3.2. Serious Adverse Events	180
12.3.3. Nonserious Clinically Significant Adverse Events	182
12.3.4. Listing of Deaths, Serious Adverse Events, and Nonserious Clinically Significant Adverse Events	183
12.3.5. Narratives of Deaths, Serious Adverse Events, and Nonserious Clinically Significant Adverse Events	183
12.4. Clinical Laboratory Evaluation	184
12.4.1. Subchronic Treatment Phase (Study Periods III-V)	184
12.4.2. Treatment-Emergent Abnormal Values	201
12.4.3. Additional Analyses of Alkaline Phosphatase Levels	201
12.4.4. Listing of Individual Laboratory Measurements by Patient and Each Abnormal Laboratory Value	204
12.5. Vital Signs, Physical Findings, and Other Observations Related to Safety	204
12.5.1. Vital Signs	204
12.5.1.1. Acute Treatment Phase (Study Periods III-IV)	204
12.5.1.2. Subchronic Treatment Phase (Study Periods III-V)	206
12.5.1.3. Additional Analyses of Height	210
12.5.1.4. Additional Analyses of Weight	211
12.5.2. Electrocardiograms	212
12.5.2.1. Subchronic Treatment Phase (Study Periods III-V)	213
12.5.2.2. Treatment-Emergent Out of Range Values	216
12.5.2.3. Additional Analyses of QTc Intervals	218
12.6. Subgroup Analyses	219
12.7. Safety Conclusions	219
13. Discussion and Overall Conclusions	222
14. Tables, Figures, and Graphics Not Included in Other Sections	225
14.1. Demographic Data Summary	225
14.2. Efficacy Data Summary	231
14.2.1. Acute Treatment Phase (Study Periods III-IV)	231
14.2.1.1. Additional Efficacy Measures	231
14.2.1.2. By-Investigator Analyses	239
14.2.1.2.1. CDRS-R Total Response	239

Table of Contents

Section **Page**

14.2.1.2.2. Mean Change in CDRS-R Total Score from Baseline to Endpoint 241
14.2.2.1.3. CGI-Improvement Score 244
14.2.2.1.4. Change in MADRS Score from Baseline to Endpoint 247
14.2.2.1.5. Change in CGI-Severity Score from Baseline to Endpoint 250
14.2.2. CDRS-R Total Response and Remission for Patients Treated at Least 5 Weeks 253
14.2.3. Subchronic Treatment Phase (Study Periods III-V) 254
14.2.3.1. Analysis of Primary Endpoint: Patients Meeting Criteria for CDRS-R Total Response 254
14.2.3.2. Additional Analyses for CDRS-R 256
14.2.3.2.1. Remission 256
14.2.3.2.2. Mean Change from Baseline to Endpoint 257
14.2.3.2.3. By-Visit Analyses 259
14.2.3.2.4. Repeated Measured Analysis 267
14.2.3.3. Secondary Efficacy Measures 269
14.2.3.4. Analyses of Subgroups 272
14.2.3.4.1. CDRS-R Total Response 272
14.2.3.4.2. CDRS-R Total Score 274
14.2.3.4.3. CGI-Improvement Score 276
14.2.3.5. Additional Efficacy Analyses 278
14.2.3.6. By-Investigator Analyses 287
14.2.3.6.1. CDRS-R Total Response 287
14.2.3.6.2. Change in CDRS-R Total Score from Baseline to Endpoint 289
14.2.3.6.3. CGI-Improvement Score 292
14.2.3.6.4. Change in MADRS Score from Baseline to Endpoint 295
14.2.3.6.5. Change in CGI-Severity Score from Baseline to Endpoint 298
14.2.4. Secondary Statistical Models 301
14.3. Safety Data Summary 305
14.3.1. Displays of Adverse Events 306
14.3.1.1. Acute Treatment Phase (Study Periods III-IV) 306
14.3.1.1.1. Treatment-Emergent Non-Solicited Adverse Events by Body System 306

Table of Contents

Section **Page**

14.3.1.1.2. Treatment-Emergent Non-Solicited Adverse Events by Maximum Severity 317
14.3.1.1.3. Treatment-Emergent Solicited Adverse Events from the Side-Effects Checklist by Maximum Intensity 342
14.3.1.2. Subchronic Treatment Phase (Study Periods III-V) 350
14.3.1.2.1. Treatment-Emergent Non-Solicited Adverse Events by Body System 350
14.3.1.2.2. Treatment-Emergent Non-Solicited Adverse Events by Maximum Severity 363
14.3.1.2.3. Treatment-Emergent Solicited Adverse Events 392
14.3.1.2.4. Treatment-Emergent Solicited Adverse Events from the Side-Effects Checklist by Maximum Intensity 397
14.3.1.3. Adverse Events in All Randomized Patients Entering Study Period V 404
14.3.1.3.1. Non-Solicited Events 404
14.3.1.3.2. Solicited Events 407
14.3.2. Subgroup Analyses 412
14.3.2.1. Acute Treatment Phase (Study Periods III-IV) 412
14.3.2.1.1. By Age 412
14.3.2.1.2. By Gender 481
14.3.2.1.3. By Family History of Depression 550
14.3.2.2. Subchronic Treatment Phase (Study Periods III-V) 614
14.3.2.2.1. By Age 614
14.3.2.2.2. By Gender 694
14.3.2.2.3. By Family History of Depression 774
14.3.3. Listings of Deaths, Other Serious, and Nonserious Clinically Significant Adverse Events 848
14.3.4. Narratives of Deaths, Other Serious, and Nonserious Clinically Significant Adverse Events 872
14.3.5. Vital Signs 921
14.3.5.1. Out of Range Vital Signs 921
14.3.5.2. Change from Baseline to Endpoint for Study Period V 925
14.3.6. Electrocardiograms 928
14.3.7. Abnormal Laboratory Values 931

Table of Contents

Section **Page**

14.3.7.1. Out of Range Laboratory Values 931
14.3.7.2. Change from Baseline to Endpoint for Study Period V 977
14.3.7.3. Abnormal Laboratory Values Listing 985

15. Reference List 1466

16. Appendices 1470

Table of Contents

Table **Page**

Table 6.1.
Study Administrative Structure
B1Y-MC-HCJE 49

Table 9.1.
Study Medication
Study Periods II-V
B1Y-MC-HCJE 64

Table 9.2.
Patients Undergoing Rescue Therapy
Study Periods I-V
B1Y-MC-HCJE 67

Table 9.3.
Schedule of Events for the Acute and Subchronic Phases of
B1Y-MC-HCJE 72

Table 10.1.
Summary of Reasons for Discontinuation by Visit
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE 90

Table 10.2.
Summary of Reasons for Discontinuation
All Randomized Patients
Acute Treatment Phase (Study Periods III-IV)
B1Y-MC-HCJE 93

Table 10.3.
Summary of Reasons for Discontinuation
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE 94

Table 10.4.
Patient Allocation by Investigator
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE 95

Table 11.1.
Baseline Patient Characteristics
All Randomized Patients
B1Y-MC-HCJE 100

Table of Contents

Table **Page**

Table 11.2.
Patient Habits
All Randomized Patients
B1Y-MC-HCJE 102

Table 11.3.
Psychiatric History
All Randomized Patients
B1Y-MC-HCJE 103

Table 11.4.
Biological Family History
All Randomized Patients
B1Y-MC-HCJE 104

Table 11.5.
Previous Treatment for Depressive Disorders Within Past Year
All Randomized Patients
B1Y-MC-HCJE 105

Table 11.6.
Concomitant Medications
All Randomized Patients
Acute Treatment Phase (Study Periods III-IV)
B1Y-MC-HCJE 106

Table 11.7.
Concomitant Medications
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE 111

Table 11.8.
Patient Compliance by Visit
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE 116

Table 11.9.
Baseline Psychiatric Evaluation
All Randomized Patients
B1Y-MC-HCJE 120

Table of Contents

Table **Page**

Table 11.10.
CDRS-R Total Score
Number of Patients Meeting Criteria for Response
All Randomized Patients
Acute Treatment Phase (Study Period IV)
B1Y-MC-HCJE 122

Table 11.11.
CDRS-R Total Score
Number of Patients Meeting Criteria for Remission
All Randomized Patients
Acute Treatment Phase (Study Period IV)
B1Y-MC-HCJE 124

Table 11.12.
CDRS-R Scores
Change from Baseline to Endpoint
All Randomized Patients
Acute Treatment Phase (Study Periods III-IV)
B1Y-MC-HCJE 126

Table 11.13.
CGI-Improvement Score
Endpoint Analysis
All Randomized Patients
Acute Treatment Phase (Study Periods III-IV)
B1Y-MC-HCJE 129

Table 11.14.
CGI-Improvement Score
Number of Patients Meeting Criteria for Response
All Randomized Patients
Acute Treatment Phase (Study Periods III-IV)
B1Y-MC-HCJE 130

Table 11.15.
CDRS-R Total and CGI-Improvement Scores
Number of Patients Meeting Criteria for Recovery
All Randomized Patients
Acute Treatment Phase (Study Period IV)
B1Y-MC-HCJE 131

Table 11.16.
CDRS-R Total Score
Number of Patients Meeting Criteria for Response
Efficacy Subgroup Analysis, All Randomized Patients
Acute Treatment Period (Study Period IV)
B1Y-MC-HCJE 133

Table of Contents

Table **Page**

Table 11.17.
CDRS-R Total Score
Change from Baseline to Endpoint
Efficacy Subgroup Analysis, All Randomized Patients
Acute Treatment Phase (Study Periods III-IV)
B1Y-MC-HCJE 135

Table 11.18.
CGI-Improvement Score
Endpoint Analysis
Efficacy Subgroup Analysis, All Randomized Patients
Acute Treatment Phase (Study Periods III-IV)
B1Y-MC-HCJE 137

Table 11.19.
Secondary Efficacy Variables
Change from Baseline to Endpoint
All Randomized Patients
Acute Treatment Phase (Study Periods III-IV)
B1Y-MC-HCJE 139

Table 11.20.
CDRS-R Total Score
Number of Patients Meeting Criteria for Response
All Nonresponders with Study Period V Data
Study Period V, B1Y-MC-HCJE 141

Table 11.21.
Efficacy Scores
Change from Study Period V Baseline to Endpoint
All Nonresponders with Study Period V Data
Study Period V, B1Y-MC-HCJE 142

Table 11.22.
CGI-Improvement Score
Endpoint Analysis
All Nonresponders with Study Period V Data
Study Period V, B1Y-MC-HCJE 143

Table 11.23
Categorical Efficacy Analyses
All Randomized Patients
B1Y-MC-HCJE 146

Table 11.24.
Continuous Efficacy Analyses
All Randomized Patients
B1Y-MC-HCJE 147

Table of Contents

Table **Page**

Table 11.25.
Patient Demographics
Pharmacokinetic Dataset
B1Y-MC-HCJE 150

Table 11.26.
Observed Fluoxetine and Norfluoxetine Concentrations at
Steady-State After Dosing with Fluoxetine 20 mg/day
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE 152

Table 12.1.
Duration of Study Drug Exposure
All Randomized Patients
Acute and Subchronic Treatment Phases
Study Periods III-IV and III-V, B1Y-MC-HCJE 159

Table 12.2.
Treatment-Emergent Non-Solicited Adverse Events
Incidence by Decreasing Frequency (Ordered by Fluoxetine)
All Randomized Patients
Acute Treatment Phase (Study Periods III-IV)
B1Y-MC-HCJE 163

Table 12.3.
Treatment-Emergent Solicited Adverse Events
Side-Effects Checklist
Incidence by Decreasing Frequency (Ordered by Fluoxetine)
All Randomized Patients
Acute Treatment Phase (Study Periods III-IV)
B1Y-MC-HCJE 167

Table 12.4.
Treatment-Emergent Non-Solicited Adverse Events
Incidence by Decreasing Frequency (Ordered by Fluoxetine)
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE 170

Table 12.5.
Treatment-Emergent Solicited Adverse Events
Side-Effects Checklist
Incidence by Decreasing Frequency (Ordered by Fluoxetine)
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE 175

Table of Contents

Table **Page**

Table 12.6.
Treatment-Emergent Non-Solicited Adverse Events
Incidence by Decreasing Frequency (Ordered by Flx 20 mg)
All Nonresponders
Study Period V, B1Y-MC-HCJE 178

Table 12.7.
Treatment-Emergent Solicited Adverse Events
Side Effects Checklist
Incidence by Decreasing Frequency (Ordered by Flx 20 mg)
All Nonresponders
Study Period V, B1Y-MC-HCJE 179

Table 12.8.
Serious Adverse Events
All Randomized Patients
B1Y-MC-HCJE 181

Table 12.9.
Adverse Events Leading to Discontinuation
Incidence by Decreasing Frequency (Ordered by Fluoxetine)
All Randomized Patients
Acute Treatment Phase (Study Periods III-IV)
B1Y-MC-HCJE 182

Table 12.10.
Adverse Events Leading to Discontinuation
Incidence by Decreasing Frequency (Ordered by Fluoxetine)
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE 183

Table 12.11.
Laboratory Analysis
Change from Baseline to Endpoint
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE 185

Table 12.12.
Laboratory Analysis
Change from Baseline to Endpoint
All Randomized Patients Completing Study Period V
B1Y-MC-HCJE 193

Table of Contents

Table **Page**

Table 12.13.
Alkaline Phosphatase Levels
Intent-to-Treat and Completers' Analyses
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE 202

Table 12.14.
Alkaline Phosphatase Levels
Subgroup Analysis by Age
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE 203

Table 12.15.
Alkaline Phosphatase Levels
Subgroup Analysis by Serum Concentration Groups
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE 204

Table 12.16.
Vital Signs
Change from Baseline to Endpoint
All Randomized Patients
Acute Treatment Phase (Study Periods III-IV)
B1Y-MC-HCJE 205

Table 12.17.
Vital Signs
Change from Baseline to Endpoint
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE 207

Table 12.18.
Vital Signs
Change from Baseline to Endpoint
All Patients Completing Study Period V
B1Y-MC-HCJE 209

Table 12.19.
Height
Change from Baseline to Endpoint
Intent-to-Treat and Completers' Analyses
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE 211

Table of Contents

Table **Page**

Table 12.20.
Weight
Change from Baseline to Endpoint
Intent-to-Treat and Completers' Analyses
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE 212

Table 12.21.
Electrocardiogram Measures [redacted]
Change from Baseline to Endpoint
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE 214

Table 12.22.
Electrocardiogram Measures [redacted]
Change from Baseline to Endpoint
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE 216

Table 12.23.
Electrocardiogram Measures [redacted]
Incidence of Out of Range Measurements
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE 217

Table 12.24.
Electrocardiogram Measures [redacted]
Incidence of Out of Range Measurements
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE 218

Table 12.25.
QTc Interval (Fridericia's Method)
Change from Baseline to Endpoint [redacted]
Subgroup Analysis by Age
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE 219

Table 14.1.
Physician Checklist at Baseline
All Randomized Patients
B1Y-MC-HCJE 226

Table of Contents

Table **Page**

Table 14.2.
CDRS-R Individual Item Scores
Change from Baseline to Endpoint
All Randomized Patients
Acute Treatment Phase (Study Periods III-IV)
B1Y-MC-HCJE 232

Table 14.3.
CGI-Efficacy Index Score
Endpoint Analysis
All Randomized Patients
Acute Treatment Phase (Study Periods III-IV)
B1Y-MC-HCJE 238

Table 14.4.
K-SADS-PL
Endpoint Analysis
All Randomized Patients
Acute Treatment Phase (Study Periods III-IV)
B1Y-MC-HCJE 239

Table 14.5.
CDRS-R Total Score
Number of Patients Meeting Criteria for Response
All Randomized Patients by Investigator
Acute Treatment Phase (Study Period IV)
B1Y-MC-HCJE 240

Table 14.6.
CDRS-R Total Score
Change from Baseline to Endpoint
All Randomized Patients by Investigator
Acute Treatment Phase (Study Periods III-IV)
B1Y-MC-HCJE 242

Table 14.7.
CGI-Improvement Score
Endpoint Analysis
All Randomized Patients by Investigator
Acute Treatment Phase (Study Periods III-IV)
B1Y-MC-HCJE 245

Table 14.8.
MADRS Score
Change from Baseline to Endpoint
All Randomized Patients by Investigator
Acute Treatment Phase (Study Periods III-IV)
B1Y-MC-HCJE 248

Table of Contents

Table **Page**

Table 14.9.
CGI-Severity Score
Change from Baseline to Endpoint
All Randomized Patients by Investigator
Acute Treatment Phase (Study Periods III-IV)
B1Y-MC-HCJE 251

Table 14.10.
CDRS-R Total Score
Number of Patients Meeting Criteria for Response
All Patients Treated at Least 5 Weeks
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE 253

Table 14.11.
CDRS-R Total Score
Number of Patients Meeting Criteria for Remission
All Patients Treated at Least 5 Weeks
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE 254

Table 14.12.
CDRS-R Total Score
Number of Patients Meeting Criteria for Response
All Randomized Patients
Subchronic Treatment Phase (Study Periods IV-V)
B1Y-MC-HCJE 255

Table 14.13.
CDRS-R Total Score
Number of Patients Meeting Criteria for Remission
All Randomized Patients
Subchronic Treatment Phase (Study Periods IV-V)
B1Y-MC-HCJE 257

Table 14.14.
CDRS-R Scores
Change from Baseline to Endpoint
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE 258

Table 14.15.
CDRS-R Total Score
Change from Baseline to Each Visit (Observed Cases)
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE 261

Table of Contents

Table **Page**

Table 14.16.
CDRS-R Total Score
Change from Baseline to Each Visit (LOCF)
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE 265

Table 14.17.
CDRS-R Total Score
Repeated Measures Model Parameters
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE 267

Table 14.18.
CDRS-R Total Score
Repeated Measures Least-Squares Means
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE 268

Table 14.19.
CGI-Improvement Score
Endpoint Analysis
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE 270

Table 14.20.
CGI-Improvement Score
Number of Patients Meeting Criteria for Response
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE 271

Table 14.21.
CDRS-R Total and CGI-Improvement Scores
Number of Patients Meeting Criteria for Recovery
All Randomized Patients
Subchronic Treatment Phase (Study Periods IV-V)
B1Y-MC-HCJE 272

Table 14.22.
CDRS-R Total Score
Number of Patients Meeting Criteria for Response
Efficacy Subgroup Analysis, All Randomized Patients
Subchronic Treatment Phase (Study Periods IV-V)
B1Y-MC-HCJE 273

Table of Contents

Table **Page**

Table 14.23.
CDRS-R Total Score
Change from Baseline to Endpoint
Efficacy Subgroup Analysis, All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE 275

Table 14.24.
CGI-Improvement Score
Endpoint Analysis
Efficacy Subgroup Analysis, All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE 277

Table 14.25.
Secondary Efficacy Variables
Change from Baseline to Endpoint
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE 279

Table 14.26.
CDRS-R Individual Item Scores
Change from Baseline to Endpoint
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE 281

Table 14.27.
CGI-Efficacy Index Score
Endpoint Analysis
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE 286

Table 14.28.
K-SADS-PL
Endpoint Analysis
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE 287

Table 14.29.
CDRS-R Total Score
Number of Patients Meeting Criteria for Response
All Randomized Patients by Investigator
Subchronic Treatment Phase (Study Periods IV-V)
B1Y-MC-HCJE 288

Table of Contents

Table **Page**

Table 14.30.
CDRS-R Total Score
Change from Baseline to Endpoint
All Randomized Patients by Investigator
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE 290

Table 14.31.
CGI-Improvement Score
Endpoint Analysis
All Randomized Patients by Investigator
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE 293

Table 14.32.
MADRS Score
Change from Baseline to Endpoint
All Randomized Patients by Investigator
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE 296

Table 14.33.
CGI-Severity Score
Change from Baseline to Endpoint
All Randomized Patients by Investigator
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE 299

Table 14.34.
Efficacy Scores
Primary Statistical Model
B1Y-MC-HCJE 302

Table 14.35.
Efficacy Scores
Secondary Statistical Model 1
B1Y-MC-HCJE 303

Table 14.36.
Efficacy Scores
Secondary Statistical Model 2
B1Y-MC-HCJE 304

Table 14.37.
Efficacy Scores
Secondary Statistical Model 3
B1Y-MC-HCJE 305

Table of Contents

Table **Page**

Table 14.38.
Treatment-Emergent Non-Solicited Adverse Events
Incidence by Body System
All Randomized Patients
Acute Treatment Phase (Study Periods III-IV)
B1Y-MC-HCJE 306

Table 14.39.
Treatment-Emergent Non-Solicited Adverse Events
Incidence by Maximum Severity
All Randomized Patients
Acute Treatment Phase (Study Periods III-IV)
B1Y-MC-HCJE 318

Table 14.40.
Treatment-Emergent Solicited Adverse Events
Side-Effects Checklist
Incidence by Maximum Intensity
All Randomized Patients
Acute Treatment Phase (Study Periods III-IV)
B1Y-MC-HCJE 344

Table 14.41.
Treatment-Emergent Non-Solicited Adverse Events
Incidence by Body System
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE 351

Table 14.42.
Treatment-Emergent Non-Solicited Adverse Events
Incidence by Maximum Severity
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE 364

Table 14.43.
Treatment-Emergent Solicited Adverse Events - Method 2
Side-Effects Checklist
Incidence by Decreasing Frequency (Ordered by Fluoxetine)
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE 394

Table of Contents

Table **Page**

Table 14.44.
Treatment-Emergent Solicited Adverse Events
Side-Effects Checklist
Incidence by Maximum Intensity
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE 398

Table 14.45.
Treatment-Emergent Non-Solicited Adverse Events
Incidence by Decreasing Frequency (Ordered by Fluoxetine)
All Patients Entering Study Period V
Study Period V, B1Y-MC-HCJE 405

Table 14.46.
Treatment-Emergent Solicited Adverse Events
Side-Effects Checklist
Incidence by Decreasing Frequency (Ordered by Fluoxetine)
All Patients Entering Study Period V
Study Period V, B1Y-MC-HCJE 408

Table 14.47.
Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Age Category
All Randomized Patients
Acute Treatment Phase (Study Periods III-IV)
B1Y-MC-HCJE 413

Table 14.48.
Treatment-Emergent Solicited Adverse Events
Side Effects Checklist Subgroup Analysis by Age
Significant (p<.05) Difference in Odds Ratio
All Randomized Patients
Acute Treatment Phase (Study Periods III-IV)
B1Y-MC-HCJE 476

Table 14.49.
Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Gender
All Randomized Patients
Acute Treatment Phase (Study Periods III-IV)
B1Y-MC-HCJE 482

Table of Contents

Table **Page**

Table 14.50.
Treatment-Emergent Solicited Adverse Events
Side Effects Checklist Subgroup Analysis by Gender
Significant (p<.05) Difference in Odds Ratio
All Randomized Patients
Acute Treatment Phase (Study Periods III-IV)
B1Y-MC-HCJE 545

Table 14.51.
Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Family History of Depression
All Randomized Patients
Acute Treatment Phase (Study Periods III-IV)
B1Y-MC-HCJE 551

Table 14.52.
Treatment-Emergent Solicited Adverse Events
Side Effects Checklist Subgroup Analysis by Family History of Depression
Significant (p<.05) Difference in Odds Ratio
All Randomized Patients
Acute Treatment Phase (Study Periods III-IV)
B1Y-MC-HCJE 609

Table 14.53.
Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Age Category
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE 615

Table 14.54.
Treatment-Emergent Solicited Adverse Events
Side Effects Checklist Subgroup Analysis by Age
Significant (p<.05) Difference in Odds Ratio
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE 689

Table 14.55.
Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Gender
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE 695

Table of Contents

Table **Page**

Table 14.56.
Treatment-Emergent Solicited Adverse Events
Side Effects Checklist Subgroup Analysis by Gender
Significant (p<.05) Difference in Odds Ratio
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE 769

Table 14.57.
Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Family History of Depression
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE 775

Table 14.58.
Treatment-Emergent Solicited Adverse Events
Side Effects Checklist Subgroup Analysis by Family History of Depression
Significant (p<.05) Difference in Odds Ratio
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE 843

Table 14.59.
Listing of Serious Adverse Events, Deaths, and Adverse Events
Leading to Discontinuation
All Randomized Patients
B1Y-MC-HCJE 849

Table 14.60.
Vital Signs
Incidence of Out of Range Measurements
Acute Treatment Phase (Study Periods III-IV)
B1Y-MC-HCJE 922

Table 14.61.
Vital Signs
Incidence of Out of Range Measurements
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE 923

Table 14.62.
Vital Signs
Incidence of Out of Range Measurements
Study Period V, B1Y-MC-HCJE 924

Table of Contents

Table **Page**

Table 14.63.
Vital Signs
Change from Baseline to Endpoint
All Patients Entering Study Period V
Study Period V, B1Y-MC-HCJE 926

Table 14.64.
Electrocardiogram Measures [redacted]
Change from Baseline to Endpoint
All Patients Entering Study Period V
Study Period V, B1Y-MC-HCJE 928

Table 14.65.
Electrocardiogram Measures [redacted]
Incidence of Out of Range Measurements
Study Period V, B1Y-MC-HCJE 930

Table 14.66.
Laboratory Analysis
Treatment-Emergent Abnormal Values
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE 932

Table 14.67.
Laboratory Analysis
Treatment-Emergent Abnormal Values
All Patients Entering Study Period V
Study Period V, B1Y-MC-HCJE 956

Table 14.68.
Laboratory Analysis
Change from Baseline to Endpoint
All Patients Entering Study Period V
Study Period V, B1Y-MC-HCJE 978

Table 14.69.
Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE 986

Table of Contents

Figure **Page**

Figure 9.1.
Study Design for Study Periods I through V for B1Y-MC-HCJE. 55

Figure 9.2.
Data accountability for pharmacokinetic analyses of B1Y-MC-HCJE 84

Figure 10.1.
Overview of patient disposition by visit for Study Periods I-V of B1Y-MC-HCJE. 89

Figure 11.1.
Study dose for all randomized patients during acute and subchronic treatment phases (Study Periods III-V) of B1Y-MC-HCJE. 98

Figure 11.2.
Percent change distribution in CDRS-R total score for all randomized patients during the acute treatment phase (Study Period IV) of B1Y-MC-HCJE 123

Figure 11.3.
CDRS-R total score versus visit (observed cases) by treatment group for the acute treatment phase (Study Periods III-IV) of B1Y-MC-HCJE. 127

Figure 11.4.
CDRS-R total score versus visit (LOCF) by treatment group for the acute treatment phase (Study Periods III-IV) of B1Y-MC-HCJE 128

Figure 11.5.
Histogram illustrating the number of samples post-fluoxetine dose (fluoxetine/norfluoxetine plasma concentrations) included in the pharmacokinetic dataset for the subchronic treatment phase of B1Y-MC-HCJE 151

Figure 11.6.
Observed steady-state fluoxetine concentrations for individual patients after fluoxetine 20 mg/day during the subchronic treatment phase (Study Periods IV-V) of B1Y-MC-HCJE 153

Table of Contents

Figure **Page**

Figure 11.7.
Observed steady-state norfluoxetine concentrations for individual patients after fluoxetine 20 mg/day during the subchronic treatment phase (Study Periods IV-V) of B1Y-MC-HCJE. 154

Figure 11.8.
Dose-weight normalized steady-state fluoxetine concentrations for individual patients after fluoxetine 20 mg/day during the subchronic treatment phase (Study Periods IV-V) of B1Y-MC-HCJE. 155

Figure 11.9.
Dose-weight normalized steady-state norfluoxetine concentrations for individual patients after fluoxetine 20 mg/day during the subchronic treatment phase (Study Periods IV-V) of B1Y-MC-HCJE. 156

Figure 12.1.
Study dose for all randomized patients during acute and subchronic treatment phases (Study Periods III-V) of B1Y-MC-HCJE. 160

Figure 14.1.
CGI-Efficacy Index scoring for B1Y-MC-HCJE. 237

Figure 14.2.
CDRS-R total score for number of patients meeting criteria for response during the acute treatment phase (Study Period IV) of B1Y-MC-HCJE for all randomized patients by investigator. 241

Figure 14.3.
Percent change distribution in CDRS-R total score for all randomized patients during subchronic treatment (Study Periods IV-V) of B1Y-MC-HCJE. 256

Figure 14.4.
CDRS-R total score versus visit (observed cases) by treatment group for the subchronic treatment phase (Study Periods III-V) of B1Y-MC-HCJE. 260

Figure 14.5.
CDRS-R total score versus visit (LOCF) by treatment group for the subchronic treatment phase (Study Periods III-V) of B1Y-MC-HCJE. 264

Table of Contents

Figure **Page**

Figure 14.6.
Plot of least-square means from the reduced model of CDRS-R total score for the subchronic treatment phase (Study Periods III-V) of B1Y-MC-HCJE. 269

Figure 14.7.
CDRS-R total score for number of patients meeting criteria for response during the subchronic treatment phase (Study Periods IV-V) of B1Y-MC-HCJE for all randomized patients by investigator. 289

Table of Contents

Appendix **Page**

16.1.
Study Information 1471

16.1.1.
Protocol and Protocol Amendments 1472

16.1.2.
Sample Clinical Report Form 1535

16.1.3.
List of Investigators
and Other Key Individuals 2055

16.1.4.
Signature of Investigator or Sponsor's Responsible Medical
Officer 2420

16.1.5.
Randomization Scheme and Codes 2422

16.1.6.
Documentation of Statistical Methods 2434

16.1.7.
Publications Based on the Study 2445

16.1.8.
Important Publications Referenced in the Report 2447

16.1.9.
Ethical Review Board Information and
Protocol-Specific Informed Consent Document 2480

16.1.10.
Listing of Patients Receiving Test Drug(s) or Investigational
Product(s) From Specific Batches 2616

16.1.11.
Audit Certificates 2672

16.1.12.
Documentation of Inter-Laboratory Standardization Methods
and Quality Assurance Procedures if Used 2674

16.1.13.
Errors to the Locked Database 2682

16.1.14.
Blinding Plan and Data Monitoring Board Information 2686

Table of Contents

Appendix **Page**

16.1.15
PK Dataset 2734

16.1.16.
LC/MS Method and Validation for the Determination of
Fluoxetine and Norfluoxetine in Human Plasma 2753

16.2.
Patient Data Listings 2923

16.2.1.
Adverse Event Listings by Patient 2924

16.2.2.
Discontinued Patients 2926

16.2.3.
Protocol Violations 2928

16.2.4.
Patients Excluded from the Efficacy Analysis 3005

16.2.5.
Demographic Data 3008

16.2.6.
Compliance and/or Drug Concentration Data 3010

16.2.7.
Individual Efficacy Response Data 3012

16.2.8.
Listing of Individual Laboratory Measurements
by Patient 3014

16.3.
Clinical Report Forms (CRFs) 3016

16.4.
Individual Patient Data Listings 3018

Table of Contents

Individual Patient Data Listings **Page**

16.4.1.
Patients Excluded From Pharmacokinetic Analysis

16.4.2.
Concomitant Medications

16.4.3.
Vital Signs Listing

16.4.4.
ECG Listing

16.4.5.
Comments Listing

4. List of Abbreviations and Definitions of Terms

Adverse event	(Used as category; no definition.)
Clinical trial adverse event	An adverse event is any undesirable experience, unanticipated benefit, or pregnancy that occurs after informed consent for the study has been obtained, without regard to the possibility of a causal relationship and without regard to treatment group assignment, even if no study drug has been taken.
Clinical trial serious adverse event	Any adverse event from a clinical study that includes one of the following criteria: • death • initial or prolonged inpatient hospitalization • is life-threatening • severe or permanent disability • cancer (other than cancers diagnosed prior to enrollment in studies involving patients with cancer) • congenital anomaly • is significant for other reason.
Lack of drug effect	Any failure of expected pharmacological action.
Spontaneous adverse event	A spontaneous adverse event is any untoward happening, failure of expected pharmacological action, unanticipated benefit, or pregnancy in a patient after the onset of therapy or upon withdrawal with a Lilly/Dista product, without regard to the possibility of a causal relationship.
Unanticipated benefit	An unanticipated event that may be considered of benefit to the study participant. An event that is considered an unanticipated benefit is reported to Lilly in the same manner as an adverse event.
Affirmation statement	A listing of the study participants by identifier and a statement, signed by the investigator, confirming that all clinical data required by and relevant to the protocol regarding the study participants were submitted to the sponsor, and that the investigator's involvement was in accordance with regulatory requirements.
ANOVA	Analysis of variance.
Audit	A systematic and independent examination to determine whether the conduct of a trial complies with the agreed protocol, applicable guidelines for good clinical practice (GCP), and company policies, and to determine if the data reported are consistent with the records on site.
Audit report	Reports completed by Lilly Medical Quality Assurance (MQA) or other auditing groups after conducting an audit. These reports are filed separately from the study documentation.
Beck Depression Inventory ***BDI***	The BDI (Beck and Steer 1984) is a patient-rated scale that assesses the major symptom categories associated with depression. Total scores range from 0 to 62. The higher the total score, the more severe the depression. The BDI scale is intended for use in adolescents (patients aged 13 to <18 years).
Blinding, unblinding	(Used as category; no definition.)

Double-blind labels	Labels used in clinical studies to conceal the identity of the drug from the study participant and the investigator.
Double-blind study	A study in which neither the study participant nor the investigator is aware of the treatment received. Studies in which Lilly personnel are blinded (in addition to the study participant and the investigator) are also considered double-blind studies (sometimes called triple-blind studies).
Unblinding	The act of providing visual or verbal access to study participant treatment information obtained from secured random number tables, or emergency identification envelopes.
Unblinding at the group level	Unblinding of the randomization scheme such that summary results are identified by treatment group, but any results for individual study participants do not include treatment-group assignment.
Unblinding at the individual level	Unblinding of the randomization scheme such that the actual treatment of an individual study participant is known.
Children's Depression Inventory ***CDI***	The CDI is a patient-rated scale that assesses the major symptom categories associated with depression. The CDI was developed from the BDI (Kovacs 1985). Total scores range from 0 to 54. Like the BDI, the higher the total score, the more severe the depression. The CDI scale is intended for use in children (patients aged 8 to <13 years).
Children's Depression Rating Scale-Revised ***CDRS-R***	The CDRS-R is a clinician-rated instrument designed to measure the presence and severity of depression in children (Poznanski et al. 1983, 1984, 1985). The scale was modeled after the Hamilton Depression Rating Scale for adults and includes questions about school. The scale consists of 17 items scored on a 1 to 5 or 1 to 7 point scale. A rating of 1 indicates normal functioning. Total scores range from 17 to 113. In general, scores below 20 indicate an absence of depression, scores of 20 to 30 indicate borderline depression, and scores of 40 to 60 indicate moderate depression.
Clinical Global Impression of Improvement ***CGI-Improvement***	The CGI-Improvement scale (NIMH 1976) is a clinician-rated instrument that measures the improvement of the patient's depression. It is a 7-point scale where a score of 1 indicates that the patient is "very much improved," a score of 4 indicates that the patient has experienced "no change," and a score of 7 indicates that the patients is "very much worse."
Clinical Global Impression of Severity ***CGI-Severity***	The CGI-Severity scale (NIMH 1976) is a clinician-rated instrument that measures the severity of the patient's depression. It is a 7-point scale where a score of 1 indicates that the patient is "normal" and a score of 7 indicates that the patient has an "extremely severe case of depression."
Clinical report form ***CRF***	The form used for recording study participants' data during a clinical study, as required by the established clinical study protocol. The form operates as a direct report to the sponsor. An electronic version of this form may be used. Sometimes called case card or case report form.

Clinical trial records binder ***CTRB***	A binder furnished to study sites as a suggested tool for organizing and filing all study documents and correspondence (except financial).
Clintrace	Clintrace (previously known as the Drug Experience Network or DEN) is a computerized system of Eli Lilly and Company established in 1998 for the worldwide collection, storage, and reporting of adverse events involving Lilly products since 1983. Clintrace includes clinical trial events described as "serious" according to the US FDA (Food and Drug Administration) regulations as well as serious and nonserious events reported spontaneously from postmarketing experience (including scientific literature and media reports). The coding of events is based on the Coding Symbol and Thesaurus for Adverse Reaction Terms (see **COSTART** below) dictionary.
Coding Symbol and Thesaurus for Adverse Reaction Terms ***COSTART***	A dictionary developed by the US Food and Drug Administration (FDA) that is used to describe, catalog, analyze, and report all adverse events.
Curriculum vitae ***CV***	A document that contains a person's educational and professional background. Clinical research investigators' curriculum vitae (CVs) are collected to ensure that the investigators are qualified and have experience in the appropriate research area.
Data analysis group ***DAG***	A group of Lilly personnel (for example, pharmacokineticists, clinical laboratory medicine personnel, medical science writers, regulatory scientists, systems analysts, statisticians) who have unblinded access to clinical study data during the study. The members of the data analysis group (DAG) perform functions such as providing interim reports to the data monitoring board (DMB), testing and validating data management programs, and developing pharmacokinetic models. The members of this group are not in contact with the study sites during the study and cannot access data to make changes or corrections to it.
Declaration of Helsinki	An international standard for the conduct of clinical trials that has been adopted as legally enforceable by many countries and jurisdictions.
Diagnostic Interview for Children and Adolescents ***DICA***	The DICA (Welner et al. 1987) is a diagnostic interview based on the Diagnostic and Statistical Manual of Mental Disorder, fourth edition (DSM-IV) criteria for major depressive disorder (MDD) including questions on significant historical diagnoses and the patient's psychiatric history.
Enroll	The act of assigning an individual to a treatment group. Individuals who are *enrolled* in the study are those who have been assigned to a treatment group. A person who has been *entered* into the study is potentially eligible to be *enrolled* in the study, but must meet all criteria for enrollment specified in the protocol before being *enrolled* (assigned to a treatment group). Individuals who are *entered* into the study but fail to meet the criteria for enrollment are not eligible to participate in the study and will not be *enrolled*.

Enter

The act of obtaining informed consent for participation in a clinical study from individuals deemed potentially eligible to participate in the clinical study. Individuals *entered* into a study are those for whom informed consent documents (ICDs) for the study have been signed by the potential study participants or their legal representatives.

Adverse events are reported for each individual who has *entered* the study, even if the individual is never assigned to a treatment group (*enrolled*).

Ethical review board

ERB

A board or committee (institutional, regional, or national) composed of medical professionals and nonmedical members whose responsibility is to verify that the safety, welfare, and human rights of the subjects or patients participating in a clinical trial are protected. Sometimes called *institutional review board* (IRB) or *independent ethics committee*.

Expectedness

A term used to indicate whether a particular adverse event (as described by a particular COSTART term) is described or listed in the product information (for marketed products) or the clinical investigator's brochure (CIB) (for adverse events reported from clinical trials). Expectedness is determined for any adverse event report entered into Clintrace. Affiliates outside the US may assign expectedness to other adverse event reports (non-serious) if or when required by local regulatory authorities. Sometimes called *expectancy*.

Global Assessment of Functioning Scale

GAF

The GAF Scale (Endicott et al. 1976) is a clinician-rated instrument that assesses the patient's current and highest level of functioning in the past year. It is a scale from 1 to 90 where 90 indicates absent or minimal symptoms and good functioning in all areas.

Hamilton Anxiety Rating Scale

HAMA

The HAMA is a clinician-rated instrument that assesses the severity of the patient's anxiety (Riskind et al. 1987). The scale consists of 14 items scored on a 0 to 4 point scale. A rating of 0 indicates that the symptom is not present and a rating of 4 indicates the symptom is very severe. Total scores range from 0 to 56. The higher the total score, the more severe the anxiety.

Informed consent document

ICD

An official document that is used to obtain informed consent for a clinical study from potential study participants. See *enter*, *enroll*, *screen*.

Intent-to-treat analysis

An analysis of study participants by the groups to which they were assigned by random allocation, even if the study participant did not take the assigned treatment, did not receive the correct treatment, or otherwise did not follow the protocol. Such an analysis is sometimes stated analyze as randomized.

Interim analysis

An analysis of clinical trial data that is conducted before the final analysis. The analysis compares relative treatment effects. For example, a direct comparison in a parallel or crossover study, a historical comparison, a selection of the better treatment(s) in a study, or, the separation of treatment groups in order to assess outcomes in a small number of many treatment groups (variability assessments).

Kiddie Schedule for Affective Disorders and Schizophrenia-Present and Lifetime ***K-SADS-PL***	The K-SADS-PL (Kaufman et al. 1997) was adapted from the K-SADS (Puig-Antich and Chambers 1978; Chambers et al. 1985) which was adapted for use with children and adolescents from the Schedule for Affective Disorders and Schizophrenia (Endicott and Spitzer 1978). This clinician-rated instrument assesses the extent of depressive symptoms and allows for rating the worst part of an episode as well as for the past week. This instrument was used in this study as both a supplementary diagnostic instrument and a secondary measure of efficacy.
LOCF	Last-observation-carried-forward.
Major depressive disorder ***MDD***	Criteria according to DSM-IV: At least five of the following symptoms have been present during the same 2-week period and represent a change from previous functioning; at least one of the symptoms is either (1) depressed mood, or (2) loss of interest or pleasure. Symptoms that occur most of the day or nearly every day, as indicated by subjective account or observation by others: (1) depressed mood (can be irritable mood in children and adolescents), (2) markedly diminished interest or pleasure in all, or almost all, activities, (3) significant weight loss or weight gain when not dieting (that is, more than 5% of body weight in a month), or decrease or increase in appetite (in children, consider failure to make expected weight gains), (4) insomnia or hypersomnia, (5) psychomotor agitation or retardation, (6) fatigue or loss of energy, (7) feelings of worthlessness or excessive or inappropriate guilt (which may be delusional), (8) diminished ability to think or concentrate, or indecisiveness, and (9) recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide.
Medical quality assurance ***MQA***	A part of the corporate quality assurance component which provides corporate and research management with ongoing evaluation of the quality of processes used and data generated to support worldwide registration of drugs.
Missouri Assessment of Genetics Interview for Children ***MAGIC***	The MAGIC is a diagnostic interview adapted from the DICA. It includes questions on significant historical diagnoses, the patient's psychiatric history, and genetic components of the patient's illness. This instrument was used as a diagnostic tool.
Monitoring plan	A guide listing the minimum criteria used to monitor a study site. For those persons monitoring the study, the monitoring plan does not replace an understanding of the requirements contained in the approved protocol.
Monitoring report	A written report of a monitoring visit to the study site which contains details of issues arising at that site as well as actions taken to address the issues.
Montgomery-Asberg Depression Rating Scale ***MADRS***	The MADRS (Montgomery and Asberg 1979) is a clinician-rated instrument that measures the presence and severity of depression. This instrument consists of a 10-symptom scale, namely, apparent sadness, reported sadness, inner tension, reduced sleep, reduced appetite, concentration difficulties, lassitude, inability to feel, pessimistic thoughts, and suicidal ideation. Each symptom is rated on a defined step scale (0 to 6). Total scores ranged from 0 to 60. A high numeric rating shows a greater degree of symptom severity. This scale has been validated for use in adults, but not in children and adolescents. It was included in this study as an exploratory analysis.

Multicenter study or trial — A study conducted simultaneously by several investigators at different locations, with identical methods and following the same protocol. The aim of this type of study is to collect data as rapidly as possible, for a combined analysis leading to a single report.

Note to file — A narrative summary that documents significant decisions, rationale, actions, protocol variations, additional instructions provided to a site during the course of a study, and any other issues or situations not adequately documented by other means.

Overdose — For a drug under clinical investigation, any intentional or unintentional consumption of the drug (by any route) that exceeds the dose recommended in the clinical investigator's brochure or in an investigational protocol, whichever dose is larger. For a marketed drug, a drug overdose is any intentional or unintentional consumption of the drug (by any route) that exceeds the dose listed in product labeling, even if the larger dose is prescribed by a physician.

Protocol — A document that states the background, rationale, and objectives of a clinical trial and describes its design, methodology, and organization. This document also includes statistical considerations and conditions under which the study is to be performed and managed.

Protocol amendment — A change in the content of a protocol that affects all investigators. An amended protocol must be provided to regulatory agencies when required.

Protocol attachments — Documents attached to the protocol to provide greater detail or explanation, such as clinical report forms (CRFs) or examples of efficacy measures.

Protocol signatures — Documentation that the investigator has read the protocol and understands it, agrees to work according to the protocol and to specific ethical principles and guidelines for good clinical practices, accepts the monitor's overseeing of the study, and will abide by the agreed-upon publication plan.

Protocol violation — Any instance in a clinical trial where the current approved protocol is not followed explicitly.

Quality assurance — The implementation of appropriate planned and systematic actions to provide adequate confidence that the required quality of a function or process will be obtained. In general, quality assurance refers to an independent group or department that oversees a quality control system and establishes confidence that the system is functioning properly.

Specific to the clinical study environment, systems, processes, and quality control procedures have been established to ensure that studies are performed and data are generated in compliance with guidelines for good clinical practice (GCP). These include procedures to be followed that apply to ethical and professional conduct, standard operating procedures, reporting, and in the review of professional and personnel qualifications.

Randomization

In clinical trials, the assignment of a study participant to a treatment group in such a way that all possible treatment group assignments are equally probable, subject to certain constraints imposed by stratification or blocking (see randomization block, below), serving to avoid the introduction of known or unknown bias (for example, assignment of study participants who may be ill to the new drug).

Randomization block size

A specified number of study participants grouped in a block to achieve the desired ratios of study participants in each treatment group. After randomization occurs for the participants within a block, the desired ratios will be achieved within that block.

The block size selected must be a multiple of the sum of the allocation ratios (for example, if the study participants are allocated to the low dose, high dose, and control groups in ratios of 2:2:1; the block size would be a multiple of 5). The block size should be large enough to aid in preserving the blinding (for example, if the ratio is 1:1, a block size of 2 would not preserve blinding; because if a study participant was unblinded for an adverse event, both study participants in that block would be unblinded). Usually, each study site is assigned its own blocks in order to preserve the desired allocation within each site.

The overall plan for blocking is called the *blocking scheme*.

Randomization codes

The identification of random treatment assignments for study participants in a clinical study. For blinded studies, the treatment assignment for an individual study participant is sealed (for example, in an envelope), access to this information is carefully controlled, and unblinding before the completion of the study and creation of the final reporting database must be documented.

Randomization table (or random table)

The entire list of randomization codes for a study.

Screen

The act of determining if an individual meets minimum requirements to become part of a pool of potential candidates for participation in a clinical study.

Screening may involve asking the candidate preliminary questions to determine potential eligibility. In these cases, the screening is not invasive and does not require that *screening* informed consent be obtained.

In other cases, *screening* may involve invasive or diagnostic procedures and/or (for example, diagnostic psychological tests, x-rays, blood draws). For this type of screening, informed consent for the screening procedures and/or tests shall be obtained.

5. Ethics

5.1. Ethical Review

The protocol and its amendment (see Appendix 16.1.1) were approved by all of the appropriate ethical review boards (ERBs) at each study site prior to patient enrollment. Appendix 16.1.9 contains information about the ERBs consulted.

5.2. Ethical Conduct of the Study

This study was conducted and informed consent was obtained according to the ethical principles stated in the latest version of the Declaration of Helsinki, the applicable guidelines for good clinical practice, or the applicable laws and regulations of the United States (US) where the study was conducted, whichever provided the greater protection of the individual.

5.3. Patient Information and Consent

An informed consent document (see Appendix 16.1.9) approved by each study site's ERB was signed by the parent or guardian of the patient and the investigator on or before Visit 1. Patients may have also signed the document depending on the requirements of each site's ERB. Copies of the informed consent document were given to each patient, parent, or guardian, and the original was retained by the investigator.

6. Investigators and Study Administrative Structure

This multicenter study was conducted by 15 investigators at 16 study sites. A pediatric or adult psychiatrist was on staff at all sites. Nineteen investigators were initially recruited for this study; however, three investigators (005, 018, and 021) did not enroll any patients and one investigator (010) did not screen any patients. Appendix 16.1.3 contains information on the qualifications of these investigators and information on other key individuals at the study sites.

The coordinating investigator was [redacted] of Eli Lilly and Company. The individuals who were involved either in the coordination of the study or in reporting of results are listed in Table 6.1. All statistical analyses were performed by Eli Lilly and Company.

The sponsor's medical officer responsible for the content of this clinical study report is [redacted] of Eli Lilly and Company (see Appendix 16.1.4).

Table 6.1. Study Administrative Structure B1Y-MC-HCJE

Name/Title/Affiliation	Role
[redacted]	Responsible for clinical review of the clinical/statistical report
[redacted]	Analysis of data and preparation of the clinical/statistical report
[redacted]	Systems lead for systems and statistical reporting for the clinical/statistical report
[redacted]	Management of the study and liaison with the investigators and Eli Lilly and Company (unblinded after datalock)
[redacted]	Management of the study and liaison with the investigators and Eli Lilly and Company (blinded)
[redacted]	Preparation of the clinical/statistical report
[redacted]	Assay of pharmacokinetic blood samples
[redacted]	General interpretation of electrocardiograms (ECGs) after study entry
[redacted]	Pediatric-specific interpretation of ECGs after study entry
[redacted]	Contract research organization with the responsibility for randomization and dispensing of study drug using an interactive voice response system (TriaLine), drug accountability
[redacted]	Assay of the clinical blood and urine samples

7. Introduction

Depressive disorders are a leading cause of morbidity and mortality in children and adolescents (Brent 1987; Fleming and Offord 1990; Pfeffer et al. 1991), with prevalence estimates ranging from 0.4% to 8.3% (Lewinsohn et al. 1986, 1993, 1994; Kashani et al. 1987a, b; Fleming and Offord 1990; Burke et al. 1991). Depressive disorders are generally more prevalent in adolescents than in children, with major depressive disorder (MDD) occurring at a 2:1 ratio in adolescent girls as compared with adolescent boys (Emslie et al. 1990). Common outcomes for children and adolescents diagnosed with depression include school failure and dropout (Weinberg and Rehmet 1983; Weinberg and Emslie 1988), with suicide remaining as one of the leading causes of death in adolescents (Brent 1987; Pfeffer et al. 1991; Rao et al. 1993). The age of onset of depression appears to be decreasing (Kovacs and Gatsonis 1994), implying that many individuals will experience their first episodes of depression as children or adolescents.

Although awareness that depression is an organic disease that readily responds to treatment has become more widespread for adults, the awareness of this disease in the pediatric population remains low. As a result, improvements in our capacity to recognize, diagnose, and treat depression in children and adolescents has major public health value. Introduction of effective antidepressant treatments earlier in the progression of the disease state has the potential to effectively treat and control the disease as well as improve daily functioning and overall quality of life.

While much has been written regarding the use of antidepressants in children with various mood and anxiety disorders, there have been few adequately powered controlled clinical trials within specific diagnostic areas. Controlled studies of the use of tricyclic antidepressants in children and adolescents with depression have failed to produce a replicable pattern of efficacy (Kramer and Feiguine 1981; Petti and Law 1982; Kashani et al. 1984; Puig-Antich et al. 1987; Geller et al. 1990; Boulos et al. 1992).

The efficacy of fluoxetine in the treatment of pediatric depression was demonstrated in a double-blind, placebo-controlled study (Emslie et al. 1997). The Emslie study used a fixed-dose (20 mg/day) strategy that proved fluoxetine to be efficacious and well tolerated. Anecdotal reports have suggested that children and adolescents respond to lower doses of fluoxetine treatment, and that a slow titration to therapeutic dosage or a lower maintenance dose may be necessary. Other reports have indicated that children and adolescents may require fluoxetine doses >20 mg/day (Simeon et al. 1990; Jain et al. 1992; Colle et al. 1994).

The primary objective of this study was a comparison of response rates for patients treated with fluoxetine 20 mg/day versus patients treated with placebo following acute treatment (9 weeks). Efficacy was also compared between patients treated with fluoxetine 20 mg/day versus patients treated with fluoxetine 40 to 60 mg/day to evaluate the efficacy of increasing dose in patients who had not responded to initial acute treatment with fluoxetine 20 mg/day. In addition, efficacy was compared between

patients treated with fluoxetine 20 to 60 mg/day versus patients treated with placebo following subchronic treatment (19 weeks). Disease-specific and broad-based efficacy measures were evaluated. The safety of fluoxetine treatment in this pediatric population was evaluated by examining treatment-emergent solicited and non-solicited adverse events, laboratory measures, vital signs, and ECG data.

8. Study Objectives

8.1. Primary Objective

The primary objective of this study, based on a responder analysis of the Children's Depression Rating Scale-Revised (CDRS-R), was:

- To test the hypothesis that fluoxetine 20 mg/day was more effective than placebo in the acute treatment of child (aged 8 to <13 years) and adolescent outpatients (aged 13 to <18 years) diagnosed with DSM-IV major depression as measured by response rates on the CDRS-R. Response was defined as a decrease of at least 30% in the CDRS-R total score from baseline to endpoint.

8.2. Secondary Objectives

The secondary objectives of the study included the following:

- To compare the efficacy of continued fluoxetine 20 mg/day with fluoxetine 40 to 60 mg/day among the nonresponders to 20 mg/day following acute treatment.
- To compare the efficacy of fluoxetine 20 to 60 mg/day with placebo in subchronic treatment of child and adolescent depression as measured by response rates on the CDRS-R after up to 19 weeks.
- To compare the efficacy of fluoxetine 20 mg/day (acute) and fluoxetine 20 to 60 mg/day (subchronic) with placebo in the treatment of child and adolescent depression as measured by the mean change in CDRS-R, Clinical Global Impression of Severity (CGI-Severity), Clinical Global Impression of Improvement (CGI-Improvement), the Kiddie Schedule for Affective Disorders and Schizophrenia–Present and Lifetime (K-SADS-PL) (Affective Disorders module only), Montgomery-Asberg Depression Rating Scale (MADRS), Beck Depression Inventory (BDI), and Children's Depression Inventory (CDI) scores from baseline to endpoint. CDRS-R remission rates and CGI response rates were also analyzed.
- To compare the effects of fluoxetine 20 mg/day (acute) and fluoxetine 20 to 60 mg/day (subchronic) with placebo on symptoms of anxiety in children and adolescents with depression as measured by mean changes in the Hamilton Anxiety Rating Scale (HAMA) scores from baseline to endpoint.
- To compare the safety of fluoxetine 20 mg/day (acute) and fluoxetine 20 to 60 mg/day (subchronic) with placebo in the treatment of child and adolescent depression.

- To compare the efficacy of fluoxetine 20 to 60 mg/day with placebo in preventing relapse as determined by time to relapse among responders following subchronic treatment.
- To determine if there were any differences in the efficacy and safety of fluoxetine between subgroups defined by age, gender, and family history of depression.
- To examine steady-state serum concentrations of fluoxetine and norfluoxetine in children and adolescents receiving different dosing regimens.

9. Investigational Plan

9.1. Overall Study Design and Plan: Description

This was a multicenter, double-blind, randomized, parallel-group study. Fluoxetine was compared with placebo for efficacy and safety in children and adolescents diagnosed with major depressive disorder (MDD) according to DSM-IV criteria.

For this study, a decision was made to use age rather than pubertal status to delineate children from adolescents because of FDA Guidances in effect at the time this study was designed. Consequently, children were defined as patients aged 8 to <13 years old and adolescents as patients aged 13 to <18 years old.

The study consisted of six study periods, as described below. Overall, the study was divided into three phases for the purposes of data analysis: a 9-week acute treatment phase (Study Periods III through IV), a 19-week subchronic treatment phase (Study Periods III through V), and a 32-week relapse prevention phase (Study Period VI).

Analyses of the acute treatment phase used data from the 9-week period during which patients received either fluoxetine 20 mg/day (10 mg/day for 1 week, followed by 20 mg/day for 8 weeks) or placebo. Analyses of the subchronic treatment phase refer to the 19-week period during which patients received either fluoxetine 20 to 60 mg/day or placebo. The acute and subchronic treatment phases overlap, as indicated in Figure 9.1. Because the 32-week relapse prevention phase (Study Period VI) is ongoing, analyses of this phase are not included in this clinical study report and will be submitted as a separate clinical study report at a later date.

The six study periods are described below and presented in Figure 9.1.

- **Study Period I** was a diagnostic evaluation period that lasted for 2 weeks.
- **Study Period II** was a single-blind, placebo wash-out period that lasted for 1 week. Placebo responders were discontinued from the study.
- **Study Period III** was a double-blind adaptation period that lasted for 1 week. Patients were randomized to receive either fluoxetine 10 mg/day or placebo.
- **Study Period IV** was a double-blind, fixed-dose acute treatment period that lasted for 8 weeks. Patients randomized to fluoxetine received 20 mg/day during this period.

- **Study Period V** was a double-blind, nonresponder rerandomization period that lasted for 10 weeks. Patients were evaluated for response at Visits 10 and 12. Responders at Visit 10 remained on fluoxetine 20 mg/day or placebo. Fluoxetine nonresponders were rerandomized to either remain on fluoxetine 20 mg/day or to receive fluoxetine 40 mg/day with an option to titrate to 60 mg/day at Visit 12. Placebo nonresponders remained on placebo.
- **Study Period VI** is a double-blind, relapse prevention period that will last for 32 weeks. Fluoxetine responders were rerandomized to either continue on the current fluoxetine dose or placebo. Placebo responders remained on placebo.

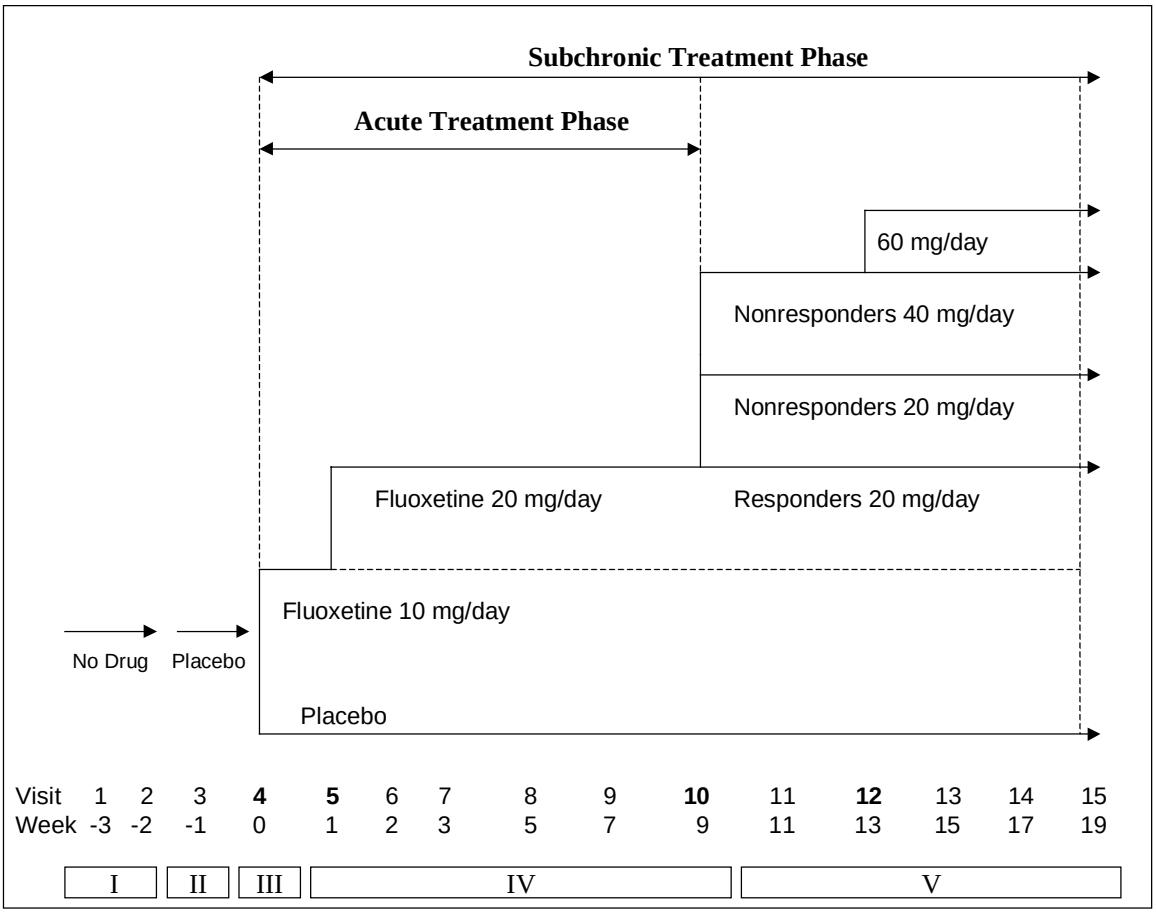


Figure 9.1. **Study Design for Study Periods I through V for B1Y-MC-HCJE.**

9.1.1. Study Period I: Diagnostic Evaluation Period

Study Period I was a 2-week diagnostic evaluation period. This period began with Visit 1 and ended with Visit 3. The visits were scheduled weekly (6 to 9 days).

Visits 1, 2, and 3 served as diagnostic evaluation visits. Each site was required to have at least three separate diagnostic interviewers. As MDD is difficult to diagnose properly in children and adolescents, patients were extensively evaluated on three separate occasions by three experienced clinicians prior to inclusion in the placebo washout periods. This comprehensive evaluation ensured that patients met DSM-IV or DSM-III-R criteria for nonpsychotic MDD (single or recurrent episodes). Comorbid psychiatric diagnoses were identified through the use of structured and semi-structured interviews.

Parents were initially screened over the telephone and if the patient met the criteria for the study (see Sections 9.3.1 and 9.3.2), the parent and patient were scheduled for an initiation evaluation. Prior to this initial interview, the study was explained to the patient and parent/guardian, and an informed consent form was signed.

A clinician that was not involved with the treatment phase of this study performed the initial evaluation of patients. During this evaluation, patients underwent a structured psychiatric interview, physical and neurological examinations, and had blood drawn for routine laboratory analysis. The parents responded to the Missouri Assessment of Genetics Interview for Children (MAGIC) parent version or the Diagnostic Interview for Children and Adolescents (DICA) questions regarding significant historical diagnoses. Parents also gave a detailed account of the patient's psychiatric history and responded to questions on the modified Family History Research Diagnostic Criteria (FHRDC). The MAGIC or DICA was conducted and reviewed by a separate interviewer at each of the three diagnostic visits.

The parent and patient were interviewed together to complete the clinician-rated CDRS-R, HAMA, and MADRS scales. In addition, several self-report measures were collected. Patients completed the BDI or CDI, depending on their age. While the patient was interviewed for completion of the MAGIC or DICA, the parent completed the FHRDC. If the patient met inclusion/exclusion criteria, he/she was scheduled for a repeat interview 1 week later.

Results from safety evaluations, including the physical examination, electrocardiogram (ECG), laboratory tests, urine screen for antidepressants, including fluoxetine/norfluoxetine, and urine drug screen were available by Visit 2. The urine drug screen results must have been negative prior to enrollment into Study Period II. If the results of the urine drug screen were positive for substances of abuse, the patient was re-tested. If results of the second urine drug screen were positive, the patient was not enrolled in the study.

The second interview (Visit 2) was conducted by a different interviewer and was independent from the previous psychiatric assessment. The interviewer reviewed the results of the MAGIC or DICA, significant historical diagnoses, and the patient's psychiatric history. Patient self-report measures were repeated and the CDRS-R and K-SADS-PL (Affective Disorders module) were administered. If all entry criteria were met, an additional interview was scheduled 1 week later.

The third interview (Visit 3) was conducted by a different interviewer and was independent from the two previous psychiatric assessments. Again, the interviewer for the visit reviewed the results of the MAGIC or DICA, significant historical diagnoses, and the patient's psychiatric history. The interviewer also reviewed results from the FHRDC. Patient self-report measures were repeated and the CDRS-R and K-SADS-PL (Affective Disorders module) were administered.

Patients who met the inclusion and exclusion criteria (including laboratory work) at all three interviews, and had a CDRS-R score of >40 at Visit 3, continued into Study Period II.

9.1.2. Study Period II: Placebo Washout Period

Study Period II was a 1-week, single-blind, placebo washout period. The period began at Visit 3 and ended at Visit 4. The visits were scheduled weekly (6 to 9 days).

Patients were assigned a medication kit and received single-blind treatment with placebo. Patients who responded to placebo (defined as a ≥30% decrease in CDRS-R score from Visit 3 to Visit 4 or a CGI-Improvement score of 1 or 2 at Visit 4 as compared with Visit 1) were discontinued.

9.1.3. Study Period III: Adaptation Period

Study Period III was a 1-week adaptation period (6 to 9 days). The period began at Visit 4 and ended at Visit 5 . Patients who continued to meet the inclusion/exclusion criteria at Visit 4 were randomized to receive either fluoxetine or placebo. Patients in the fluoxetine treatment group received fluoxetine 10 mg/day for the duration of the 1-week period. Patients who did not experience any dose-limiting adverse events on study medication continued into Study Period IV. Patients who could not tolerate study drug were discontinued.

9.1.4. Study Period IV: Fixed-Dose Period

Study Period IV was an 8-week, fixed-dose period. The period began with Visit 5 and ended with Visit 10. Visits were scheduled weekly (6 to 9 days) through Visit 7 and then biweekly (13 to 16 days) through Visit 10.

Patients randomized to the fluoxetine treatment group were required to have their dose of fluoxetine increased to 20 mg/day at Visit 5. Patients who could not tolerate fluoxetine 20 mg/day at Visits 6, 7, 8, or 9 were permitted to have their dose reduced to 10 mg/day, but then were not allowed to increase or decrease their dosage at any subsequent time during the study.

9.1.5. Study Period V: Double-Blind Nonresponder Rerandomization Period

Study Period V was a 10-week, double-blind, nonresponder rerandomization period. The period began at Visit 10 and ended at Visit 15. The visits were scheduled biweekly (13 to 16 days).

At Visit 10, patients who were responding to treatment with fluoxetine 20 mg/day remained on fluoxetine 20 mg/day. To be considered a responder, a patient must have had a ≥30% decrease in CDRS-R total score from baseline (Visit 4) to Visit 10. Nonresponders were rerandomized 1:1 to receive either continued treatment with fluoxetine 20 mg/day or to receive an increase in dose to fluoxetine 40 mg/day. Patients who could not tolerate 40 mg/day had the option to drop back to 20 mg/day, but then had no further opportunity to increase or decrease their dosage during this study period.

Patients who were rerandomized to the fluoxetine 40 mg/day treatment group and failed to respond (based on CGI-Improvement score) after 4 weeks of treatment with fluoxetine 40 mg/day had the option to undergo an additional dosage increase to fluoxetine 60 mg/day. Whether or not the optional dose increase was implemented was based on a clinical decision made by the investigator. Patients whose dose was increased to 60 mg/day at Visit 12 had a 2-week window in which their dose could be decreased, if necessary, for reasons of poor tolerability. There were no further opportunities for a dosage change after Visit 13. The final visit of this study period occurred 4 weeks (26 to 32 days) after Visit 13. This ensured that all patients had assessments made following a minimum of 4 weeks at a constant dose.

Blinding was maintained through the use of TriaLine, an interactive voice response system managed by [redacted] a contract research organization. Site personnel were instructed to enter in each patient's CDRS-R and CGI-Severity or CGI-Improvement scores for calculation of response. This system then instructed site personnel to dispense study medication through the use of package numbers based on the randomization scheme. All patients received three capsules of study medication daily during all periods of the study.

9.1.6. Study Period VI: Relapse Prevention Period

Study Period VI is ongoing. Results from this study period will be presented in a separate clinical study report.

Study Period VI is a 32-week (8-month) double-blind relapse prevention phase. This period began at Visit 15 and will end at Visit 26. The visits are scheduled biweekly for the first 3 months and monthly (26 to 32 days) thereafter.

Patients with a CDRS-R total score ≤28 at Visit 15 were eligible to participate in the relapse prevention phase. Participants were rerandomized (1:1) to placebo or to continue their current treatment as of Visit 15. Both investigators and patients were blinded to the

actual timing of the switch to the new treatment. Patients were assessed for sustained efficacy of pharmacologic treatment and for continued safety. Investigators were instructed to provide a detailed rationale for the decision to stop treatment for any patient.

Relapse during the relapse prevention phase was defined as a one-time CDRS-R total score >40 with a history of 2 weeks of clinical deterioration as determined by patient report, parent report, or clinical history.

9.2. Discussion of Study Design, Including the Choice of Control Groups

This study was designed to assess the efficacy and tolerability of various dosing strategies and to guide pharmacologic treatment of depressed children and adolescents with fluoxetine.

To obtain the most reliable assessment of a patient's condition, this study incorporated an extensive diagnostic evaluation period requiring three independent diagnostic interviews. Furthermore, to eliminate placebo responders and patients who respond to non-specific interventions, a 1-week placebo washout period was included following the evaluation period.

Results of prior studies suggested that there is a relationship between rate of dose escalation and susceptibility to adverse events (Riddle et al. 1990, 1991). As a result, this study incorporated a 1-week adaptation phase at a dose lower than that used successfully in the Emslie et al. (1997) pediatric study and in adult studies of fluoxetine.

Data from previous studies and case series suggest that unlike adults, children and adolescents with depressive illnesses respond preferentially to selective serotonin reuptake inhibitors (SSRIs). However, it is not known whether the time to onset of therapeutic effect is different between children and adults. Patients who did not respond to fluoxetine 20 mg/day after 8 weeks were rerandomized to either remain on fluoxetine 20 mg/day for an additional 10 weeks or to receive fluoxetine 40 mg/day with an option to titrate to 60 mg/day.

Control was provided by randomization of patients to fluoxetine or placebo treatment under double-blind conditions.

9.3. Selection of Study Population

9.3.1. Inclusion Criteria

Patients were included in the study **only** if they met all of the following criteria:

[1] Male and female outpatients.

[2] Children (aged 8 to <13 years) and adolescents (aged 13 to <18 years) at the time of entry into the study.

[3] A primary psychiatric diagnosis of nonpsychotic major depressive disorder (single or recurrent) as defined by the DSM-IV criteria.

[4] Depressive symptoms of at least moderate severity as defined by a CDRS-R total score >40 and a CGI-Severity rating of moderate or greater.

[5] Able to swallow whole medication without difficulty.

[6] No clinically significant laboratory findings in hematology, chemistry, and urinalysis at study entry based on the judgment of the investigator.

[7] ECG without clinically significant abnormalities. Clinical significance was determined by the investigator and the physician interpreting the ECG.

[8] Educational level and degree of understanding so that the patients and parents could communicate intelligibly with the investigator and study coordinator. Normal intelligence based on the judgment of the investigator.

[9] Patients and parents judged to be reliable who agreed to keep appointments for clinic visits and all tests and examinations required by the protocol.

9.3.2. Exclusion Criteria

Patients were excluded from the study for **any** of the following reasons:

[10] Investigators and their immediate families were not permitted to be subjects or patients in Lilly-sponsored trials. Immediate family is defined as the investigator's spouse, parent, child, grandparent, or grandchild.

[11] Persons who had previously completed or withdrawn from this study.

[12] Females who were pregnant or breastfeeding or who were sexually active and were not using medically accepted means of contraception (intrauterine device, birth control pills, barrier devices, or implanted progesterone rods stabilized for at least 3 months).

[13] Serious illness (including cardiac, hepatic, renal, respiratory, endocrinologic, neurologic, or hematologic disease) that was not stabilized so that hospitalization for treatment of that illness was likely within the next 2 months.

[14] Patients with abnormal thyroid function.

[15] Seizure disorder with a seizure occurring within the past 6 months, except for febrile seizures.

[16] Diagnosis of any of the following DSM-IV-defined disorders: bipolar I or II disorder, sleep-wake disorder, psychotic depression (lifetime), anorexia (lifetime), bulimia (lifetime), borderline personality disorder or substance abuse disorder (within the past 6 months).

[17] Patients with one or more first-degree relatives with bipolar I disorder.

[18] Organic brain diseases.

[19] Persons whose illness has previously failed to respond to adequate antidepressant treatment (at least 8 weeks treatment within the typical maximum adult therapeutic range).

[20] Serious suicidal risk.

[21] History of severe allergies, multiple adverse drug reactions, or known allergy to the study drug.

[22] Receipt of an investigational drug within 30 days prior to study entry.

[23] Receipt of any behavior-altering, centrally-acting, or excluded medication within 7 days prior to study entry.

[24] Documented hypersensitivity to fluoxetine.

[25] Prior adequate treatment with fluoxetine (12 weeks on a fixed dose of 20 mg or greater).

[26] Receipt of fluoxetine within 3 months prior to study entry.
Note: Patients who had detectable levels of fluoxetine, norfluoxetine, or any other antidepressant in their initial urine screen were discontinued.

[27] Regular use of other psychotropic or centrally-acting drugs, including lithium and the psychostimulants (ie, drugs normally prescribed for depression, mania, anxiety, insomnia, attention deficit disorder, or psychosis) within 2 weeks prior to study entry that would need to be continued during the study.

[28] Use of neuroleptics during the 2 weeks prior to study entry or of depot neuroleptics within the 6 weeks prior to study entry.

[29] Use of a monoamine oxidase inhibitor (MAOI) within 2 weeks (14 days) prior to study entry or potential need to use an MAOI within 5 weeks of discontinuation of treatment.

[30] Use of tryptophan, St John's Wort, or melatonin within 2 weeks prior to study entry.

[31] Potential need for the continuation or initiation of other treatments for depression, including cognitive behavioral therapy and behavioral therapy, except for supportive therapy on an individual or family basis.

9.3.3. Removal of Patients from Therapy or Assessment

Possible reasons for discontinuation from the study included the following:

- In the opinion of the investigator, a serious adverse event or a significant change in a laboratory value occurred. In this case, the study drug was discontinued and appropriate measures were taken. The sponsor was notified immediately.
- The patient, guardian, or attending physician requested, or the investigator decided, that the patient be withdrawn from the study.
- The patient, for any reason, required treatment with another therapeutic agent that had been demonstrated to be effective for treatment of the study indication. In this case, discontinuation from the study occurred immediately upon introduction of the new agent.
- The investigator or Lilly, for any reason, stopped the study or stopped the patient's participation in the study.

A physical examination was conducted on all patients who discontinued the study at any point after Visit 3. The investigator was responsible for ensuring that any abnormality found at the discontinuation physical examination received appropriate follow up.

9.4. Treatments

9.4.1. Treatments Administered

9.4.1.1. Study Period I: Diagnostic Evaluation Period

No study medications were administered.

9.4.1.2. Study Period II: Placebo Washout Period

At Visit 3, all patients who met the inclusion/exclusion criteria received single-blind treatment with placebo. All patients were instructed to take three capsules once daily at approximately the same time each day.

9.4.1.3. Study Period III: Adaptation Period

At Visit 4, patients were randomized to either the fluoxetine or the placebo treatment group. Patients in the fluoxetine treatment group received an initial fluoxetine dose of 10 mg/day. All randomized patients were instructed to take three capsules once daily at approximately the same time each day. Fluoxetine-treated patients received one fluoxetine 10 mg and two placebo capsules and placebo-treated patients received three placebo capsules each day.

9.4.1.4. Study Period IV: Fixed-Dose Period

Patients who were able to tolerate their study medication at Visit 5 entered an 8-week fixed-dose period. Fluoxetine-treated patients received fluoxetine 20 mg/day for 8 weeks. All patients were instructed to take three capsules once daily at approximately the same time each day. Fluoxetine-treated patients received two fluoxetine 10 mg and one placebo capsule and placebo-treated patients received three placebo capsules each day.

9.4.1.5. Study Period V: Double-Blind Nonresponder Rerandomization Period

All patients continued to take three capsules once daily at approximately the same time each day, unless otherwise instructed by the investigator.

At Visit 10, patients responding to treatment with fluoxetine 20 mg/day received two fluoxetine 10 mg and one placebo capsule each day. Responders were defined as having a ≥30% decrease in CDRS-R total score from baseline (Visit 4) to Visit 10. Placebo-treated patients remained on placebo and received three placebo capsules each day.

Fluoxetine-treated patients who were not responding to treatment at 20 mg/day were rerandomized (1:1) to receive either continued treatment with fluoxetine 20 mg/day or an increase in dose to fluoxetine 40 mg/day. Patients who were rerandomized to continue treatment with fluoxetine 20 mg/day received two fluoxetine 10 mg and one placebo capsule each day. Patients who were rerandomized to fluoxetine 40 mg/day received two fluoxetine 20 mg and one placebo capsule each day. Patients who experienced dose-limiting side effects at fluoxetine 40 mg/day were allowed to drop back to fluoxetine 20 mg/day, but had no further opportunity to increase their dosage during this study period.

Patients who were rerandomized to the fluoxetine 40 mg/day treatment group and failed to respond after 4 weeks of treatment with fluoxetine 40 mg/day underwent an optional dosage increase to fluoxetine 60 mg/day at Visit 12. Patients receiving fluoxetine 60 mg/day received three fluoxetine 20-mg capsules each day. Patients were allowed to increase to fluoxetine 60 mg/day if the patient's CGI-Improvement score at Visit 12 was between 3 and 7. Increases in dosage were prohibited if the patient's CGI-Improvement score was 1 or 2. This dosage increase was optional. If the dose was increased, the reason was documented in the clinical report form by the investigator. Patients whose dose was increased to 60 mg/day at Visit 12 had a 2-week window in which their dose could be decreased to fluoxetine 40 mg/day, if necessary, for reasons of poor tolerability. There were no further opportunities for a dosage change after Visit 13.

Decreases in dosage for safety reasons were allowed at any scheduled or unscheduled visit at any time between Visits 10 and 13. Only one dosage reduction was allowed during a given visit interval. The clinician always retained the responsibility to discontinue a patient if clinically warranted.

9.4.1.6. Study Period VI: Relapse Prevention Period

Study Period VI was ongoing at the time this clinical study report was written; therefore, data for this study period were not analyzed and will not be presented in this report.

Patients with a CDRS-R total score ≤28 at Visit 15 were enrolled in a 32-week, double-blind relapse prevention phase. Patients were rerandomized (1:1) to either placebo or to continue their current treatment at Visit 15. The timing of this change was blinded to the investigator and the patient; in the protocol, the rerandomization visit is referred to as Visit S. Patients were instructed to continue taking their study medication as prescribed at the last visit of Study Period V. Additional dosage adjustments were not allowed during the relapse prevention phase. All patients were instructed to take three capsules once daily.

9.4.2. Identity of Investigational Products

Medication was packaged in blister cards and labeled with a package number (blister card), kit number, carton number (final assembly), and expiration date (see Table 9.1). If a patient forgot to take a dose of medication, he/she was instructed to take the next dose at the regularly scheduled time. At each visit, the patient returned the blister cards so that the remaining capsules could be counted. The number of remaining capsules was recorded. The study site used this information to individually counsel patients regarding compliance. Appendix 16.1.10 provides a listing of patients receiving study drug from each lot of study medication.

Table 9.1. Study Medication Study Periods II-V B1Y-MC-HCJE

Treatment Group	Strength (mg) Dose Form	Lot Number[a]	Bulk Number[b]	Expiration Date
Fluoxetine	10-mg Capsule	CT07620	B02752	1 Sept 2000
		CT12697		31 Oct 2000
	20-mg Capsule	CT09678	B00874	1 Sept 2000
		CT10738		1 Sept 2000 and 31 Oct 2000
Placebo	Capsule	CT09679	B00875	1 Sept 2000
		CT10799		1 Sept 2000

[a]Lot number refers to the lot number of the raw material provided for packaging into blister cards (packages), kits, and cartons.
[b]Bulk number refers to the bulk lot number for the raw material provided for packaging into lots.

9.4.3. Method of Assigning Patients to Treatment Groups

A patient number was assigned to each patient at the time the informed consent document was signed (Visit 1). Patients who qualified for Study Period III were randomly assigned to one of the two treatment groups at Visit 4. The treatment group to which the patient

was assigned was determined by a computer-generated randomization sequence. Randomization at Visit 4 was stratified by gender and age category (child versus adolescent) across investigative sites.

At Visit 10, all patients were evaluated for response status. Fluoxetine-treated responders remained on fluoxetine 20 mg/day. Fluoxetine-treated nonresponders were rerandomized (1:1) to either fluoxetine 20 mg/day or fluoxetine 40 to 60 mg/day as determined by a computer-generated randomization sequence. Placebo-treated patients were evaluated for response; however, all remained on placebo.

Patients with a CDRS-R total score ≤28 at Visit 15 were eligible to continue into the double-blind relapse prevention phase (Study Period VI). This phase lasted up to 32 weeks (8 months). Patients were rerandomized (1:1) to either continue their current treatment or switch to placebo at Visit 15; however, the timing of the change in medications was blinded to the investigator and the patient. Again, the treatment group to which the patient was assigned was determined by a computer-generated randomization sequence.

9.4.4. Selection of Doses in the Study

The dosing regimen used in this study was designed to allow adaptation to drug by administering a starting dose of fluoxetine 10 mg/day, then treatment with 20 mg/day. The dosing regimen also included an option to gradually titrate the dose to a maximum of fluoxetine 60 mg/day based on response to treatment, and an option to incrementally decrease the dose if not tolerated.

9.4.5. Selection and Timing of Dose for Each Patient

Patient kits were assigned at Visit 3. Patients were instructed to take three capsules once daily, preferably in the morning. If the investigator thought the patient would benefit from dosing in the evening, doses could be taken in the evening.

9.4.6. Blinding

In order to preserve the integrity of the study, only a minimum number of Lilly personnel had access to the randomization table and codes before the study was complete. These codes are presented in Appendix 16.1.5.

Emergency codes, generated by a computer drug-labeling system, were available to each investigator. These codes, which revealed the patient's treatment group, were opened during the study only in the case of emergency and if the choice of follow-up treatment depended on the patient's therapy assignment.

Each investigator made every effort to contact the Lilly clinical research physician prior to unblinding a patient's therapy assignment. If a patient's therapy assignment was unblinded, Lilly was notified immediately by telephone. Unblinding of a patient's

therapy assignment was performed by an individual not affiliated with the study. After all patients had completed the study, the investigator returned all sealed and any opened codes.

If investigators, site personnel performing assessments, or patients were unblinded, the patient was discontinued from the study unless there were ethical reasons to have the patient remain in the study. In these special cases, the investigator obtained specific approval from a Lilly clinical research physician for the patient to continue in the study.

Fluoxetine-treated patients not responding to acute treatment at 20 mg/day were rerandomized (1:1) to either fluoxetine 20 mg/day or fluoxetine 40 mg/day at Visit 10. Blinding was maintained through the use of TriaLine, an interactive voice response system managed by [redacted] Site personnel were instructed to enter in each patient's CDRS-R total and CGI-Severity or CGI-Improvement scores for calculation of response. This system then instructed site personnel to dispense study medication through the use of package numbers based on the randomization scheme.

A rescue therapy option was available for patients who discontinued the study. A process was established to allow patients to receive rescue therapy while maintaining the blind for the study. This process provided for the unblinding of a "new" physician. The "new" physician was not associated with the study and agreed to maintain the study blind from study personnel.

If a patient discontinued from the study and the investigator believed that the patient required rescue therapy, the investigator referred the patient to an outside physician who requested that Lilly allow unblinding of the patient's therapy assignment by completing a form provided by Lilly. If the clinical research associate at Lilly approved the request, the request was faxed to the Study Drug Coordinator at Lilly. The Study Drug Coordinator then contacted the outside physician to reveal the patient's therapy assignment. Documentation of these instances of unblinding has been retained in the investigator binders.

Twenty-two patients (15 fluoxetine-treated, 7 placebo-treated) received rescue treatment under this procedure and are listed in Table 9.2. The therapy assignments for these patients were revealed to the treating physician, who was not affiliated with the study site.

Table 9.2. Patients Undergoing Rescue Therapy Study Periods I-V B1Y-MC-HCJE

Patient Number	Therapy Assignment	Date of Request from Treating Physician
401	Fluoxetine	7 October 1998
413	Fluoxetine	10 March 1999
415	Fluoxetine	10 May 1999
416	Fluoxetine	9 June 1999
419	Fluoxetine	13 April 1999
422	Fluoxetine	21 September 1999
424	Fluoxetine	10 January 2000
425	Placebo	13 September 1999
432	Placebo	10 June 1999
433	Fluoxetine	29 September 1999
441	Fluoxetine	14 September 1999
916	Placebo	1 November 1999
1105	Placebo	10 May 1999
1107	Placebo	9 November 1998
1109	Fluoxetine	16 October 1998
1120	Placebo	25 January 1999
1121	Placebo	19 January 1999
1131	Fluoxetine	12 April 1999
1137	Fluoxetine	3 September 1999
1141	Fluoxetine	1 July 1999
1153	Fluoxetine	3 November 1999
1510	Fluoxetine	27 October 1999

No patients or site personnel were unblinded to individual patient treatment assignments during Study Periods I through V.

9.4.7. Prior and Concomitant Therapy

All nonstudy medications taken during the study were recorded on the clinical report form. Patients were instructed to consult with the investigator or study coordinator at the site before taking any new medications or supplements.

9.4.7.1. Excluded Medications

Medications excluded by the protocol included antidepressants, monoaminase oxidase inhibitors (MAOIs), central nervous system stimulants, anxiolytics, antipsychotics, antimigraine compounds, sedative-hypnotics/sleep aids, antimanic medication, and xanthine bronchodilators. Other treatments for depression, including cognitive behavioral therapy and behavioral therapy were also excluded, with the exception of supportive therapy on an individual or family basis. Patients requiring excluded concomitant medication (or therapies) were discontinued from the study.

9.4.7.2. Permitted Medications

Patients were allowed to take over-the-counter or prescription medications not specifically excluded by the protocol. Acceptable medications included Tylenol®, cold preparations, birth control pills, and vitamins. A patient could be given chloral hydrate up to 1.0 g/day as needed at bedtime for sleep. Ambien® could also be prescribed for the short-term treatment of insomnia. Use was limited to no more than 5 days within a 4-week time period.

9.4.8. Treatment Compliance

The investigator had the responsibility to explain the correct use of the investigational product(s) to the patient and his or her parent/legal guardian(s) and to check at appropriate intervals to ensure that each study participant was following instructions properly.

Study medication was distributed by qualified personnel at the study site at each visit and recorded on designated worksheets. Compliance with the protocol and treatment regimen was assessed by direct questioning and counting of returned medication. All unused medication was returned to the sponsor at the end of the study. Patients who missed their medication for 3 consecutive days at any time during Study Periods III through V, or for 7 consecutive days in Study Period VI were deemed noncompliant and were discontinued from the study, unless the clinical research physician gave approval for the patient to remain in the study.

Patients who failed to cooperate in tests or examinations or did not attend visits within the stated periods could be deemed noncompliant and subsequently discontinued from the study.

9.5. Efficacy and Safety Variables

9.5.1. Efficacy and Safety Measurements Assessed and Schedule of Events

The following efficacy measures were collected at the times shown in Table 9.3 (Schedule of Events).

- **Children's Depression Rating Scale-Revised (CDRS-R):**
  The CDRS-R is a clinician-rated instrument designed to measure the presence and severity of depression in children (Poznanski et al. 1983, 1984, 1985). The scale was modeled after the Hamilton Depression Rating Scale for adults and includes questions about school. The scale consists of 17 items scored on a 1 to 5 or 1 to 7 point scale. A rating of 1 indicates normal functioning. Total scores range from 17 to 113. In general, scores below 20 indicate an absence of depression, scores of 20 to 30 indicate borderline depression, and scores of 40 to 60 indicate moderate depression.

- **Clinical Global Impression of Severity (CGI-Severity):**
  The CGI-Severity scale (NIMH 1976) is a clinician-rated instrument that measures the severity of the patient's depression. It is a 7-point scale where a score of 1 indicates that the patient is "normal" and a score of 7 indicates that the patient has an "extremely severe case of depression."

- **Clinical Global Impression of Improvement (CGI-Improvement):**
  The CGI-Improvement scale (NIMH 1976) is a clinician-rated instrument that measures the improvement of the patient's depression. It is a 7-point scale where a score of 1 indicates that the patient is "very much improved," a score of 4 indicates that the patient has experienced "no change," and a score of 7 indicates that the patient is "very much worse."

- **Beck Depression Inventory (BDI):**
  The BDI (Beck and Steer 1984) is a patient-rated scale that assesses the major symptom categories associated with depression. Total scores range from 0 to 62. The higher the total score, the more severe the depression. The BDI scale is intended for use in adolescents (patients aged 13 to <18 years).

- **Children's Depression Inventory (CDI):**
  The CDI is a patient-rated scale that assesses the major symptom categories associated with depression. The CDI was developed from the BDI (Kovacs 1985). Total scores range from 0 to 54. Like the BDI, the higher the total score, the more severe the depression. The CDI scale is intended for use in children (patients aged 8 to <13 years).

- **Kiddie Schedule for Affective Disorders and Schizophrenia–Present and Lifetime (K-SADS-PL):**
  The K-SADS-PL (Kaufman et al. 1997) was adapted from the K-SADS (Puig-Antich and Chambers 1978; Chambers et al. 1985) which was adapted for use with children and adolescents from the Schedule for Affective Disorders and Schizophrenia (Endicott and Spitzer 1978). This clinician-rated instrument assesses the extent of depressive symptoms and allows for rating the worst part of an episode as well as symptoms for the past week. This instrument was used in this study as both a supplementary diagnostic instrument and a measure of efficacy.

- **Montgomery-Asberg Depression Rating Scale (MADRS):**
  The MADRS (Montgomery and Asberg 1979) is a clinician-rated instrument that measures the presence and severity of depression. This instrument consists of a 10-symptom scale, namely, apparent sadness, reported sadness, inner tension, reduced sleep, reduced appetite, concentration difficulties, lassitude, inability to feel, pessimistic thoughts, and suicidal ideation. Each symptom is rated on a defined step scale (0 to 6). Total scores ranged from 0 to 60. A high numeric rating shows a greater degree of symptom severity.

This scale has been validated for use in adults, but not in children and adolescents. It was included in this study as an exploratory analysis.

- **Hamilton Anxiety Rating Scale (HAMA):**
  The HAMA is a clinician-rated instrument that measures the severity of the patient's anxiety (Riskind et al. 1987). The scale consists of 14 items scored on a 0 to 4 point scale. A rating of 0 indicates that the symptom is not present and a rating of 4 indicates the symptom is very severe. Total scores range from 0 to 56. The higher the total score, the more severe the anxiety.

- **Global Assessment of Functioning (GAF):**
  The GAF Scale (Endicott et al. 1976) is a clinician-rated instrument that assesses the patient's current and highest level of functioning. It is a scale from 1 to 90 where 90 indicates absent or minimal symptoms and good functioning in all areas.

The following safety measures were collected at the times shown in Table 9.3 (Schedule of Events).

- **Non-Solicited Adverse Events:**
  During the study, non-solicited adverse events were collected systematically. Patients were questioned about the presence of adverse events at the beginning of each visit (non-solicited) and the Side-Effects Checklist was administered at the end of each visit (solicited). Non-solicited adverse events were captured regardless of relationship to study medication. These events were captured as actual terms and coded to COSTART terms by blinded Lilly clinical personnel and verified by a blinded Lilly clinical research physician.

- **Side-Effects Checklist:**
  The Side-Effects Checklist is a 30-item symptom checklist based on the Subjective Treatment Emergent Symptoms Scale (STESS) developed by the NIMH. The items on the checklist include general symptoms, such as trouble sleeping, diarrhea, headaches, and trouble eating (see Appendix 16.1.2). The patient was asked by the clinician if he/she had trouble with the symptoms on the checklist. The clinician also recorded the frequency of these symptoms based on conversation with the patient.

- **Concomitant Medications:**
  All concomitant medications taken during the study were recorded.

- **Laboratory Data:**
  Standard laboratory tests included chemistry, hematology, and urinalysis panels. A urine drug screen, thyroid function test, and pregnancy test (if applicable) were completed at baseline.

- **Vital Signs:**
  Vital signs included sitting blood pressure (systolic and diastolic), heart rate, weight, and height.

- **Electrocardiograms (ECG):**
  ECGs were collected to determine eligibility of the patient for entry into the study and at various time points during the study. It should be noted that this study was not designed to systematically evaluate ECG changes. ECG equipment was not standardized among the study sites, and the interval between the last dose of study drug and the ECG procedure was not standardized.

Table 9.3. Schedule of Events for the Acute and Subchronic Phases of B1Y-MC-HCJE

Study Period	I		II	III	IV						V						
Visit Activity (Week)	V1 (-3)	V2 (-2)	V3 (-1)	V4 (0)	V5 (1)	V6 (2)	V7 (3)	V8 (5)	V9 (7)	V10 (9)	V11 (11)	V12 (13)	V13 (15)	V14 (17)	V15 (19)	Unscheduled Visit	Early Discontinuation
Patient informed consent	x																
Parent informed consent	x																
MAGIC or DICA (Patient Version)	x	R	R														
MAGIC or DICA (Parent Version)	x	R	R														
K-SADS-PL[a]		x	x	x						x	x				x		x
Historical diagnosis	x	R	R														
Psychiatric history / Previous therapy	x	R	R														
Modified Family History RDC	x	R	R														
Urine Drug Screen	x																
Urine Antidepressant Screen	x																
Laboratory tests[b]	x														x		x
Fluoxetine/nor-fluoxetine levels	x									x					x		x
Consumptive habits	x																
Demographics	x																
Physical examination	x														x		x
Weight	x														x		x
Height	x														x		

(continued)

Table 9.3. Schedule of Events for the Acute and Subchronic Phases of B1Y-MC-HCJE (continued)

Study Period	I		II	III	IV						V						
Visit Activity (Week)	V1 (-3)	V2 (-2)	V3 (-1)	V4 (0)	V5 (1)	V6 (2)	V7 (3)	V8 (5)	V9 (7)	V10 (9)	V11 (11)	V12 (13)	V13 (15)	V14 (17)	V15 (19)	Unscheduled Visit	Early Discontinuation
ECG	x														x		x
Vitals	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Secondary conditions	x																
Non-Solicited Adverse Events		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Side-Effects Checklist				x	x	x	x	x	x	x	x	x	x	x	x		x
Dosage adjustment[c]				x↑	x↑	x↓				x↑	x↑	x↓					
Concomitant Medications	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
CDRS-R	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
CGI-Severity	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
CGI-Improvement		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
MADRS	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
BDI[d]	x	x	x	x				x		x	x		x		x		x
CDI[e]	x	x	x	x				x		x	x		x		x		x
GAF		x	x	x						x					x		x
HAMA	x	x	x	x				x		x					x		x
Patient summary																	x

(continued)

Table 9.3. Schedule of Events for the Acute and Subchronic Phases of B1Y-MC-HCJE (concluded)

R = reviewed at this visit; x = performed at this visit.

Abbreviations: BDI = Beck Depression Inventory; CDI = Children's Depression Inventory; CDRS-R = Childhood Depression Rating Scale-Revised; CGI-Improvement = Clinical Global Impression of Improvement; CGI-Severity = Clinical Global Impression of Severity; DICA= Diagnostic Interview for Children and Adolescents; ECG = electrocardiogram; GAF = Global Assessment of Functioning; HAMA = Hamilton Anxiety Rating Scale; K-SADS-PL = Kiddie Schedule for Affective Disorders and Schizophrenia- Present and Lifetime; MADRS = Montgomery-Asberg Depression Rating Scale; MAGIC= Missouri Assessment of Genetics Interview for Children;.

[a]Affective Disorders module only.

[b]Specified in the protocol (see Appendix 16.1.1).

[c]Arrows indicate the direction of dosage adjustments. All fluoxetine-treated patients had their dosage increased to fluoxetine 20 mg/day at Visit 5. Patients who could not tolerate fluoxetine 20 mg/day at Visits 6, 7, 8, or 9 had their dose decreased to fluoxetine 10 mg/day and remained on 10 mg/day for the remainder of the study. Nonresponders were rerandomized (1:1) to fluoxetine 20 or 40 mg/day at Visit 10.

[d]The BDI was administered to adolescents (aged 13 to <18) only.

[e]The CDI was administered to children (aged 8 to <13) only.

9.5.2. Appropriateness of Measurements

All efficacy and safety assessments have been well documented and are generally regarded as reliable, accurate, and relevant. Details for each scale are provided in Section 9.5.1.

9.5.3. Primary Efficacy Variable

The primary efficacy variable for this study was the CDRS-R total score. The primary analysis to support efficacy of fluoxetine 20 mg/day in the acute treatment of MDD was the analysis of response, defined as a decrease of at least 30% in the CDRS-R total score from baseline to endpoint.

A 30% decrease in CDRS-R total score is considered to be clinically significant, as it is representative of a change in the patient's condition from active depression to remission (Poznanski et al. 1985). At study entry, patients were required to have a score >40 on the CDRS-R in order to be enrolled (the minimum score correlated with active depression). Remission of depressive symptoms is defined as achieving a score of 28 or less on the CDRS-R. This difference between the minimum entry criterion for depression and remission is 30%.

9.5.4. Drug Concentration Measurements

Formal pharmacokinetic data were not collected. Baseline fluoxetine serum concentrations were assayed. Fluoxetine, norfluoxetine, and other antidepressants and their metabolites were nondetectable by urine screen at baseline for inclusion into the study. Steady-state serum concentrations of fluoxetine and norfluoxetine were collected as indicated in the Schedule of Events (see Table 9.3).

9.6. Data Quality Assurance

To ensure accurate, complete, and reliable data, Lilly or its representatives did the following:

- provided instructional material to the study sites, as appropriate
- sponsored a start-up training session to instruct the investigators and study coordinators
- made periodic visits to the study site
- were available for consultation and stayed in contact with the study site personnel by mail, telephone, and/or fax
- reviewed and evaluated clinical report form data and used standard computer edits to detect errors in data collection
- conducted quality review of database.

A central laboratory was used to maintain consistency of methods and to combine laboratory data across study sites and/or across studies.

9.7. Statistical Methods Planned in the Protocol and Determination of Sample Size

9.7.1. Statistical and Analytical Plans

It should be noted that this clinical study report includes data for all patients for the acute and subchronic phases of this study. Analyses of the relapse prevention phase (Study Period VI) will be presented in a separate clinical study report.

9.7.1.1. General Considerations

Two hundred nineteen patients were randomized to treatment, with 109 patients receiving fluoxetine 10 to 60 mg/day and 110 patients receiving placebo treatment. The distribution of patients across investigators was expected to be approximately equal. Investigators who enrolled no patients into one or more treatment groups were pooled together for the purpose of statistical analyses when assessing treatment-by-investigator interactions.

Analyses were conducted on an intent-to-treat basis unless otherwise specified. An intent-to-treat analysis is an analysis of data by the groups to which patients are assigned by random allocation, even if the patient did not take the assigned treatment, did not receive the correct treatment, or otherwise did not follow the protocol. Patients who had their fluoxetine dose reduced to 10 mg/day during the study were to be included in all analyses as if they had remained on 20 mg/day; however, there were no patients who had their dose reduced to 10 mg/day.

Additional exploratory analyses of the data were conducted as deemed appropriate. Statistical analysis of this study was the responsibility of Eli Lilly and Company. All tests of hypotheses were considered statistically significant if the two-sided p-value was less than .05. No adjustments for multiple comparisons were made.

9.7.1.2. Data Analyzed

All randomized patients with a baseline and at least two postbaseline measurements (at least 1 week taking fluoxetine 20 mg/day) were included in the primary efficacy analyses. All patients with a randomization (Visit 4) and at least one postrandomization visit were included in additional analyses of efficacy for the acute treatment phase. All randomly assigned patients were included in the analyses of safety data for the acute and subchronic treatment phases.

During the relapse prevention phase (Study Period VI), participants were rerandomized (1:1) to placebo or to continue their current treatment as of Visit 15. Both investigators and patients were blinded to the actual timing of the switch to the new treatment.

Baseline for Study Period VI is the visit at which the switch to a new treatment occurred (Visit 15). All patients with a Study Period VI baseline visit and at least one visit beyond baseline will be included in the analyses of efficacy for the relapse prevention phase. All patients remaining in the study at Visit 15 will be included in the analyses of safety for the relapse prevention phase.

9.7.1.3. Patient Disposition

The reasons for discontinuation during this study were summarized across all study periods. The percentages of patients discontinuing for lack of efficacy, adverse event, or for any other reason were compared between treatment groups using Fisher's exact test for the acute treatment phase (Study Periods III through IV) and the subchronic treatment phase (Study Periods III through V).

9.7.1.4. Patient Characteristics

The patient characteristics that were collected include demographics (age, gender, origin) and psychiatric history. Baseline patient characteristics were summarized for all patients enrolled in this study. Mean ages were compared between treatment groups using a t-test. Gender, origin, age category (child or adolescent), and psychiatric history distributions were compared using Fisher's exact test. Since randomization was stratified by gender and age category (children, adolescents), no differences between age category and gender were expected.

9.7.1.5. Efficacy Analyses

The primary efficacy measure was the CDRS-R response rate. Secondary efficacy measures included the CGI-Severity, CGI-Improvement, BDI, CDI, MADRS, HAMA, GAF, and K-SADS-PL (Affective Disorders module).

Acute Treatment Phase (Study Periods III-IV)

CDRS-R response rates were compared between fluoxetine 20 mg/day and placebo treatment groups as the primary analysis for the acute treatment phase. Response was defined as a decrease of 30% or greater in CDRS-R total score from baseline (Visit 4) to endpoint (last of Visits 6 through 10).

The above analysis included only patients treated at least 1 week with fluoxetine 20 mg/day (2 weeks of fluoxetine treatment total). The mean change in CDRS-R total score from baseline (Visit 4) to endpoint was compared between fluoxetine and placebo treatment groups as a secondary efficacy analysis. Endpoint was defined as the last measurement from Visits 5 through 10. Change in CDRS-R total scores from baseline (Visit 4) to each subsequent visit (Visits 5 through 10) and CDRS-R remission rates were compared between treatment groups as additional secondary analyses of the CDRS-R score. By-visit analyses were performed: 1) by including only patients active in the study at the visit of interest (observed cases), and 2) by including all patients with at least

one postrandomization measure using a LOCF approach. A repeated measures analysis of variance on the CDRS-R total score was also performed.

Remission was defined as an endpoint CDRS-R total score ≤28. Analyses of remission included only those patients treated at least 1 week with 20 mg/day (2 weeks of fluoxetine treatment total).

The changes in CDRS-R subtotal, CGI-Severity, BDI, CDI, MADRS, HAMA, and GAF scores from baseline (Visit 4) to endpoint were also compared between fluoxetine and placebo groups as secondary efficacy analyses.

For the analysis of CGI-Improvement, an ANOVA was performed only on endpoint values, since this scale inherently measures total improvement in direct comparison with the patient's condition at enrollment. CGI-defined response rates were also compared between treatment groups. A CGI responder was defined as a patient whose endpoint CGI-Improvement score was 1 (very much improved) or 2 (much improved). All patients with at least one postrandomization measure were included in the analysis. In addition, patients who met criteria for recovery were compared between treatment groups. Recovery was defined as a CDRS-R total score ≤28 in combination with a CGI-Improvement score of 1 or 2.

The percentage of patients with a diagnosis of depression using the K-SADS-PL (Affective Disorders module) was compared between treatment groups at endpoint of the acute treatment phase (last measurement from Visits 5 through 10).

An ANOVA (Type III sums of squares) with the term treatment in the model was used when comparing change scores or endpoint scores between treatments. Analyses were performed on both the original and the rank-transformed data. The analysis of the original data was considered primary unless there was evidence to suggest non-normality. As secondary analyses, an ANOVA with treatment, investigator, gender, age category, and the treatment-by-investigator interaction in the model was used. Fisher's exact test was used to compare percentages. Logistic regression models with treatment, investigator, gender, age category, and the treatment-by-investigator interaction were also used to compare percentages, but were considered secondary. The repeated measures analysis of variance was performed using a mixed-model approach with the dependent variable being the baseline and postbaseline CDRS-R total scores. The independent factors were treatment, investigator, treatment-by-investigator interaction, visit as the within-subject factor, and treatment-by-visit interaction. If the treatment-by-investigator interaction was not statistically significant at the level .10, then this interaction effect was excluded from the model. All main effects and interaction tests were made using the approximate F test reported by SAS PROC MIXED. An unstructured covariance matrix was used.

Analyses of Patients Not Responding to Acute Treatment (Study Period V)

To address the clinical question of whether patients who did not respond to fluoxetine 20 mg/day following acute treatment would respond to a dose increase, CDRS-R response rates were compared between nonresponders rerandomized to fluoxetine 20 mg/day and nonresponders rerandomized to fluoxetine 40 or 60 mg/day. Baseline for this analysis was Visit 4 and endpoint was the last of Visits 11 through 15. Comparisons were also made between treatment groups for mean change in CDRS-R total, CGI-Severity, BDI, and CDI scores.

Subchronic Treatment Phase (Study Periods III-V)

Additional analyses of treatment effects for all randomized patients during the 19-week subchronic treatment phase were performed. These analyses were the same as those performed for the 9-week acute treatment phase. In addition, CGI-Efficacy Index and K-SADS-PL (Affective Disorders module) were also analyzed. Baseline for the subchronic treatment phase was Visit 4 and endpoint was last of Visits 5 through 15.

Additional analyses of the primary outcome measure, CDRS-R total response, were also performed. These analyses included those patients who received at least 5 weeks of treatment (at least 4 weeks of fluoxetine 20 mg/day). Baseline for these analyses was Visit 4 and endpoint was the last of Visits 8 through 15. A categorical analysis of remission rates was conducted in the same manner.

Relapse Prevention Phase (Study Period VI)

Study Period VI, the relapse prevention phase, was ongoing at the time this clinical study report was written; therefore, data for this study period were not analyzed and will not be presented in this report. These data will be presented in a separate clinical study report.

Time to relapse during the relapse prevention phase will be compared between fluoxetine (20 to 60 mg/day) and placebo. A relapser will be defined as a patient whose CDRS-R total score increases to over 40 at any one time during the relapse prevention phase in the presence of a history of 2 weeks of clinical deterioration as determined by patient report, parent report, or clinical history. If the physician believes a patient has experienced relapse sufficient enough to discontinue the patient from the study but has not met criteria for relapse, the patient will also be considered a relapser for the primary analysis of relapse. As a secondary analysis of relapse, only those patients meeting the protocol-defined criteria will be considered a relapser. Time to relapse will be analyzed using Kaplan-Meier survival curves (log-rank test). Change in CDRS-R, CGI-Severity, CGI-Improvement, BDI, CDI, MADRS, HAMA, and K-SADS-PL (Affective Disorders module) scores from baseline (Visit 15) to each visit during the relapse prevention therapy phase (Visits 15 through 26) will be summarized between fluoxetine and placebo by: 1) including only patients active in the study at the visit of interest (observed cases), and 2) by including all patients with at least one measure beyond Visit 17 using a LOCF

approach. The same statistical methods described for the acute and subchronic treatment phases will be used for these analyses.

9.7.1.6. Safety Analyses

Acute Treatment Phase (Study Periods III-IV)

Adverse events were analyzed by comparing the incidence of treatment-emergent non-solicited adverse events between treatment groups during the acute treatment phase. Study Periods I and II were defined as baseline for non-solicited adverse events. Treatment-emergent solicited adverse events from the Side-Effects Checklist were also compared between treatment groups using Study Period II as baseline. (The Side-Effects Checklist was not collected during Study Period I.) An event was considered treatment-emergent if it first occurred or worsened after baseline.

The changes in vital signs from baseline (Visit 4) to endpoint were compared between fluoxetine and placebo treatment groups. Endpoint was defined as the last measurement from Visits 5 through 10 for the acute treatment phase. Because laboratory analytes and ECGs were not collected routinely at Visits 2 through 15, these data were analyzed for the subchronic treatment phase only.

Fisher's exact test was used to compare percentages. An ANOVA (Type III sums of squares) with the term treatment in the model was used when comparing change scores or endpoint scores between treatments.

Subchronic Treatment Phase (Study Periods III-V)

Analyses of safety data for all randomized patients during the 19-week subchronic treatment phase were the same as those performed for the 9-week acute treatment phase. Baseline for the subchronic treatment phase was Visit 4 and endpoint was the last of Visits 5 through 15.

The changes in vital signs, continuous laboratory analytes, and ECG values (heart rate, RR interval, PR interval, QRS interval, QT interval, and QTc interval) from baseline to endpoint were also compared between fluoxetine and placebo treatment groups during the subchronic treatment phase. Because laboratory analytes and ECGs were not collected routinely at Visits 2 through 15, baseline was Visit 1 and endpoint was Visit 15 (or discontinuation). In addition to analyzing the change in the raw QT interval, two "corrected" QT intervals, based on Bazett's and Fridericia's methods, were also analyzed. Bazett's method divides the QT interval by the square root of the RR interval while Fridericia's method uses the same formula but with a cube root of the RR interval.

The incidence of treatment-emergent abnormal laboratory values (using [redacted] Reference Ranges for pediatric patients) during the subchronic treatment phase was also compared between treatment groups for continuous laboratory analytes. The [redacted] Reference Ranges for pediatric patients are presented in Appendix 16.2.8. The percentages of patients whose values changed from normal or low during Study Periods I

and II to high at any time during the subchronic treatment phase were compared between treatment groups. Similarly, percentages of patients whose values changed from normal or high during Study Periods I and II to low at any time during the subchronic treatment phase were compared between treatment groups. For non-numeric laboratory analytes, the percentages of patients whose values changed from normal during Study Periods I and II to abnormal at anytime during the subchronic treatment phase were compared between treatment groups.

Similarly, the incidences of treatment-emergent abnormal ECG values were also analyzed. ECG reference ranges used to evaluate ECG findings are presented in Appendix 16.1.12. The incidence of treatment-emergent high values was analyzed similarly for blood pressure values. Age and height specific 95th percentile values were obtained from the National Institutes of Health and compared against each patient's postbaseline visit for those patients who had normal or low blood pressure values at baseline. Blood pressure reference ranges are presented in Appendix 16.1.12.

As supplemental analyses for longer-term data, adverse events, vital signs, laboratories, and ECG values were analyzed for all patients entering Study Period V (fluoxetine treatment groups pooled versus placebo). Change from baseline (last measurement from Visits 1 through 10) to Study Period V endpoint (last measurement from Visits 11 through 15) in vital signs, continuous laboratory analytes, and ECG values were compared between treatment groups. The incidence of treatment-emergent abnormal laboratory values (using [redacted] Reference Ranges for pediatric patients) during Study Period V was also compared between treatments for continuous laboratory analytes. The percentages of patients whose laboratory values changed from normal or low during Study Periods I through IV to high at any time during Study Period V were compared between treatment groups among patients with normal or low values during Study Periods I through IV. Similarly, the percentages of patients whose laboratory values changed from normal or high during Study Periods I through IV to low at any time during Study Period V were compared between treatment groups. For non-numeric laboratory analytes, the percentages of patients whose values changed from normal during Study Periods I through IV to abnormal at anytime during Study Period V were compared between treatment groups. Similar analyses were performed for abnormally high blood pressure values.

Analyses of Patients Not Responding to Acute Treatment (Study Period V)

To compare the impact of titration to fluoxetine 40 or 60 mg/day, the incidences of treatment-emergent non-solicited and solicited adverse events during Study Period V were compared between the nonresponders rerandomized to fluoxetine 20 mg/day and the nonresponders rerandomized to fluoxetine 40 or 60 mg/day. Study Periods I through IV were used as baseline for this analysis.

Relapse Prevention Phase (Study Period VI)

Study Period VI, the relapse prevention phase, was ongoing at the time this clinical study report was written; therefore, data for this study period were not analyzed and will not be presented in this report. These data will be presented in a separate clinical study report.

Adverse events will be analyzed by comparing the incidence of treatment-emergent non-solicited adverse events between treatment groups during Study Period VI (after Visit 15) using Study Periods I through V (and up through Visit 15) as baseline for non-solicited adverse events. Treatment-emergent solicited adverse events during Study Period VI (after Visit 15) will also be compared between treatments using Study Period II through V (and up through Visit 15) as baseline for events collected by the Side-Effects Checklist. (The Side-Effects Checklist was not collected during Study Period I.)

The same statistical methods described above will be used for these analyses.

9.7.1.7. Subgroup Analyses

Efficacy analyses of the CDRS-R total score (response and mean change from baseline), CGI-Improvement, treatment-emergent non-solicited adverse events, and treatment-emergent solicited adverse events were performed for children and adolescents separately, males and females separately, and for patients with and without a family history of depression. To test for a treatment-by-subgroup interaction on mean change, an ANOVA with treatment, subgroup, and the treatment-by-subgroup interaction in the model was performed. For response and solicited treatment-emergent adverse events, a Breslow-Day test for the homogeneity of odds ratios across subgroups was performed.

9.7.1.8. Interim Analyses

One interim analysis, which is the final analysis of Study Periods I through V, was planned for this study and is presented in this clinical study report. The interim analysis took place after all patients completed Study Period V (Visit 15). This interim analysis was conducted in order to obtain and communicate the results from the 9-week acute and 19-week subchronic treatment phases in a more timely manner. Although the protocol allowed for external publication of these results, the data monitoring board (DMB) assigned to this study decided that the results from this analysis unblinded at the treatment level would only be presented to regulatory agencies. There were no plans to stop the study; thus adjustment of p-values was not required. To minimize the bias for the relapse prevention therapy phase (Study Period VI), no one at the study site was unblinded at the patient level. The Lilly clinical research administrator and clinical research physician communicating with the sites also remained blinded to treatment assignments.

The planned interim analysis was conducted under the auspices of the DMB assigned to this study. Only the DMB was authorized to review completely unblinded interim efficacy and safety analyses and, if necessary, to disseminate those results. The DMB

disseminated interim results in a manner that minimized bias. The protocol provided that study sites would not receive information about interim results unless they needed to know for the safety of their patients. No study sites have requested this information as of the time of this clinical study report. Appendix 16.1.14 contains detailed information about the blinding plan and DMB communications.

9.7.2. Determination of Sample Size

The total number of randomized patients planned for in this study was approximately 220 patients or 110 patients per treatment group. The sample size was designed to detect a difference of 20 percentage points in the proportion of patients responding between fluoxetine 20 mg/day and placebo with approximately 80% power and a .05 significance level (two-sided). Response was defined as at least a 30% decrease in the CDRS-R total score from baseline (Visit 4) to endpoint (last measurement from Visits 6 through 10) for patients treated at least one week with fluoxetine 20 mg/day (2 weeks total). The calculation assumed the true proportions were 70% for fluoxetine and 50% for placebo and assumed no more than 7 patients in either treatment group discontinued prior to the first postrandomization visit with fluoxetine 20 mg/day (Visit 6). These estimates were based on a previous placebo-controlled trial in depressed children and adolescents (Emslie et al. 1997).

9.7.3. Pharmacokinetic Methods

9.7.3.1. Biological Sampling

Blood samples (10 mL) were obtained in a heparinized vacutainer and centrifuged within 20 minutes to harvest the plasma. Plasma samples were frozen and stored at approximately -20°C until assayed for fluoxetine and norfluoxetine concentrations. A single baseline sample was scheduled for collection at Visit 1 to confirm drug washout from fluoxetine exposure prior to the study. In addition, steady-state blood samples were scheduled for collection at Visits 10 and 15 following at least 4 weeks of fixed fluoxetine dosing, that is, steady-state dosing conditions. All blood samples were collected randomly within a dosing interval. A blood sample was also collected from those patients who discontinued early from the study. Blood samples collected from patients randomized to the placebo treatment group were not analyzed for drug concentration.

9.7.3.2. Bioanalytical Methods

Plasma concentrations of fluoxetine and norfluoxetine were determined by a validated liquid chromatograph/mass spectrometry method (LC/MS) at [redacted] The limit of detection for both fluoxetine and norfluoxetine concentrations was 1.0 ng/mL. The results are summarized in this report and details of the method and validation are provided in Appendix 16.1.16 (LC/MS Method and Validation for the Determination of Fluoxetine and Norfluoxetine in Human Plasma).

9.7.3.3. Dataset for Pharmacokinetic Analyses

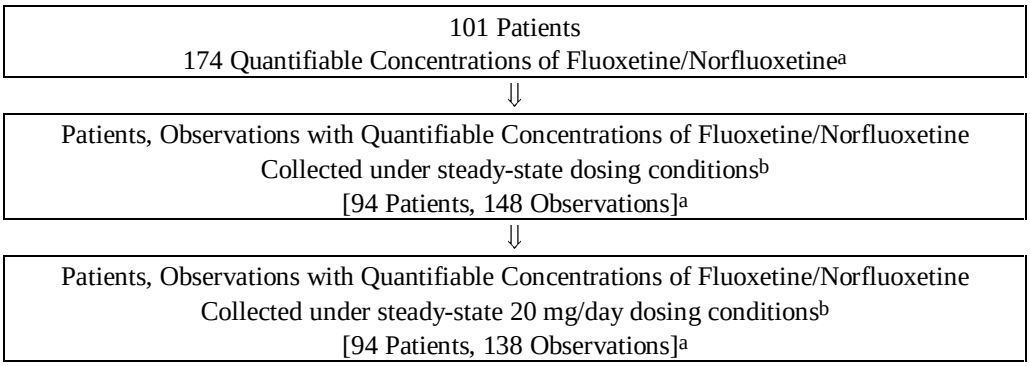
Patients (N=220) were screened at Visit 1 for fluoxetine/norfluoxetine concentrations. Of the 220 samples screened, 218 were below the limit of detection of the assay (BQL) and two samples (2 patients) with detectable fluoxetine and norfluoxetine concentrations were not randomized.

Figure 9.2 outlines the disposition of available data to obtain the data included in the pharmacokinetic dataset used in the analysis. Quantifiable plasma fluoxetine and norfluoxetine concentrations were available from 174 blood samples from 101 patients randomized to the fluoxetine treatment group. Of these, 148 samples were collected under steady-state dosing conditions (at least 4 weeks of fixed dosing).

Two samples were collected prior to Visit 8 and five samples were collected after Visit 15. Nineteen samples were collected after more than 48 hours had elapsed since the last fluoxetine dose. Therefore, these 26 samples were not included in the analysis.

Eight samples collected from patients receiving fluoxetine 40 mg/day and two samples from patients receiving fluoxetine 60 mg/day were not included in the descriptive summary. Thus, pharmacokinetic data were summarized for 138 observations from 94 pediatric patients.

The concentration records omitted from the analysis are presented in Appendix 16.4.1.



Source file: \\proton\proton.grp\pkregsub\fluoxtne\HCJE \2_Original Data Files\1_Orignal\hcje_DESC_13MAR00_rev.xls.

[a]Quantifiable observations for both fluoxetine or norfluoxetine after Visit 1.

[b]Steady-state conditions, at least 4 weeks of fixed dosing (Visits 8 through 15) and time from most recent fluoxetine dose ≤48 hours.

Figure 9.2. Data accountability for pharmacokinetic analyses of B1Y-MC-HCJE.

Additional data, such as the time of blood sampling, the time of the last fluoxetine dose, the last dose amount, and patient demographic factors (age, gender, weight, height, and ethnic origin) were collected and combined with drug concentration data.

A representative pharmacokinetic dataset is presented in Appendix 16.1.15.

9.7.3.4. Pharmacokinetic Data Analysis: Descriptive Statistics and Data Visualization

Steady-state fluoxetine and norfluoxetine plasma concentrations from pediatric patients receiving fluoxetine 20 mg/day were included in the analysis. Approximately 14% of the measurable concentrations were obtained from patients at non-scheduled sampling visits. At each of the non-scheduled visits, one to seven samples were collected. All available steady-state concentration data were used in the analysis and data were pooled regardless of study visit.

Concentration data were summarized descriptively (mean, standard deviation, etc) and illustrated graphically. In addition, select demographic data (gender, age, weight, ethnic origin, etc) were also summarized. Pediatric patients were categorized as children (aged 8 to <13 years) and adolescents (aged 13 to <18 years).

9.8. Changes in the Conduct of the Study or Planned Analyses

9.8.1. Changes in the Conduct of the Study

An amended protocol was approved on 30 June 1998, approximately 2 months after enrollment of patients was initiated in this study (see Appendix 16.1.1.). The following changes were made to the protocol at that time.

- The primary and the first of the secondary objectives were interchanged. The primary objective was originally constructed to compare all doses of fluoxetine (20 to 60 mg/day) allowed in the study with placebo after up to 19 weeks of treatment. A secondary objective was originally constructed to conduct an analysis of fluoxetine 20 mg/day versus placebo for 8 weeks in order to replicate findings as published by Emslie et al. (1997). Following discussion with the Neuropharmacology Division of the FDA regarding the appropriateness of the study design, the Lilly team agreed to accept the principal suggestion regarding the analysis plan, which was to reverse the primary and secondary objectives.
- Language was updated to clarify that separate diagnostic interviewers were to conduct the three necessary interviews for diagnosis of MDD.
- Language was added to allow investigators to use the MAGIC (hard copy), the DICA (hard copy), or the electronic version of the DICA. All three diagnostic tools were considered equally sufficient for the diagnostic interviews.

Other minor wording changes were made to clarify meaning. Full details are included in Appendix 16.1.1.

A rescue therapy option was available for patients who discontinued the study. This option was established in response to a request from an investigator following a start-up meeting held on 25 March 1998 and is documented in a Note to File. If a patient

discontinued from the study and the investigator believed that the patient required rescue therapy, the investigator referred the patient to an outside physician who requested that Lilly allow unblinding of the patient's therapy assignment by completing a form provided by Lilly. If the clinical research associate at Lilly approved the request, the request was faxed to the Study Drug Coordinator at Lilly. The Study Drug Coordinator then contacted the outside physician to reveal the patient's therapy assignment. Documentation of these instances of unblinding has been retained in the investigator binders. This process provided for the unblinding of a "new" physician. The "new" physician was not associated with the study and agreed to maintain the study blind from study personnel. Lilly also paid for up to four visits to the "new" physician, if requested.

9.8.2. Changes in the Planned Analyses

An updated statistical plan was completed after the protocol had been approved and the study was ongoing. The updated plan was completed prior to unblinding of the data to the statistician. The updated plan was approved by the statistician and other members of the team on 7 February 2000 and is presented in Appendix 16.1.6.

In order to provide as much long-term data as possible, an interim analysis was performed after all patients completed the 19-week subchronic treatment phase (end of Study Period V), rather than after all patients completed the 9-week acute treatment phase (end of Study Period IV) as planned. A DMB was formed to review this data. The DMB decided to maintain blinding except for those individuals involved in the preparation of this clinical study report and those necessary for strategic planning. Data for patients who completed Study Period V are considered final. As the relapse prevention phase (Study Period VI) is ongoing, data for this treatment phase will be presented in a separate clinical study report. The blinding plan and DMB information are presented in Appendix 16.1.14.

In the protocol, Pearson's Chi-square test was to be used for comparison of all percentages (including the primary analysis) between treatment groups. Fisher's exact test was used instead.

In addition, supplemental analyses to evaluate safety for longer-term data as well as specifics regarding the repeated-measures model and subgroup analyses were included in the updated statistical analysis plan. Analysis of ECG data was also specified in the updated plan.

After reviewing some of the results of this study, additional exploratory analyses were performed. These included additional subgroup analyses and "completers" analysis of laboratory, ECG, and vital signs data. "Completers" analyses refers to analyses based on those patients who completed the subchronic treatment phase of the study, that is, through Visit 15. A second set of blinded ECG readings performed by a pediatric cardiologist supplemented the original readings.

For consistency with other pediatric protocols, it was decided to analyze treatment-emergent out-of-range laboratory values by using baseline as last of Visits 1 through 4. In the original analysis plan, the baseline period encompassed all of Study Periods I through II. The percent of potentially clinically abnormal elevations in blood pressure were analyzed in a similar fashion.

Pharmacokinetic analyses were only performed for patients receiving fluoxetine 20 mg per day due to the sparseness of data at other dose levels.

10. Study Patients

10.1. Disposition of Patients

An overview of patient disposition is provided in Figure 10.1. Four hundred twenty patients entered the study. Of these, 201 patients either decided not to participate in the study or were considered screen failures, including 8 patients who were considered placebo responders during placebo lead-in. Two hundred nineteen patients were randomized to treatment at Visit 4. One hundred nine patients received fluoxetine and 110 patients received placebo. One hundred fifty-eight (72%) patients completed acute treatment (Study Periods III through IV). Ninety (83%) fluoxetine-treated patients and 68 (62%) placebo-treated patients completed this phase of the study.

A total of 75 (34%) patients completed subchronic treatment (Study Periods III through V), with 40 (37%) fluoxetine-treated patients completing subchronic treatment as compared with 35 (32%) placebo-treated patients.

Figure 12.1 (see Section 12.1) presents the study doses received by all randomized patients during Study Periods III through V.

Study Period I			
Diagnostic Evaluation	Visit 1	Entered (N = 420)	
	Visit 2		
Study Period II			
Placebo Washout	Visit 3		
Study Period III			
Adaptation		Randomized to Treatment (N = 219)	
Randomization (Fluoxetine 10 mg/day)	Visit 4	Fluoxetine (n = 109)	Placebo (n = 110)
Study Period IV			
Fixed-Dose (Fluoxetine 20 mg/day)	Visit 5	Fluoxetine (n = 109)	Placebo (n = 109)
	Visit 6	n = 109	n = 104
	Visit 7	n = 109	n = 100
	Visit 8	n = 106	n = 96
	Visit 9	n = 100	n = 87
Study Period V			
Nonresponder Rerandomization (Fluoxetine 20-60 mg/day)	Visit 10	Fluoxetine (n = 94)	Placebo (n = 77)
	Visit 11	n = 90	n = 68
	Visit 12	n = 75	n = 64
	Visit 13	n = 65	n = 57
	Visit 14	n = 57	n = 52
	Visit 15	n = 40	n = 35
		Completed Study Period V	

Data for this figure were taken from RMP.B1YP.JCLLIB2 (RDS2JEKB).

Figure 10.1. Overview of patient disposition by visit for Study Periods I-V of B1Y-MC-HCJE.

10.1.1. Early Discontinuation of Patients

The reasons for discontinuation for all randomized patients during subchronic treatment are summarized by visit and treatment group in Table 10.1.

Table 10.1. Summary of Reasons for Discontinuation by Visit
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE

Visit (Week of Treatment)	Number of Patients Continuing	Number of Patients Discontinued	Reason Discontinued	Fluoxetine	Placebo
Visit 4	**218**	**1**	Adverse event	0	0
(Week 0)			Lack of efficacy	0	0
Randomization	↓		Patient decision	0	1
			Physician decision	0	0
			Protocol requirement	0	0
			Lost to follow-up	0	0
Visit 5	**213**	**5**	Adverse event	0	1
(Week 1)			Lack of efficacy	0	1
	↓		Patient decision	0	0
			Physician decision	0	0
			Protocol requirement	0	0
			Lost to follow-up	0	3
Visit 6	**209**	**4**	Adverse event	0	1
(Week 2)			Lack of efficacy	0	1
	↓		Patient decision	0	2
			Physician decision	0	0
			Protocol requirement	0	0
			Lost to follow-up	0	0
Visit 7	**202**	**7**	Adverse event	2	1
(Week 3)			Lack of efficacy	0	0
	↓		Patient decision	0	2
			Physician decision	0	0
			Protocol requirement	1	0
			Lost to follow-up	0	1

(continued)

Table 10.1. Summary of Reasons for Discontinuation by Visit
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE (continued)

Visit (Week of Treatment)	Number of Patients Continuing	Number of Patients Discontinued	Reason Discontinued	Fluoxetine	Placebo
Visit 8	**187**	**15**	Adverse event	2	4
(Week 5)			Lack of efficacy	1	3
	↓		Patient decision	2	0
			Physician decision	1	0
			Protocol requirement	0	1
			Lost to follow-up	0	1
Visit 9	**171**	**16**	Adverse event	1	1
(Week 7)			Lack of efficacy	3	2
	↓		Patient decision	1	4
			Physician decision	0	0
			Protocol requirement	1	1
			Lost to follow-up	0	2
Visit 10	**158**	**13**	Adverse event	0	1
(Week 9)			Lack of efficacy	1	5
	↓		Patient decision	0	2
			Physician decision	0	0
			Protocol requirement	2	1
			Lost to follow-up	1	0
Visit 11	**139**	**19**	Adverse event	2	0
(Week 11)			Lack of efficacy	5	3
	↓		Patient decision	4	1
			Physician decision	1	0
			Protocol requirement	1	0
			Lost to follow-up	2	0
Visit 12	**122**	**17**	Adverse event	2	0
(Week 13)			Lack of efficacy	5	4
	↓		Patient decision	3	2
			Physician decision	0	0
			Protocol requirement	0	0
			Lost to follow-up	0	1

(continued)

Table 10.1. Summary of Reasons for Discontinuation by Visit
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE (concluded)

Visit (Week of Treatment)	Number of Patients Continuing	Number of Patients Discontinued	Reason Discontinued	Fluoxetine	Placebo
Visit 13 (Week 15)	**109** ↓	**13**	Adverse event	1	1
			Lack of efficacy	1	2
			Patient decision	1	0
			Physician decision	0	0
			Protocol requirement	3	1
			Lost to follow-up	2	1
Visit 14 (Week 17)	**101** ↓	**8**	Adverse event	1	1
			Lack of efficacy	2	1
			Patient decision	0	1
			Physician decision	1	0
			Protocol requirement	1	0
			Lost to follow-up	0	0
Visit 15 (Week 19)	**75**	**26**	Adverse event	0	0
			Lack of efficacy	0	1
			Patient decision	3	1
			Physician decision	0	0
			Protocol requirement	9	12
			Lost to follow-up	0	0

Data for this table were taken from RMP.B1YP.JCLLIB2 (RDS2JEKB).

Two hundred nineteen patients were randomized at Visit 4 (Study Period III) and 158 (72%) patients completed the acute treatment phase. Sixty-one (28%) patients discontinued prior to completing the acute treatment phase. The primary reasons for discontinuation during the acute treatment phase are summarized in Table 10.2.

There was a statistically significant difference between treatment groups with respect to completion of the acute treatment phase, with 90 (83%) fluoxetine-treated patients completing this phase as compared with 68 (62%) placebo-treated patients (p=.001). The most common reason for discontinuation for the combined treatment groups was lack of efficacy (17 patients), followed by patient decision (14 patients), adverse event (14 patients), lost to follow up (8 patients), protocol requirement (7 patients), and physician decision (1 patient). Statistically significantly (p=.05) more placebo-treated patients (11, 10%) discontinued due to patient decision compared with fluoxetine treated patients (3, 3%).

Table 10.2. Summary of Reasons for Discontinuation
All Randomized Patients
Acute Treatment Phase (Study Periods III-IV)
B1Y-MC-HCJE

Primary Reason for Discontinuation	Flx 20 (N=109) n (%)	Placebo (N=110) n (%)	Total (N=219) n (%)	p-Value*
Study Period IV Complete	90 (82.6)	68 (61.8)	158 (72.1)	.001
Adverse Event	5 (4.6)	9 (8.2)	14 (6.4)	.408
Lack of Efficacy	5 (4.6)	12 (10.9)	17 (7.8)	.128
Patient Decision	3 (2.8)	11 (10.0)	14 (6.4)	.050
Physician Decision	1 (0.9)	0	1 (0.5)	.498
Protocol Requirement	4 (3.7)	3 (2.7)	7 (3.2)	.721
Lost to Follow-Up	1 (0.9)	7 (6.4)	8 (3.7)	.065

RMP.B1YP.JCLLIB2(RDS1JEKC)
RMP.B1YO.HCJEREP(RDS1JEKC)
* Frequencies are analyzed using a Fisher's Exact test.
XRDS0001

Of the 219 patients randomized at Visit 4 (Study Period III), 75 patients (34%) completed the subchronic treatment phase and 144 (66%) discontinued prior to the completion of the subchronic treatment phase. A summary of primary reasons for discontinuation during the subchronic treatment phase is presented in Table 10.3. The most common reason for discontinuation for the combined treatment groups was lack of efficacy (41 patients), followed by protocol requirement (34 patients), patient decision (30 patients), adverse event (22 patients), lost to follow up (14 patients), and physician decision (3 patients). There were no statistically significant differences between treatment groups in the number of patients completing the subchronic treatment phase, or for any reason for discontinuation.

Table 10.3. Summary of Reasons for Discontinuation
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE

Primary Reason for Discontinuation	Flx (N=109) n (%)	Placebo (N=110) n (%)	Total (N=219) n (%)	p-Value*
Subchronic Phase Complete	40 (36.7)	35 (31.8)	75 (34.2)	.479
Adverse Event	11 (10.1)	11 (10.0)	22 (10.0)	1.00
Lack of Efficacy	18 (16.5)	23 (20.9)	41 (18.7)	.489
Patient Decision	14 (12.8)	16 (14.5)	30 (13.7)	.845
Physician Decision	3 (2.8)	0	3 (1.4)	.122
Protocol Requirement	18 (16.5)	16 (14.5)	34 (15.5)	.713
Lost to Follow-Up	5 (4.6)	9 (8.2)	14 (6.4)	.408

RMP.B1YP.JCLLIB2(RDS1JEKD)
RMP.B1YO.HCJEREP(RDS1JEKD)
* Frequencies are analyzed using a Fisher's Exact test.
XRDS0001

10.1.2. Patient Allocation

Table 10.4 summarizes the allocation of patients to each treatment group by investigator. Of the 19 investigators recruited for the study, four did not randomize any patients. Investigator 6 had no patients randomized to the fluoxetine group and only 1 patient randomized to the placebo group. As specified in the protocol, investigators with no patients randomized into one or more treatment groups were to be pooled for statistical analysis purposes. Since no other investigator experienced this situation, Investigator 6 was pooled with the next lowest enroller, Investigator 17. The randomization scheme and codes are listed in Appendix 16.1.5.

Table 10.4. Patient Allocation by Investigator
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE

Investigator	No. Patients Entered at Visit 1	No. Patients Randomized at Visit 4		No. Patients Completed at Visit 10		No. Patients Completed at Visit 15	
001	57	Fluoxetine	14	Fluoxetine	11	Fluoxetine	4
		Placebo	11	Placebo	6	Placebo	2
002	14	Fluoxetine	3	Fluoxetine	1	Fluoxetine	0
		Placebo	6	Placebo	4	Placebo	2
003	57	Fluoxetine	13	Fluoxetine	9	Fluoxetine	7
		Placebo	15	Placebo	12	Placebo	6
004	41	Fluoxetine	11	Fluoxetine	10	Fluoxetine	5
		Placebo	7	Placebo	4	Placebo	3
005	8	Fluoxetine	0	Fluoxetine	0	Fluoxetine	0
		Placebo	0	Placebo	0	Placebo	0
006	2	Fluoxetine	0	Fluoxetine	0	Fluoxetine	0
		Placebo	1	Placebo	0	Placebo	0
008	15	Fluoxetine	6	Fluoxetine	5	Fluoxetine	2
		Placebo	5	Placebo	3	Placebo	1
009	20	Fluoxetine	5	Fluoxetine	5	Fluoxetine	3
		Placebo	5	Placebo	4		2
011	56	Fluoxetine	10	Fluoxetine	9	Fluoxetine	5
		Placebo	13	Placebo	10	Placebo	9
012	27	Fluoxetine	12	Fluoxetine	11	Fluoxetine	5
		Placebo	8	Placebo	7	Placebo	5
013	11	Fluoxetine	1	Fluoxetine	1	Fluoxetine	1
		Placebo	8	Placebo	5	Placebo	3
015	17	Fluoxetine	5	Fluoxetine	4	Fluoxetine	2
		Placebo	4	Placebo	2	Placebo	2
016	31	Fluoxetine	13	Fluoxetine	12	Fluoxetine	6
		Placebo	7	Placebo	3	Placebo	2

(continued)

Table 10.4. Patient Allocation by Investigator
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE (concluded)

Investigator	No. Patients Entered at Visit 1	No. Patients Randomized at Visit 4		No. Patients Completed at Visit 10		No. Patients Completed at Visit 15	
017	7	Fluoxetine	2	Fluoxetine	2	Fluoxetine	2
		Placebo	2	Placebo	2	Placebo	2
018	3	Fluoxetine	0	Fluoxetine	0	Fluoxetine	0
		Placebo	0	Placebo	0	Placebo	0
019	30	Fluoxetine	7	Fluoxetine	7	Fluoxetine	5
		Placebo	8	Placebo	7	Placebo	6
021	3	Fluoxetine	0	Fluoxetine	0	Fluoxetine	0
		Placebo	0	Placebo	0	Placebo	0
022	21	Fluoxetine	7	Fluoxetine	7	Fluoxetine	5
		Placebo	10	Placebo	8	Placebo	5

Data for this table were taken from RMP.B1YO.HCJEREP (CUSTJEPA).

10.2. Significant Protocol Violations

One significant protocol violation occurred in which one patient was inadvertently randomized. Patient 810 had a greater than 30% increase in CDRS-R score from Visit 3 to Visit 4. An error was made in calculating the change and the patient was inadvertently randomized. The patient was permitted to continue in the study under compassionate use guidelines.

All protocol violations are presented in Appendix 16.2.3. Any effect these violations may have had on the study results is likely to be of minimal significance in interpreting the findings of this study.

11. Efficacy Evaluation

11.1. Data Sets Analyzed

Lilly Medical uses *intent-to-treat* analysis which is an analysis of study participants by the groups to which they were assigned by random allocation, even if the study participant did not take the assigned treatment, did not receive the correct treatment, or otherwise did not follow the protocol. Such an analysis is sometimes stated *analyze as randomized*.

The data cut-off date for this clinical study report was 16 December 1999. The database used for this clinical study report includes data for all patients participating in Study Periods I through V. The final analyses of the 9-week acute and 19-week subchronic treatment phases of this study are presented in this clinical study report. Study Period VI is ongoing. Results from this study period will be presented in a separate clinical study report.

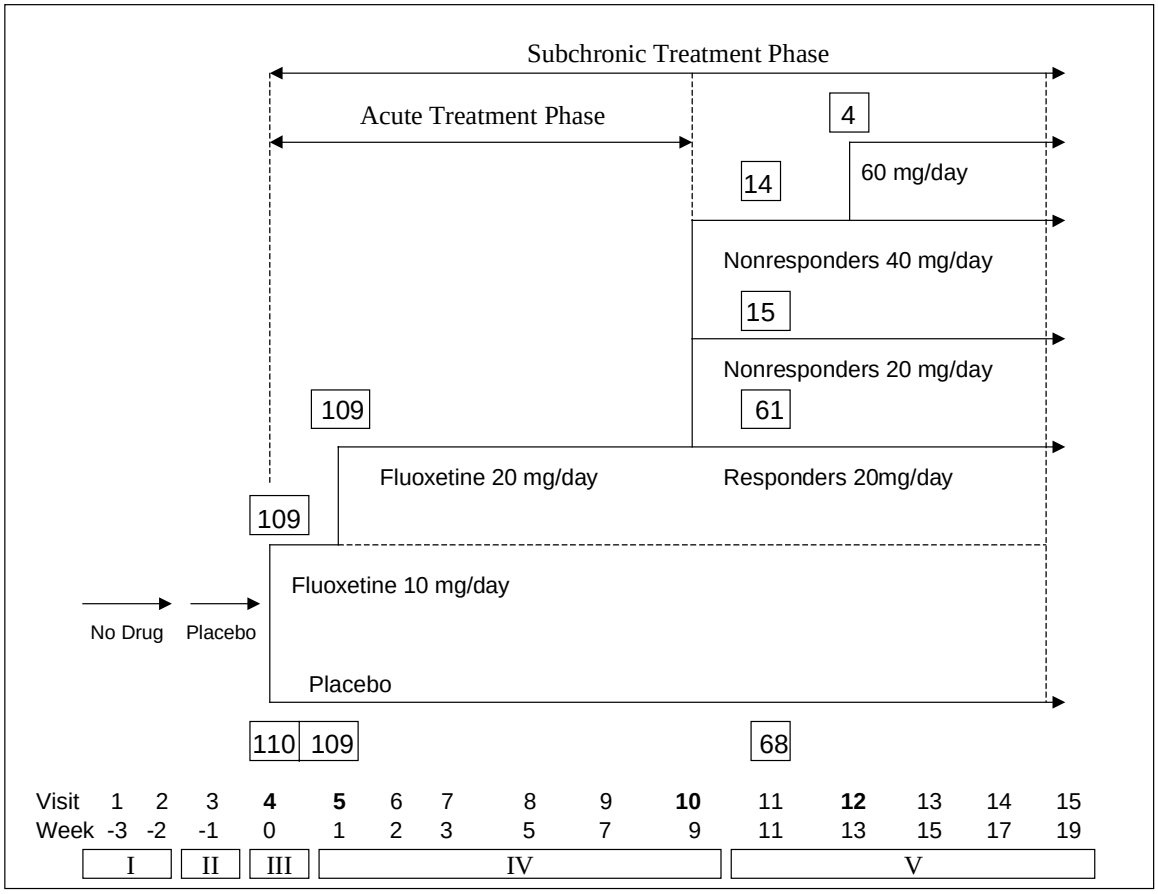
On 18 February 2000, the final analysis database was validated and locked. Subsequent to data lock, errors in the database were discovered. These errors were corrected through programming of the patient demographic dataset on 20 March 2000 and the database was re-locked on 23 March 2000 (see Appendix 16.1.13 for documentation). All analyses were re-run with the corrected dataset.

Appendix 16.2.4 contains a list of patients and observations excluded from the primary efficacy analysis. All randomized patients with a baseline and at least two postbaseline measurements (at least 1 week taking fluoxetine 20 mg/day) were included in the primary efficacy analyses. Of the 219 randomized patients, 210 patients were included in the primary analysis. One patient (Patient 1139) was randomized to placebo treatment at Visit 4. The patient discontinued at Visit 4 due to patient decision and never ingested any study medication.

There were a total of 19 investigators recruited for this study. Four investigators never randomized patients. Investigator 6 did not randomize any patients to fluoxetine treatment and only randomized 1 patient to placebo treatment. As specified in the protocol, investigators who did not randomize patients into one or more treatment groups were to be pooled for statistical analysis purposes. Since no other investigator experienced this situation, Investigator 6 was pooled with the next lowest enroller, Investigator 17. As a result of this pooling, all by-investigator analyses include 14 investigators.

Figure 11.1 is a graphical representation of the numbers of patients at the various dosing levels during the study. At Visit 4, 109 patients were randomized to fluoxetine and 110 patients were randomized to placebo. Fluoxetine-treated patients received 10 mg/day during Study Period III (1 week) and 20 mg/day for Study Period IV (8 weeks). All fluoxetine-treated patients were able to tolerate the required titration from 10 mg/day to

20 mg/day in Study Period IV. At the beginning of Study Period V (Visit 10), response to treatment was evaluated. Placebo-treated patients remained on placebo regardless of their response to treatment. Sixty-one fluoxetine-treated patients had responded to acute treatment and continued taking 20 mg/day. Of the 29 fluoxetine-treated patients who did not respond to treatment, 15 were rerandomized to fluoxetine 20 mg/day and 14 were rerandomized to fluoxetine 40 mg/day. After 4 weeks of continued treatment (Visit 12), response to treatment was re-evaluated in patients receiving fluoxetine 40 mg/day. Due to insufficient response at the 40 mg/day dose, 4 patients had their dose increased to fluoxetine 60 mg/day.



Data for this figure were taken from: RMP.B1YSHCJE.SASPGM (DOSING), RMP.B1YO.HCJEREP (RDS2JEKB).

Figure 11.1. **Study dose for all randomized patients during acute and subchronic treatment phases (Study Periods III-V) of B1Y-MC-HCJE.**

11.2. Demographic and Other Baseline Characteristics

11.2.1. Patient Characteristics

Baseline demographic characteristics for all randomized patients are summarized in Table 11.1. The patients randomized in this study were predominantly Caucasian (82%). The mean age was 12.7 years (range = 8.0 to 17.9 years). The treatment groups were balanced with respect to the number of children (61 fluoxetine-treated, 61 placebo-treated) and the number of adolescents (48 fluoxetine-treated, 49 placebo-treated) due to the use of stratified randomization. Of the 219 patients randomized to treatment, 111 (51%) patients were male and 108 (49%) were female.

The mean height of the patients was 155 cm (range = 122 cm to 188 cm) and the mean weight was 57 kg (range = 21 kg to 141 kg). The treatment groups were comparable with respect to baseline demographic characteristics.

Table 14.1 (see Section 14.1) presents patient demographic data from the Physician's Checklist. There were no statistically significant differences observed between treatment groups. Complete listings of patient demographic characteristics and secondary conditions are presented in Appendix 16.2.5.

Table 11.1. Baseline Patient Characteristics
All Randomized Patients
B1Y-MC-HCJE

Variable	Flx 20 (N=109)	Placebo (N=110)	Total (N=219)	p-Value
Origin				
No. Patients	109	110	219	.071*
Caucasian	96 (88.1)	84 (76.4)	180 (82.2)	
East, SE Asian	1 (0.9)	0	1 (0.5)	
African American	6 (5.5)	8 (7.3)	14 (6.4)	
Hispanic	3 (2.8)	10 (9.1)	13 (5.9)	
Other	3 (2.8)	8 (7.3)	11 (5.0)	
Age				
No. Patients	109	110	219	.983**
Mean	12.70	12.69	12.70	
Median	12.56	12.50	12.56	
Standard Dev.	2.46	2.67	2.56	
Minimum	8.26	8.01	8.01	
Maximum	17.52	17.85	17.85	
Age Category				
No. Patients	109	110	219	1.00*
8 - < 13 yrs.	61 (56.0)	61 (55.5)	122 (55.7)	
13 - < 18 yrs.	48 (44.0)	49 (44.5)	97 (44.3)	
Gender				
No. Patients	109	110	219	1.00*
Female	54 (49.5)	54 (49.1)	108 (49.3)	
Male	55 (50.5)	56 (50.9)	111 (50.7)	
Height(cm)				
No. Patients	108	110	218	.409**
Mean	155.53	153.98	154.75	
Median	156.21	154.94	154.94	
Standard Dev.	14.55	13.05	13.80	
Minimum	124.46	121.92	121.92	
Maximum	187.96	182.88	187.96	
Unspecified	1	0	1	

RMP.B1YP.JCLLIB2(DES1JEAA)
RMP.B1YO.HCJEREP(DES1JEAA)
* Frequencies are analyzed using a Fishers-Exact test.
** Means are analyzed using a Type III Sum of Squares analysis of variance (ANOVA): PROC GLM model=treatment.
XDES0001

Table 11.1. Baseline Patient Characteristics
All Randomized Patients
B1Y-MC-HCJE (concluded)

Variable	Flx 20 (N=109)	Placebo (N=110)	Total (N=219)	p-Value
Weight(kg)				
No. Patients	108	110	218	.937**
Mean	57.06	56.85	56.96	
Median	53.30	55.57	54.43	
Standard Dev.	19.33	19.96	19.61	
Minimum	20.87	26.76	20.87	
Maximum	102.97	140.61	140.61	
Unspecified	1	0	1	

RMP.B1YP.JCLLIB2(DES1JEAA)
RMP.B1YO.HCJEREP(DES1JEAA)
* Frequencies are analyzed using a Fishers-Exact test.
** Means are analyzed using a Type III Sum of Squares analysis of variance (ANOVA): PROC GLM model=treatment.
XDES0001

Patient habits for all randomized patients are presented in Table 11.2. Few patients reported using tobacco or alcohol (<12%). The majority of patients reported use of caffeinated beverages (80%). There were no statistically significant differences in the reported use of tobacco, alcohol, or caffeine between treatment groups.

Table 11.2. Patient Habits
All Randomized Patients
B1Y-MC-HCJE

Variable	Flx 20 (N=109)	Placebo (N=110)	p-Value
Smoking and/or Tobacco Use			
No. Patients	109	110	.660*
No	99 (90.8)	97 (88.2)	
Yes	10 (9.2)	13 (11.8)	
Alcohol Use			
No. Patients	109	110	.784*
No	102 (93.6)	104 (94.5)	
Yes	7 (6.4)	6 (5.5)	
Caffeine Use			
No. Patients	109	110	1.00*
No	22 (20.2)	22 (20.0)	
Yes	87 (79.8)	88 (80.0)	

RMP.B1YP.JCLLIB2(DES1JEAB)
RMP.B1YO.HCJEREP(DES1JEAB)
* Frequencies are analyzed using a Fishers-Exact test.
XDES0001

11.2.2. Psychiatric History

The psychiatric histories of all randomized patients at baseline are presented in Table 11.3. The mean age of onset of MDD was 10.3 years (range = 2 years to 16 years). The mean duration of the current episode was 61 weeks (range = 2 weeks to 572 weeks). Forty-six (21%) patients reported at least one previous episode.

There were no statistically significant differences between treatment groups for onset age, duration of current episode, or the occurrence of prior episodes of MDD.

Complete patient listings of psychiatric histories by patient are presented in Appendix 16.2.5.

Table 11.3. Psychiatric History
All Randomized Patients
B1Y-MC-HCJE

Variable	Flx 20 (N=109)	Placebo (N=110)	Total (N=219)	p-Value
Age at Onset (yrs)				
No. Patients	109	110	219	.715**
Mean	10.41	10.26	10.34	
Median	11.00	10.00	10.00	
Standard Dev.	2.92	3.11	3.01	
Minimum	2.00	4.00	2.00	
Maximum	16.00	16.00	16.00	
Duration of Current Episode (wks)				
No. Patients	109	110	219	.936**
Mean	60.44	61.29	60.87	
Median	32.00	32.00	32.00	
Standard Dev.	82.58	73.73	78.08	
Minimum	4.00	2.00	2.00	
Maximum	572.00	450.00	572.00	
Previous Episodes				
No. Patients	109	110	219	.868*
No	87 (79.8)	86 (78.2)	173 (79.0)	
Yes	22 (20.2)	24 (21.8)	46 (21.0)	

RMP.B1YP.JCLLIB2(DES1JEAC)
RMP.B1YO.HCJEREP(DES1JEAC)
* Frequencies are analyzed using a Fishers-Exact test.
** Means are analyzed using a Type III Sum of Squares analysis of variance (ANOVA): PROC GLM model=treatment.
XDES0001

Table 11.4 summarizes the biological family history for all randomized patients. A "No" response indicated that no first-degree relative (mother, father, or sibling) had a history of the illness. A "Yes" response indicated that any first-degree relative (mother, father, or sibling) had a history of the illness. An "Unspecified" response indicated that the history for at least one first-degree relative (mother, father, or sibling) was unknown and the remaining relatives did not have a positive family history. If at least one relative had a positive history, the response was "Yes." "Unspecified" responses were not included in the calculation of p-values.

Over half of the randomized patients (60%) had a family history of depression and 21% reported a family history of anxiety disorders. Although a family history of bipolar disorder was an exclusion criterion, the mother of 1 placebo-treated patient (1304) did have a history of bipolar disorder. This patient was lost to follow up and was discontinued at Visit 9.

There were no statistically significant differences between treatment groups in reported biological family history.

Complete patient listings of biological family history are presented in Appendix 16.2.5.

Table 11.4. Biological Family History
All Randomized Patients
B1Y-MC-HCJE

Variable	Flx 20 (N=109)	Placebo (N=110)	p-Value
Family History of Depression			
No. Patients	109	108	1.00*
No	41 (40.2)	39 (39.4)	
Yes	61 (59.8)	60 (60.6)	
Unspecified	7	9	
Family History of Anxiety Disorders			
No. Patients	109	108	.860*
No	78 (78.8)	77 (80.2)	
Yes	21 (21.2)	19 (19.8)	
Unspecified	10	12	
Family History of Manic Depression (Bipolar)			
No. Patients	109	108	1.00*
No	98 (100)	97 (99.0)	
Yes	0	1 (1.0)	
Unspecified	11	10	

RMP.B1YP.JCLLIB2(DES1JEAD)
RMP.B1YO.HCJEREP(DES1JEAD)
* Frequencies are analyzed using a Fishers-Exact test.
XDES0001

11.2.3. Previous Treatment

Table 11.5 presents a summary of the treatments previously used by all randomized patients for the treatment of depressive disorders within the past year. The majority of patients (80%) had not received previous treatment for depressive disorders in the past year. Treatments used by ≥1% of patients included psychotherapy (4.1%), methylphenidate hydrochloride (3.2%), sertraline hydrochloride (2.3%), Adderal® (dexamfetamine/amfetamine/dexam) (1.8%), hypericum extract (1.8%), hypericum perforatum (1.8%), and fluoxetine hydrochloride (1.4%).

A by-patient data listing of treatments for depressive disorders within the past year is presented in Appendix 16.2.5.

Table 11.5. Previous Treatment for Depressive Disorders Within Past Year
All Randomized Patients
B1Y-MC-HCJE

Drug Name	Flx 20 (N=109) n (%)	Placebo (N=110) n (%)	Total (N=219) n (%)
PATIENTS WITH >= 1 DRUG	22 (20.2)	21 (19.1)	43 (19.6)
PATIENTS WITH NO DRUGS	87 (79.8)	89 (80.9)	176 (80.4)
PSYCHOTHERAPY	6 (5.5)	3 (2.7)	9 (4.1)
METHYLPHENIDATE HYDROCHLORIDE	2 (1.8)	5 (4.5)	7 (3.2)
SERTRALINE HYDROCHLORIDE	3 (2.8)	2 (1.8)	5 (2.3)
DEXAMFETAMINE/AMFETAMINE/DEXAM	2 (1.8)	2 (1.8)	4 (1.8)
HYPERICUM EXTRACT	3 (2.8)	1 (0.9)	4 (1.8)
HYPERICUM PERFORATUM	3 (2.8)	1 (0.9)	4 (1.8)
FLUOXETINE HYDROCHLORIDE	2 (1.8)	1 (0.9)	3 (1.4)
AMFEBUTAMONE HYDROCHLORIDE	0	2 (1.8)	2 (0.9)
DESIPRAMINE	1 (0.9)	1 (0.9)	2 (0.9)
DEXAMFETAMINE SULFATE	0	1 (0.9)	1 (0.5)
GUANFACINE HYDROCHLORIDE	1 (0.9)	0	1 (0.5)
HERBAL PREPARATION	1 (0.9)	0	1 (0.5)
MELATONIN	0	1 (0.9)	1 (0.5)
METHYLPHENIDATE	0	1 (0.9)	1 (0.5)
PAROXETINE HYDROCHLORIDE	0	1 (0.9)	1 (0.5)
SERTRALINE	0	1 (0.9)	1 (0.5)
ST. JOHN'S WORT	1 (0.9)	0	1 (0.5)

RMP.B1YP.JCLLIB2(DTS1JEAA)
RMP.B1YO.HCJEREP(DTS1JEAA)
XDTS0001

11.2.4. Concomitant Medication

Tables 11.6 and 11.7 present summaries of concomitant medications used by randomized patients during the acute and subchronic treatment phases, respectively. During the 9-week acute treatment phase, 162 (74%) patients used concomitant medications. During the 19-week subchronic treatment phase, 171 (78%) patients used concomitant medications. There was a statistically significant difference between treatment groups in reported use of concomitant medications during both the acute treatment phase (82% fluoxetine, 66% placebo; p=.013) and the subchronic treatment phase (84% fluoxetine, 72% placebo; p=.033).

The most commonly used concomitant medications were the over-the-counter, non-steroidal anti-inflammatory medications, paracetamol and ibuprofen. There was a statistically significant difference between treatment groups in reported use of one medication, paracetamol. This difference was observed during both the acute treatment phase (35% fluoxetine, 21% placebo; p=.024) and the subchronic treatment phase (39% fluoxetine, 26% placebo; p=.043).

A by-patient listing of all concomitant medications used during these study periods is presented in Appendix 16.4.2.

Table 11.6. **Concomitant Medications**
All Randomized Patients
Acute Treatment Phase (Study Periods III-IV)
B1Y-MC-HCJE

Drug Name	Flx 20 (N=109) n (%)	Placebo (N=110) n (%)	Total (N=219) n (%)	p-Value*
PATIENTS WITH >= 1 DRUG	89 (81.7)	73 (66.4)	162 (74.0)	.013
PATIENTS WITH NO DRUGS	20 (18.3)	37 (33.6)	57 (26.0)	.013
PARACETAMOL	38 (34.9)	23 (20.9)	61 (27.9)	.024
IBUPROFEN	29 (26.6)	24 (21.8)	53 (24.2)	.434
SALBUTAMOL	12 (11.0)	9 (8.2)	21 (9.6)	.501
DIPHENHYDRAMINE HYDROCHLORIDE	10 (9.2)	10 (9.1)	20 (9.1)	1.00
LORATADINE	9 (8.3)	7 (6.4)	16 (7.3)	.615
BISMUTH SUBSALICYLATE	6 (5.5)	6 (5.5)	12 (5.5)	1.00
NAPROXEN SODIUM	6 (5.5)	4 (3.6)	10 (4.6)	.538
AMOXICILLIN	5 (4.6)	4 (3.6)	9 (4.1)	.748
ERGOCALCIFEROL/ASCORBIC ACID/F	5 (4.6)	4 (3.6)	9 (4.1)	.748
LIDOCAINE/PRILOCAINE	4 (3.7)	5 (4.5)	9 (4.1)	1.00
ACETYLSALICYLIC ACID	4 (3.7)	4 (3.6)	8 (3.7)	1.00
ACETYLSALICYLIC ACID/CAFFEINE/	2 (1.8)	5 (4.5)	7 (3.2)	.446
CALCIUM/MAGNESIUM/MAGNESIUM TR	3 (2.8)	3 (2.7)	6 (2.7)	1.00
CEFALEXIN	5 (4.6)	1 (0.9)	6 (2.7)	.119
FEXOFENADINE HYDROCHLORIDE	3 (2.8)	3 (2.7)	6 (2.7)	1.00
FLUTICASONE PROPIONATE	4 (3.7)	2 (1.8)	6 (2.7)	.446
CLAVULANATE/AMOXICILLIN	4 (3.7)	1 (0.9)	5 (2.3)	.212
GUAIFENESIN	2 (1.8)	3 (2.7)	5 (2.3)	1.00
ASCORBIC ACID	2 (1.8)	2 (1.8)	4 (1.8)	1.00
BECLOMETASONE DIPROPIONATE	2 (1.8)	2 (1.8)	4 (1.8)	1.00
PARACETAMOL/PSEUDOEPHEDRINE	4 (3.7)	0	4 (1.8)	.060
PHENYLEPHRINE/PHENYLPROPANOLAM	2 (1.8)	2 (1.8)	4 (1.8)	1.00
PROMETHAZINE HYDROCHLORIDE	2 (1.8)	2 (1.8)	4 (1.8)	1.00
PSEUDOEPHEDRINE HYDROCHLORIDE	1 (0.9)	3 (2.7)	4 (1.8)	.622
SULFAMETHOXAZOLE/TRIMETHOPRIM	1 (0.9)	3 (2.7)	4 (1.8)	.622
TRIAMCINOLONE ACETONIDE	2 (1.8)	2 (1.8)	4 (1.8)	1.00
AZITHROMYCIN	2 (1.8)	1 (0.9)	3 (1.4)	.622
BUDESONIDE	3 (2.8)	0	3 (1.4)	.122
CLEMASTINE FUMARATE	3 (2.8)	0	3 (1.4)	.122
ETHANOL/GUAIFENESIN/DEXTROMETH	3 (2.8)	0	3 (1.4)	.122
ETHANOL/PARACETAMOL/DEXTROMETH	2 (1.8)	1 (0.9)	3 (1.4)	.622
GUAIFENESIN/PARACETAMOL/DEXTRO	2 (1.8)	1 (0.9)	3 (1.4)	.622
HOMEOPATHIC AGENT	1 (0.9)	2 (1.8)	3 (1.4)	1.00
MAGNESIUM/ALUMINIUM HYDROXIDE	2 (1.8)	1 (0.9)	3 (1.4)	.622
PARACETAMOL/CHLORPHENAMINE/DEX	1 (0.9)	2 (1.8)	3 (1.4)	1.00
PARACETAMOL/HYDROCODONE	1 (0.9)	2 (1.8)	3 (1.4)	1.00
PSEUDOEPHEDRINE/LORATADINE	3 (2.8)	0	3 (1.4)	.122
TRETINOIN	3 (2.8)	0	3 (1.4)	.122
AMOXICILLIN TRIHYDRATE	2 (1.8)	0	2 (0.9)	.247

RMP.B1YP.JCLLIB2(DTS1JEKE)
RMP.B1YO.HCJEREP(DTS1JEKE)
* Frequencies are analyzed using a Fisher's Exact test.
XDTS0001

Table 11.6. Concomitant Medications
All Randomized Patients
Acute Treatment Phase (Study Periods III-IV)
B1Y-MC-HCJE (continued)

Drug Name	Flx 20 (N=109) n	(%)	Placebo (N=110) n	(%)	Total (N=219) n	(%)	p-Value*
ANESTHETIC NOS	1	(0.9)	1	(0.9)	2	(0.9)	1.00
CALAMINE	1	(0.9)	1	(0.9)	2	(0.9)	1.00
CEFPROZIL	1	(0.9)	1	(0.9)	2	(0.9)	1.00
CETIRIZINE HYDROCHLORIDE	2	(1.8)	0		2	(0.9)	.247
CHLORAL HYDRATE	0		2	(1.8)	2	(0.9)	.498
CODEINE/PARACETAMOL	1	(0.9)	1	(0.9)	2	(0.9)	1.00
CORTISONE	2	(1.8)	0		2	(0.9)	.247
DIMENHYDRINATE	0		2	(1.8)	2	(0.9)	.498
DIPHENHYDRAMINE/PARACETAMOL	1	(0.9)	1	(0.9)	2	(0.9)	1.00
ECHINACEA EXTRACT	1	(0.9)	1	(0.9)	2	(0.9)	1.00
GUAIFENESIN/PHENYLPROPANOLAMIN	1	(0.9)	1	(0.9)	2	(0.9)	1.00
HYDROCORTISONE	2	(1.8)	0		2	(0.9)	.247
HYDROCORTISONE/NEOMYCIN/POLYMY	0		2	(1.8)	2	(0.9)	.498
LOPERAMIDE HYDROCHLORIDE	0		2	(1.8)	2	(0.9)	.498
MINOCYCLINE	2	(1.8)	0		2	(0.9)	.247
MOMETASONE FUROATE	1	(0.9)	1	(0.9)	2	(0.9)	1.00
PIRBUTEROL ACETATE	0		2	(1.8)	2	(0.9)	.498
PREDNISONE	2	(1.8)	0		2	(0.9)	.247
SENNA FRUIT	1	(0.9)	1	(0.9)	2	(0.9)	1.00
TERBINAFINE HYDROCHLORIDE	1	(0.9)	1	(0.9)	2	(0.9)	1.00
TRIAMCINOLONE	2	(1.8)	0		2	(0.9)	.247
VITAMINS	1	(0.9)	1	(0.9)	2	(0.9)	1.00
ZOLPIDEM TARTRATE	1	(0.9)	1	(0.9)	2	(0.9)	1.00
ACETYLSALICYLIC ACID/CODEINE/C	0		1	(0.9)	1	(0.5)	1.00
AMFEBUTAMONE HYDROCHLORIDE	0		1	(0.9)	1	(0.5)	1.00
AMPICILLIN	0		1	(0.9)	1	(0.5)	1.00
ANTIBIOTIC NOS	1	(0.9)	0		1	(0.5)	.498
ANTIBIOTICS	1	(0.9)	0		1	(0.5)	.498
ANTIHISTAMINES FOR SYSTEMIC US	1	(0.9)	0		1	(0.5)	.498
ATROPINE	0		1	(0.9)	1	(0.5)	1.00
AZELASTINE	0		1	(0.9)	1	(0.5)	1.00
BENZOYL PEROXIDE/ERYTHROMYCIN	1	(0.9)	0		1	(0.5)	.498
BORIC ACID	1	(0.9)	0		1	(0.5)	.498
CALCIUM	0		1	(0.9)	1	(0.5)	1.00
CEFIXIME	0		1	(0.9)	1	(0.5)	1.00
CEFOXITIN	0		1	(0.9)	1	(0.5)	1.00
CEFUROXIME AXETIL	1	(0.9)	0		1	(0.5)	.498
CETIRIZINE	1	(0.9)	0		1	(0.5)	.498
CIMETIDINE	0		1	(0.9)	1	(0.5)	1.00
CLEMASTINE	1	(0.9)	0		1	(0.5)	.498
CLOTRIMAZOLE	0		1	(0.9)	1	(0.5)	1.00

RMP.B1YP.JCLLIB2(DTS1JEKE)
RMP.B1YO.HCJEREP(DTS1JEKE)
* Frequencies are analyzed using a Fisher's Exact test.
XDTS0001

Table 11.6. **Concomitant Medications**
All Randomized Patients
Acute Treatment Phase (Study Periods III-IV)
B1Y-MC-HCJE (continued)

Drug Name	Flx 20 (N=109) n	(%)	Placebo (N=110) n	(%)	Total (N=219) n	(%)	p-Value*
CODEINE/CAFFEINE/PARACETAMOL/P	0		1	(0.9)	1	(0.5)	1.00
DEXBROMPHENIRAMINE/PSEUDOEPHED	1	(0.9)	0		1	(0.5)	.498
DIHYDROXYALUMINUM SODIUM CARBO	1	(0.9)	0		1	(0.5)	.498
DIPHENHYDRAMINE/PSEUDOEPHEDRIN	0		1	(0.9)	1	(0.5)	1.00
DOXYLAMINE SUCCINATE	0		1	(0.9)	1	(0.5)	1.00
EMOLLIENTS AND PROTECTIVES	1	(0.9)	0		1	(0.5)	.498
ETHANOL	1	(0.9)	0		1	(0.5)	.498
ETHINYLESTRADIOL/LEVONORGESTRE	0		1	(0.9)	1	(0.5)	1.00
FOLIC ACID/IRON/VITAMINS NOS	0		1	(0.9)	1	(0.5)	1.00
GENTAMICIN SULFATE	0		1	(0.9)	1	(0.5)	1.00
GLUCOSAMINE/CHONDROITIN	1	(0.9)	0		1	(0.5)	.498
GLYCEROL/CAMPHOR/DIPHENHYDRAMI	0		1	(0.9)	1	(0.5)	1.00
GLYCEROL/SODIUM CITRATE/BENTON	1	(0.9)	0		1	(0.5)	.498
GUAIFENESIN/HYDROCODONE	1	(0.9)	0		1	(0.5)	.498
GUAIFENESIN/PSEUDOEPHEDRINE	0		1	(0.9)	1	(0.5)	1.00
HEPATITIS B VACCINE	0		1	(0.9)	1	(0.5)	1.00
HOMEOPATHIC AGENT/GARLIC	1	(0.9)	0		1	(0.5)	.498
HOMEOPATHIC MEDICINE	0		1	(0.9)	1	(0.5)	1.00
INFLUENZA VIRUS VACCINE POLYVA	1	(0.9)	0		1	(0.5)	.498
ISOPROPANOL/BENZOXIQUINE/MENTH	0		1	(0.9)	1	(0.5)	1.00
ISOTRETINOIN	1	(0.9)	0		1	(0.5)	.498
KETAMINE HYDROCHLORIDE	0		1	(0.9)	1	(0.5)	1.00
KETOROLAC TROMETHAMINE	0		1	(0.9)	1	(0.5)	1.00
LACTIC ACID/SALICYLIC ACID	1	(0.9)	0		1	(0.5)	.498
LACTOBACILLUS ACIDOPHILUS	1	(0.9)	0		1	(0.5)	.498
LACTULOSE	1	(0.9)	0		1	(0.5)	.498
LORACARBEF	1	(0.9)	0		1	(0.5)	.498
LORAZEPAM	0		1	(0.9)	1	(0.5)	1.00
MAGNESIUM HYDROXIDE	1	(0.9)	0		1	(0.5)	.498
MAGNESIUM PHOSPHATE	0		1	(0.9)	1	(0.5)	1.00
MEDROXYPROGESTERONE ACETATE	1	(0.9)	0		1	(0.5)	.498
MENTHOL/CETYLPYRIDINIUM	1	(0.9)	0		1	(0.5)	.498
MENTHOL/EUCALYPTUS	1	(0.9)	0		1	(0.5)	.498
MEPYRAMINE/PARACETAMOL	0		1	(0.9)	1	(0.5)	1.00
MERCURIC OXIDE, YELLOW/ZINC SU	1	(0.9)	0		1	(0.5)	.498
MIDAZOLAM HYDROCHLORIDE	0		1	(0.9)	1	(0.5)	1.00
MINERAL	1	(0.9)	0		1	(0.5)	.498
MORPHINE	0		1	(0.9)	1	(0.5)	1.00
NEOMYCIN/POLYMYXIN B SULFATE/B	1	(0.9)	0		1	(0.5)	.498
NITROUS OXIDE	0		1	(0.9)	1	(0.5)	1.00
NORETHISTERONE/ETHINYLESTRADIO	1	(0.9)	0		1	(0.5)	.498

RMP.B1YP.JCLLIB2(DTS1JEKE)
RMP.B1YO.HCJEREP(DTS1JEKE)
* Frequencies are analyzed using a Fisher's Exact test.
XDTS0001

Table 11.6. Concomitant Medications
All Randomized Patients
Acute Treatment Phase (Study Periods III-IV)
B1Y-MC-HCJE (continued)

Drug Name	Flx 20 (N=109) n	(%)	Placebo (N=110) n	(%)	Total (N=219) n	(%)	p-Value*
ORAL CONTRACEPTIVE NOS	1	(0.9)	0		1	(0.5)	.498
ORCIPRENALINE SULFATE	0		1	(0.9)	1	(0.5)	1.00
OXYMETAZOLINE HYDROCHLORIDE	1	(0.9)	0		1	(0.5)	.498
PARACETAMOL/CHLORPHENAMINE/PSE	1	(0.9)	0		1	(0.5)	.498
PARACETAMOL/DICHLORALPHENAZONE	0		1	(0.9)	1	(0.5)	1.00
PETROLATUM/LANOLIN	1	(0.9)	0		1	(0.5)	.498
PHENAGLYCODOL	1	(0.9)	0		1	(0.5)	.498
PHENOL	1	(0.9)	0		1	(0.5)	.498
PHENOXYMETHYLPENICILLIN POTASS	0		1	(0.9)	1	(0.5)	1.00
PHENYLEPHRINE/DIPHENYLPYRALINE	0		1	(0.9)	1	(0.5)	1.00
PHENYLPROPANOLAMINE/CLEMASTINE	1	(0.9)	0		1	(0.5)	.498
PHOSPHORIC ACID/INVERT SUGAR	1	(0.9)	0		1	(0.5)	.498
PIROXICAM	0		1	(0.9)	1	(0.5)	1.00
POLYMYXIN B	0		1	(0.9)	1	(0.5)	1.00
POLYMYXIN B SULFATE/GRAMICIDIN	1	(0.9)	0		1	(0.5)	.498
POTASSIUM	0		1	(0.9)	1	(0.5)	1.00
PREDNISOLONE ACETATE	0		1	(0.9)	1	(0.5)	1.00
PROCHLORPERAZINE MALEATE	1	(0.9)	0		1	(0.5)	.498
PROPOFOL	0		1	(0.9)	1	(0.5)	1.00
PSEUDOEPHEDRINE/BROMPHENIRAMIN	1	(0.9)	0		1	(0.5)	.498
PSEUDOEPHEDRINE/CHLORPHENAMINE	0		1	(0.9)	1	(0.5)	1.00
PSEUDOEPHEDRINE/FEXOFENADINE	1	(0.9)	0		1	(0.5)	.498
PSEUDOEPHEDRINE/GUAIFENESIN/PA	0		1	(0.9)	1	(0.5)	1.00
PSEUDOEPHEDRINE/IBUPROFEN	0		1	(0.9)	1	(0.5)	1.00
PSYLLIUM HYDROPHILIC MUCILLOID	0		1	(0.9)	1	(0.5)	1.00
RANITIDINE HYDROCHLORIDE	0		1	(0.9)	1	(0.5)	1.00
RIMANTADINE HYDROCHLORIDE	1	(0.9)	0		1	(0.5)	.498
SALBUTAMOL SULFATE	1	(0.9)	0		1	(0.5)	.498
SELENIUM SULFIDE	1	(0.9)	0		1	(0.5)	.498
SODIUM BICARBONATE/ALUMINIUM H	1	(0.9)	0		1	(0.5)	.498
SODIUM CHLORIDE	0		1	(0.9)	1	(0.5)	1.00
SODIUM CHLORIDE COMPOUND INJEC	0		1	(0.9)	1	(0.5)	1.00
SODIUM FLUORIDE	1	(0.9)	0		1	(0.5)	.498
SODIUM LACTATE	0		1	(0.9)	1	(0.5)	1.00
SORBITOL/AMINOACETIC ACID/PHEN	1	(0.9)	0		1	(0.5)	.498
SUXAMETHONIUM	0		1	(0.9)	1	(0.5)	1.00
TETANUS ANTITOXIN	1	(0.9)	0		1	(0.5)	.498
TRAMADOL HYDROCHLORIDE	0		1	(0.9)	1	(0.5)	1.00
TRIMETHOPRIM/POLYMYXIN B SULFA	1	(0.9)	0		1	(0.5)	.498
TROLAMINE SALICYLATE	0		1	(0.9)	1	(0.5)	1.00
VITAMINS NOS	0		1	(0.9)	1	(0.5)	1.00

RMP.B1YP.JCLLIB2(DTS1JEKE)
RMP.B1YO.HCJEREP(DTS1JEKE)
* Frequencies are analyzed using a Fisher's Exact test.
XDTS0001

Table 11.6. Concomitant Medications
All Randomized Patients
Acute Treatment Phase (Study Periods III-IV)
B1Y-MC-HCJE (concluded)

Drug Name	Flx 20 (N=109) n (%)	Placebo (N=110) n (%)	Total (N=219) n (%)	p-Value*
VITAMINS WITH MINERALS	0	1 (0.9)	1 (0.5)	1.00

RMP.B1YP.JCLLIB2(DTS1JEKE)
RMP.B1YO.HCJEREP(DTS1JEKE)
* Frequencies are analyzed using a Fisher's Exact test.
XDTS0001

Table 11.7. Concomitant Medications
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE

Drug Name	Flx (N=109) n (%)	Placebo (N=110) n (%)	Total (N=219) n (%)	p-Value*
PATIENTS WITH >= 1 DRUG	92 (84.4)	79 (71.8)	171 (78.1)	.033
PATIENTS WITH NO DRUGS	17 (15.6)	31 (28.2)	48 (21.9)	.033
PARACETAMOL	42 (38.5)	28 (25.5)	70 (32.0)	.043
IBUPROFEN	33 (30.3)	26 (23.6)	59 (26.9)	.289
DIPHENHYDRAMINE HYDROCHLORIDE	11 (10.1)	11 (10.0)	22 (10.0)	1.00
SALBUTAMOL	13 (11.9)	9 (8.2)	22 (10.0)	.379
LORATADINE	10 (9.2)	7 (6.4)	17 (7.8)	.462
AMOXICILLIN	10 (9.2)	5 (4.5)	15 (6.8)	.193
NAPROXEN SODIUM	9 (8.3)	5 (4.5)	14 (6.4)	.285
BISMUTH SUBSALICYLATE	6 (5.5)	6 (5.5)	12 (5.5)	1.00
ACETYLSALICYLIC ACID	5 (4.6)	6 (5.5)	11 (5.0)	1.00
LIDOCAINE/PRILOCAINE	5 (4.6)	6 (5.5)	11 (5.0)	1.00
CLAVULANATE/AMOXICILLIN	6 (5.5)	4 (3.6)	10 (4.6)	.538
ERGOCALCIFEROL/ASCORBIC ACID/F	6 (5.5)	4 (3.6)	10 (4.6)	.538
ACETYLSALICYLIC ACID/CAFFEINE/	2 (1.8)	6 (5.5)	8 (3.7)	.280
CEFALEXIN	5 (4.6)	2 (1.8)	7 (3.2)	.280
CALCIUM/MAGNESIUM/MAGNESIUM TR	3 (2.8)	3 (2.7)	6 (2.7)	1.00
FEXOFENADINE HYDROCHLORIDE	3 (2.8)	3 (2.7)	6 (2.7)	1.00
FLUTICASONE PROPIONATE	4 (3.7)	2 (1.8)	6 (2.7)	.446
PARACETAMOL/CHLORPHENAMINE/DEX	3 (2.8)	3 (2.7)	6 (2.7)	1.00
PSEUDOEPHEDRINE HYDROCHLORIDE	3 (2.8)	3 (2.7)	6 (2.7)	1.00
ASCORBIC ACID	2 (1.8)	3 (2.7)	5 (2.3)	1.00
CODEINE/PARACETAMOL	2 (1.8)	3 (2.7)	5 (2.3)	1.00
ETHANOL/PARACETAMOL/DEXTROMETH	4 (3.7)	1 (0.9)	5 (2.3)	.212
GUAIFENESIN	2 (1.8)	3 (2.7)	5 (2.3)	1.00
PARACETAMOL/PSEUDOEPHEDRINE	4 (3.7)	1 (0.9)	5 (2.3)	.212
PHENYLEPHRINE/PHENYLPROPANOLAM	3 (2.8)	2 (1.8)	5 (2.3)	.683
TRIAMCINOLONE ACETONIDE	3 (2.8)	2 (1.8)	5 (2.3)	.683
BECLOMETASONE DIPROPIONATE	2 (1.8)	2 (1.8)	4 (1.8)	1.00
GUAIFENESIN/PARACETAMOL/DEXTRO	3 (2.8)	1 (0.9)	4 (1.8)	.369
PROMETHAZINE HYDROCHLORIDE	2 (1.8)	2 (1.8)	4 (1.8)	1.00
PSEUDOEPHEDRINE/LORATADINE	3 (2.8)	1 (0.9)	4 (1.8)	.369
SULFAMETHOXAZOLE/TRIMETHOPRIM	1 (0.9)	3 (2.7)	4 (1.8)	.622
AZITHROMYCIN	2 (1.8)	1 (0.9)	3 (1.4)	.622
BUDESONIDE	3 (2.8)	0	3 (1.4)	.122
CLEMASTINE FUMARATE	3 (2.8)	0	3 (1.4)	.122
ETHANOL/GUAIFENESIN/DEXTROMETH	3 (2.8)	0	3 (1.4)	.122
GUAIFENESIN/PHENYLPROPANOLAMIN	1 (0.9)	2 (1.8)	3 (1.4)	1.00
HOMEOPATHIC AGENT	1 (0.9)	2 (1.8)	3 (1.4)	1.00
HYDROCORTISONE/NEOMYCIN/POLYMY	0	3 (2.7)	3 (1.4)	.247
LOPERAMIDE HYDROCHLORIDE	0	3 (2.7)	3 (1.4)	.247

RMP.B1YP.JCLLIB2(DTS1JEKF)
RMP.B1YO.HCJEREP(DTS1JEKF)
* Frequencies are analyzed using a Fisher’s Exact test.
XDTS0001

Table 11.7. Concomitant Medications
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE (continued)

Drug Name	Flx (N=109) n	(%)	Placebo (N=110) n	(%)	Total (N=219) n	(%)	p-Value*
MAGNESIUM/ALUMINIUM HYDROXIDE	2	(1.8)	1	(0.9)	3	(1.4)	.622
PARACETAMOL/HYDROCODONE	1	(0.9)	2	(1.8)	3	(1.4)	1.00
TRETINOIN	3	(2.8)	0		3	(1.4)	.122
AMOXICILLIN TRIHYDRATE	2	(1.8)	0		2	(0.9)	.247
ANESTHETIC NOS	1	(0.9)	1	(0.9)	2	(0.9)	1.00
CALAMINE	1	(0.9)	1	(0.9)	2	(0.9)	1.00
CEFALEXIN MONOHYDRATE	1	(0.9)	1	(0.9)	2	(0.9)	1.00
CEFPROZIL	1	(0.9)	1	(0.9)	2	(0.9)	1.00
CETIRIZINE HYDROCHLORIDE	2	(1.8)	0		2	(0.9)	.247
CHLORAL HYDRATE	0		2	(1.8)	2	(0.9)	.498
CORTISONE	2	(1.8)	0		2	(0.9)	.247
COUGH AND COLD PREPARATIONS	2	(1.8)	0		2	(0.9)	.247
CROMOGLICATE SODIUM	0		2	(1.8)	2	(0.9)	.498
DIMENHYDRINATE	0		2	(1.8)	2	(0.9)	.498
DIPHENHYDRAMINE/PARACETAMOL	1	(0.9)	1	(0.9)	2	(0.9)	1.00
ECHINACEA EXTRACT	1	(0.9)	1	(0.9)	2	(0.9)	1.00
ERYTHROMYCIN	0		2	(1.8)	2	(0.9)	.498
GLYCEROL/SODIUM CITRATE/BENTON	1	(0.9)	1	(0.9)	2	(0.9)	1.00
GUAIFENESIN/PSEUDOEPHEDRINE	1	(0.9)	1	(0.9)	2	(0.9)	1.00
HEPATITIS B VACCINE	1	(0.9)	1	(0.9)	2	(0.9)	1.00
HYDROCORTISONE	2	(1.8)	0		2	(0.9)	.247
MINOCYCLINE	2	(1.8)	0		2	(0.9)	.247
MOMETASONE FUROATE	1	(0.9)	1	(0.9)	2	(0.9)	1.00
PHENOXYMETHYLPENICILLIN POTASS	1	(0.9)	1	(0.9)	2	(0.9)	1.00
PIRBUTEROL ACETATE	0		2	(1.8)	2	(0.9)	.498
POLYMYXIN B	1	(0.9)	1	(0.9)	2	(0.9)	1.00
POLYMYXIN B SULFATE/GRAMICIDIN	1	(0.9)	1	(0.9)	2	(0.9)	1.00
PREDNISONE	2	(1.8)	0		2	(0.9)	.247
PSYLLIUM HYDROPHILIC MUCILLOID	1	(0.9)	1	(0.9)	2	(0.9)	1.00
SENNA FRUIT	1	(0.9)	1	(0.9)	2	(0.9)	1.00
TERBINAFINE HYDROCHLORIDE	1	(0.9)	1	(0.9)	2	(0.9)	1.00
TRIAMCINOLONE	2	(1.8)	0		2	(0.9)	.247
VITAMINS	1	(0.9)	1	(0.9)	2	(0.9)	1.00
VITAMINS NOS	0		2	(1.8)	2	(0.9)	.498
ZOLPIDEM TARTRATE	1	(0.9)	1	(0.9)	2	(0.9)	1.00
ACETYLSALICYLIC ACID/CODEINE/C	0		1	(0.9)	1	(0.5)	1.00
AMFEBUTAMONE HYDROCHLORIDE	0		1	(0.9)	1	(0.5)	1.00
AMPICILLIN	0		1	(0.9)	1	(0.5)	1.00
ANTIBIOTIC NOS	1	(0.9)	0		1	(0.5)	.498
ANTIBIOTICS	1	(0.9)	0		1	(0.5)	.498
ANTIHISTAMINES FOR SYSTEMIC US	1	(0.9)	0		1	(0.5)	.498

RMP.B1YP.JCLLIB2(DTS1JEKF)
RMP.B1YO.HCJEREP(DTS1JEKF)
* Frequencies are analyzed using a Fisher’s Exact test.
XDTS0001

Table 11.7. Concomitant Medications
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE (continued)

Drug Name	Flx (N=109) n	(%)	Placebo (N=110) n	(%)	Total (N=219) n	(%)	p-Value*
ATROPINE	0		1	(0.9)	1	(0.5)	1.00
AZELASTINE	0		1	(0.9)	1	(0.5)	1.00
BENZOYL PEROXIDE/ERYTHROMYCIN	1	(0.9)	0		1	(0.5)	.498
BORIC ACID	1	(0.9)	0		1	(0.5)	.498
CALCIUM	0		1	(0.9)	1	(0.5)	1.00
CEFACLOR	1	(0.9)	0		1	(0.5)	.498
CEFIXIME	0		1	(0.9)	1	(0.5)	1.00
CEFOXITIN	0		1	(0.9)	1	(0.5)	1.00
CEFUROXIME AXETIL	1	(0.9)	0		1	(0.5)	.498
CETIRIZINE	1	(0.9)	0		1	(0.5)	.498
CHARCOAL, ACTIVATED	0		1	(0.9)	1	(0.5)	1.00
CHLORPHENAMINE MALEATE	1	(0.9)	0		1	(0.5)	.498
CHLORPHENAMINE/HYOSCINE METHON	0		1	(0.9)	1	(0.5)	1.00
CIMETIDINE	0		1	(0.9)	1	(0.5)	1.00
CLARITHROMYCIN	0		1	(0.9)	1	(0.5)	1.00
CLEMASTINE	1	(0.9)	0		1	(0.5)	.498
CLOTRIMAZOLE	0		1	(0.9)	1	(0.5)	1.00
CODEINE/CAFFEINE/PARACETAMOL/P	0		1	(0.9)	1	(0.5)	1.00
DEXBROMPHENIRAMINE/PSEUDOEPHED	1	(0.9)	0		1	(0.5)	.498
DEXTROMETHORPHAN HYDROBROMIDE	1	(0.9)	0		1	(0.5)	.498
DIHYDROXYALUMINUM SODIUM CARBO	1	(0.9)	0		1	(0.5)	.498
DIPHENHYDRAMINE	0		1	(0.9)	1	(0.5)	1.00
DIPHENHYDRAMINE/PSEUDOEPHEDRIN	0		1	(0.9)	1	(0.5)	1.00
DOXYLAMINE SUCCINATE	0		1	(0.9)	1	(0.5)	1.00
EMOLLIENTS AND PROTECTIVES	1	(0.9)	0		1	(0.5)	.498
ESTRADIOL	1	(0.9)	0		1	(0.5)	.498
ETHANOL	1	(0.9)	0		1	(0.5)	.498
ETHINYLESTRADIOL/LEVONORGESTRE	0		1	(0.9)	1	(0.5)	1.00
EVENING PRIMROSE OIL	1	(0.9)	0		1	(0.5)	.498
FOLIC ACID/IRON/VITAMINS NOS	0		1	(0.9)	1	(0.5)	1.00
GENTAMICIN SULFATE	0		1	(0.9)	1	(0.5)	1.00
GLUCOSAMINE/CHONDROITIN	1	(0.9)	0		1	(0.5)	.498
GLYCEROL/CAMPHOR/DIPHENHYDRAMI	0		1	(0.9)	1	(0.5)	1.00
GUAIFENESIN/HYDROCODONE	1	(0.9)	0		1	(0.5)	.498
HOMEOPATHIC AGENT/GARLIC	1	(0.9)	0		1	(0.5)	.498
HOMEOPATHIC MEDICINE	0		1	(0.9)	1	(0.5)	1.00
INFLUENZA VIRUS VACCINE POLYVA	1	(0.9)	0		1	(0.5)	.498
IRON	1	(0.9)	0		1	(0.5)	.498
ISOPROPANOL/BENZOXIQUINE/MENTH	0		1	(0.9)	1	(0.5)	1.00
ISOTRETINOIN	1	(0.9)	0		1	(0.5)	.498
KETAMINE HYDROCHLORIDE	0		1	(0.9)	1	(0.5)	1.00

RMP.B1YP.JCLLIB2(DTS1JEKF)
RMP.B1YO.HCJEREP(DTS1JEKF)
* Frequencies are analyzed using a Fisher’s Exact test.
XDTS0001

Table 11.7. Concomitant Medications
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE (continued)

Drug Name	Flx (N=109) n	(%)	Placebo (N=110) n	(%)	Total (N=219) n	(%)	p-Value*
KETOROLAC TROMETHAMINE	0		1	(0.9)	1	(0.5)	1.00
LACTIC ACID/SALICYLIC ACID	1	(0.9)	0		1	(0.5)	.498
LACTOBACILLUS ACIDOPHILUS	1	(0.9)	0		1	(0.5)	.498
LACTULOSE	1	(0.9)	0		1	(0.5)	.498
LORACARBEF	1	(0.9)	0		1	(0.5)	.498
LORAZEPAM	0		1	(0.9)	1	(0.5)	1.00
MAGNESIUM HYDROXIDE	1	(0.9)	0		1	(0.5)	.498
MAGNESIUM PHOSPHATE	0		1	(0.9)	1	(0.5)	1.00
MAGNESIUM/DIMETICONE, ACTIVATE	0		1	(0.9)	1	(0.5)	1.00
MEDROXYPROGESTERONE ACETATE	1	(0.9)	0		1	(0.5)	.498
MENTHOL/CETYLPYRIDINIUM	1	(0.9)	0		1	(0.5)	.498
MENTHOL/EUCALYPTUS	1	(0.9)	0		1	(0.5)	.498
MEPYRAMINE/PARACETAMOL	0		1	(0.9)	1	(0.5)	1.00
MERCURIC OXIDE, YELLOW/ZINC SU	1	(0.9)	0		1	(0.5)	.498
MIDAZOLAM HYDROCHLORIDE	0		1	(0.9)	1	(0.5)	1.00
MINERAL	1	(0.9)	0		1	(0.5)	.498
MINERALS NOS	0		1	(0.9)	1	(0.5)	1.00
MORPHINE	0		1	(0.9)	1	(0.5)	1.00
NEOMYCIN/POLYMYXIN B SULFATE/B	1	(0.9)	0		1	(0.5)	.498
NITROUS OXIDE	0		1	(0.9)	1	(0.5)	1.00
NORETHISTERONE/ETHINYLESTRADIO	1	(0.9)	0		1	(0.5)	.498
NORETHISTERONE/MESTRANOL	0		1	(0.9)	1	(0.5)	1.00
OFLOXACIN	0		1	(0.9)	1	(0.5)	1.00
ORAL CONTRACEPTIVE NOS	1	(0.9)	0		1	(0.5)	.498
ORCIPRENALINE SULFATE	0		1	(0.9)	1	(0.5)	1.00
OXYMETAZOLINE HYDROCHLORIDE	1	(0.9)	0		1	(0.5)	.498
PARACETAMOL/CHLORPHENAMINE/PSE	1	(0.9)	0		1	(0.5)	.498
PARACETAMOL/DICHLORALPHENAZONE	0		1	(0.9)	1	(0.5)	1.00
PETROLATUM/LANOLIN	1	(0.9)	0		1	(0.5)	.498
PHENAGLYCODOL	1	(0.9)	0		1	(0.5)	.498
PHENAZONE/BENZOCAINE	1	(0.9)	0		1	(0.5)	.498
PHENOL	1	(0.9)	0		1	(0.5)	.498
PHENYLEPHRINE/DIPHENYLPYRALINE	0		1	(0.9)	1	(0.5)	1.00
PHENYLPROPANOLAMINE/CLEMASTINE	1	(0.9)	0		1	(0.5)	.498
PHOSPHORIC ACID/INVERT SUGAR	1	(0.9)	0		1	(0.5)	.498
PIROXICAM	0		1	(0.9)	1	(0.5)	1.00
POTASSIUM	0		1	(0.9)	1	(0.5)	1.00
PREDNISOLONE ACETATE	0		1	(0.9)	1	(0.5)	1.00
PROCHLORPERAZINE MALEATE	1	(0.9)	0		1	(0.5)	.498
PROMETHAZINE	1	(0.9)	0		1	(0.5)	.498
PROPOFOL	0		1	(0.9)	1	(0.5)	1.00

RMP.B1YP.JCLLIB2(DTS1JEKF)
RMP.B1YO.HCJEREP(DTS1JEKF)
* Frequencies are analyzed using a Fisher’s Exact test.
XDTS0001

Table 11.7. Concomitant Medications
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE (concluded)

Drug Name	Flx (N=109) n	(%)	Placebo (N=110) n	(%)	Total (N=219) n	(%)	p-Value*
PSEUDOEPHEDRINE	0		1	(0.9)	1	(0.5)	1.00
PSEUDOEPHEDRINE/BROMPHENIRAMIN	1	(0.9)	0		1	(0.5)	.498
PSEUDOEPHEDRINE/CHLORPHENAMINE	0		1	(0.9)	1	(0.5)	1.00
PSEUDOEPHEDRINE/FEXOFENADINE	1	(0.9)	0		1	(0.5)	.498
PSEUDOEPHEDRINE/GUAIFENESIN/PA	0		1	(0.9)	1	(0.5)	1.00
PSEUDOEPHEDRINE/IBUPROFEN	0		1	(0.9)	1	(0.5)	1.00
RANITIDINE HYDROCHLORIDE	0		1	(0.9)	1	(0.5)	1.00
RIMANTADINE HYDROCHLORIDE	1	(0.9)	0		1	(0.5)	.498
SALBUTAMOL SULFATE	1	(0.9)	0		1	(0.5)	.498
SELENIUM SULFIDE	1	(0.9)	0		1	(0.5)	.498
SENNA	0		1	(0.9)	1	(0.5)	1.00
SODIUM BICARBONATE/ALUMINIUM H	1	(0.9)	0		1	(0.5)	.498
SODIUM CHLORIDE	0		1	(0.9)	1	(0.5)	1.00
SODIUM CHLORIDE COMPOUND INJEC	0		1	(0.9)	1	(0.5)	1.00
SODIUM FLUORIDE	1	(0.9)	0		1	(0.5)	.498
SODIUM LACTATE	0		1	(0.9)	1	(0.5)	1.00
SORBITOL/AMINOACETIC ACID/PHEN	1	(0.9)	0		1	(0.5)	.498
SULFADIAZINE SILVER	1	(0.9)	0		1	(0.5)	.498
SUXAMETHONIUM	0		1	(0.9)	1	(0.5)	1.00
TERPIN/OPIUM/ANTIMONY POTASSIU	0		1	(0.9)	1	(0.5)	1.00
TETANUS ANTITOXIN	1	(0.9)	0		1	(0.5)	.498
TRAMADOL HYDROCHLORIDE	0		1	(0.9)	1	(0.5)	1.00
TRIMETHOPRIM/POLYMYXIN B SULFA	1	(0.9)	0		1	(0.5)	.498
TROLAMINE SALICYLATE	0		1	(0.9)	1	(0.5)	1.00
VITAMINS WITH MINERALS	0		1	(0.9)	1	(0.5)	1.00

RMP.B1YP.JCLLIB2(DTS1JEKF)
RMP.B1YO.HCJEREP(DTS1JEKF)
* Frequencies are analyzed using a Fisher's Exact test.
XDTS0001

11.3. Measurements of Treatment Compliance

Table 11.8 presents a summary of study drug compliance by visit for the entire 19-week subchronic treatment phase, which includes the 9-week acute treatment phase (Study Periods III through V). Compliance with the study drug regimen was assessed by direct questioning and counting returned medication. Patients who missed their study medication for 3 consecutive days at any time during the acute and subchronic treatment phases were deemed noncompliant, but could have remained in the study with the approval of the clinical research physician. The percentage of patients who were compliant with the study drug regimen ranged from a high of 100% at Visit 5 to a low of 94% at Visit 9.

A complete listing of patient compliance with the study drug regimen by visit is presented in Appendix 16.2.6.

Table 11.8. Patient Compliance by Visit
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE

Variable	Flx (N=109)	Placebo (N=110)	Total (N=219)
Compliance (Visit: 5)			
No. Patients	109	109	218
YES	109 (100)	109 (100)	218 (100)
Compliance (Visit: 6)			
No. Patients	109	104	213
YES	109 (100)	102 (98.1)	211 (99.1)
NO	0	2 (1.9)	2 (0.9)
Compliance (Visit: 7)			
No. Patients	109	100	209
YES	107 (98.2)	99 (99.0)	206 (98.6)
NO	2 (1.8)	1 (1.0)	3 (1.4)
Compliance (Visit: 8)			
No. Patients	106	96	202
YES	105 (99.1)	91 (94.8)	196 (97.0)
NO	1 (0.9)	5 (5.2)	6 (3.0)
Compliance (Visit: 9)			
No. Patients	100	87	187
YES	95 (95.0)	80 (92.0)	175 (93.6)
NO	5 (5.0)	7 (8.0)	12 (6.4)
Compliance (Visit: 10)			
No. Patients	94	77	171
YES	92 (97.9)	74 (96.1)	166 (97.1)
NO	2 (2.1)	3 (3.9)	5 (2.9)
Compliance (Visit: 11)			
No. Patients	90	68	158
YES	88 (97.8)	65 (95.6)	153 (96.8)
NO	2 (2.2)	3 (4.4)	5 (3.2)
Compliance (Visit: 12)			
No. Patients	75	64	139
YES	72 (96.0)	61 (95.3)	133 (95.7)
NO	3 (4.0)	3 (4.7)	6 (4.3)

RMP.B1YP.JCLLIB2(DES1JEKG)
RMP.B1YO.HCJEREP(DES1JEKG)
XDES0001

Table 11.8. Patient Compliance by Visit
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE (concluded)

Variable	Flx (N=109)	Placebo (N=110)	Total (N=219)
Compliance (Visit: 13)			
No. Patients	65	57	122
YES	61 (93.8)	55 (96.5)	116 (95.1)
NO	4 (6.2)	2 (3.5)	6 (4.9)
Compliance (Visit: 14)			
No. Patients	57	52	109
YES	53 (93.0)	50 (96.2)	103 (94.5)
NO	4 (7.0)	2 (3.8)	6 (5.5)
Compliance (Visit: 15)			
No. Patients	52	49	101
YES	50 (96.2)	48 (98.0)	98 (97.0)
NO	2 (3.8)	1 (2.0)	3 (3.0)

RMP.B1YP.JCLLIB2(DES1JEKG)
RMP.B1YO.HCJEREP(DES1JEKG)
XDES0001

11.4. Efficacy Results and Tabulations of Individual Patient Data

11.4.1. Analysis of Efficacy

A total of 219 patients were randomized, with 109 patients receiving fluoxetine treatment and 110 patients receiving placebo treatment. The primary efficacy outcome measure was the CDRS-R, which was administered and scored by the investigator. Additional efficacy evaluations were based on the CGI-Severity, CGI-Improvement, BDI, CDI, MADRS, HAMA, GAF, and K-SADS-PL (Affective Disorders module). As the relapse prevention phase (Study Period VI) is ongoing, data from this treatment phase will be presented in a separate clinical study report.

11.4.1.1. Acute Treatment Phase (Study Periods III through IV)

The primary efficacy analysis was a comparison of response rates between fluoxetine-treated and placebo-treated patients. Response was defined as a 30% or greater decrease in the CDRS-R total score from baseline to endpoint of the acute treatment phase. Baseline for the acute treatment phase was Visit 4 and endpoint was last of Visits 6 through 10 (approximately 9 weeks of active drug treatment).

CDRS-R total scores were also evaluated using mean change from baseline to endpoint. Secondary categorical analyses were performed using an alternate criterion for response (based on CGI-Improvement scores) and recovery (based on CDRS-R total and CGI-Improvement scores). A categorical analysis of patients meeting the criteria for

remission (based on CDRS-R total score) was performed. Mean CDRS-R total scores were also evaluated on a visitwise basis and using repeated measures to assess temporal changes in the primary measure.

Secondary continuous analyses included evaluation of the change from baseline to endpoint for the following variables: CDRS-R total, CDRS-R subtotals (Mood, Somatic, Subjective, and Behavior), CGI-Severity, MADRS, CDI, BDI, GAF (Current Functioning), and HAMA scores. An endpoint analysis was performed for CGI-Improvement scores.

Subgroup analyses on the basis of age category, gender, and family history of depression were performed for CDRS-R response, change from baseline to endpoint for CDRS-R total score, and response based on CGI-Improvement scores. Analyses of the acute treatment phase are presented in Section 11.4.2.

11.4.1.2. Analyses of Patients Not Responding to Acute Treatment (Study Period V)

At the end of Study Period IV, response (defined as 30% or greater reduction in CDRS-R total score) was evaluated. Nonresponders were rerandomized, with fluoxetine-treated nonresponders being rerandomized 1:1 to remain on fluoxetine 20 mg/day or increase dose to 40 mg/day with an option to increase further to 60 mg/day. Placebo-treated patients remained on placebo.

To evaluate the effects of dose titration, CDRS-R response as well as mean change in CDRS-R total, CGI-Severity, CDI, and BDI scores from the Study Period V baseline (Visit 4) to endpoint (last of Visits 11 through 15) and endpoint CGI-Improvement scores were compared between treatment groups. Comparisons were made between nonresponders rerandomized to fluoxetine 20 mg/day and nonresponders rerandomized to fluoxetine 40 or 60 mg/day. These analyses are presented in Section 11.4.3.

11.4.1.3. Subchronic Treatment Phase (Study Periods III through V)

Additional analyses of treatment effects for all randomized patients during the 19-week subchronic treatment phase were performed. These analyses were the same as those performed for the 9-week acute treatment phase. Baseline for the subchronic treatment phase was Visit 4 and endpoint was last of Visits 5 through 15. Analyses of the subchronic treatment phase are presented in Section 14.2.3.

11.4.1.4. Additional Analyses

Additional analyses of the primary outcome measure, CDRS-R total response, were performed. These analyses included those patients who received at least 5 weeks of treatment (at least 4 weeks of fluoxetine 20 mg/day). Baseline was Visit 4 and endpoint was the last of Visits 8 through 15.

A categorical analysis of remission rates was conducted in the same manner. The CGI-Efficacy Index and K-SADS-PL (Affective Disorders module) were also analyzed. These results are presented in Section 14.2.2.

11.4.1.5. Baseline Variability

Treatment-group comparisons at baseline (Visit 4) were performed for the primary efficacy scale (CDRS-R), as well as the secondary scales CGI-Severity, MADRS, and HAMA (see Table 11.9).

A CDRS-R total score >40 indicates the presence of moderate to severe depression in children and adolescents who meet diagnostic criteria for MDD (Poznanski et al. 1984). The mean CDRS-R total score at baseline was 57.1 for fluoxetine-treated patients and 55.4 for placebo-treated patients (p=.231).

The mean CGI-Severity score at baseline was 4.5 for fluoxetine-treated patients and 4.4 for placebo-treated patients (p=.037). This difference was not considered to be clinically meaningful. The two treatment groups were comparable with regard to mean scores on both the MADRS and the HAMA at baseline.

Table 11.9. Baseline Psychiatric Evaluation
All Randomized Patients
B1Y-MC-HCJE

Variable	Flx 20 (N=109)	Placebo (N=110)	Total (N=219)	p-Value
CDRS-R Total				
No. Patients	109	110	219	.231**
Mean	57.1	55.4	56.2	
Median	55.0	55.0	55.0	
Standard Dev.	9.9	11.6	10.8	
Minimum	42.0	32.0	32.0	
Maximum	77.0	94.0	94.0	
CGI-Severity				
No. Patients	109	110	219	.037**
Mean	4.5	4.4	4.5	
Median	4.0	4.0	4.0	
Standard Dev.	0.6	0.6	0.6	
Minimum	4.0	3.0	3.0	
Maximum	6.0	6.0	6.0	
MADRS				
No. Patients	109	110	219	.908**
Mean	21.6	21.4	21.5	
Median	22.0	21.0	22.0	
Standard Dev.	7.5	8.3	7.9	
Minimum	3.0	0.0	0.0	
Maximum	38.0	44.0	44.0	
HAMA				
No. Patients	108	110	218	.216**
Mean	10.2	11.1	10.7	
Median	9.0	10.0	10.0	
Standard Dev.	5.1	5.9	5.6	
Minimum	1.0	0.0	0.0	
Maximum	29.0	28.0	29.0	
Unspecified	1	0	1	

RMP.B1YP.JCLLIB2(DES1JEKH)
RMP.B1YO.HCJEREP(DES1JEKH)
** Means are analyzed using a Type III Sum of Squares analysis of variance (ANOVA): PROC GLM model=treatment.
XDES0001

11.4.2. Acute Treatment Phase (Study Periods III-IV)

11.4.2.1. Analysis of Primary Endpoint: Patients Meeting Criteria for CDRS-R Total Response

The number of randomized patients who met response criteria based on CDRS-R total score for the acute treatment phase is summarized in Table 11.10. This analysis includes all patients who were treated at least 1 week with fluoxetine 20 mg/day.

A greater number of fluoxetine-treated patients responded to treatment compared with placebo-treated patients when response was defined as a 30% or greater decrease in CDRS-R total score. A strong numerical trend was observed, with 71 (65%) fluoxetine-treated patients meeting response criteria compared with 54 (54%) placebo-treated patients; however, the difference between treatment groups was not statistically significant (p=.093) for this 9-week treatment period.

A complete data listing of CDRS-R total scores by patient is presented in Appendix 16.2.7.

Table 11.10. CDRS-R Total Score
Number of Patients Meeting Criteria for Response
All Randomized Patients
Acute Treatment Phase (Study Period IV)
B1Y-MC-HCJE

Protocol: B1Y-MC-HCJE
Outcome Variable: RESPONSE - 30% REDUCTION FROM BASELINE
Stratification Variable: INVESTIGATOR (number of strata = 14)

		NO		YES	
Therapy	N	n	%	n	%
A. Flx 20	109	38	34.9	71	65.1
B. Placebo	101	47	46.5	54	53.5

Comparison of All Treatments

STATISTICS	P-VALUE
Fisher's exact test (2-tailed)	0.093
Pearson's chi-square test df=1	0.085
# Cochran-Mantel-Haenszel general association test df=1	0.077

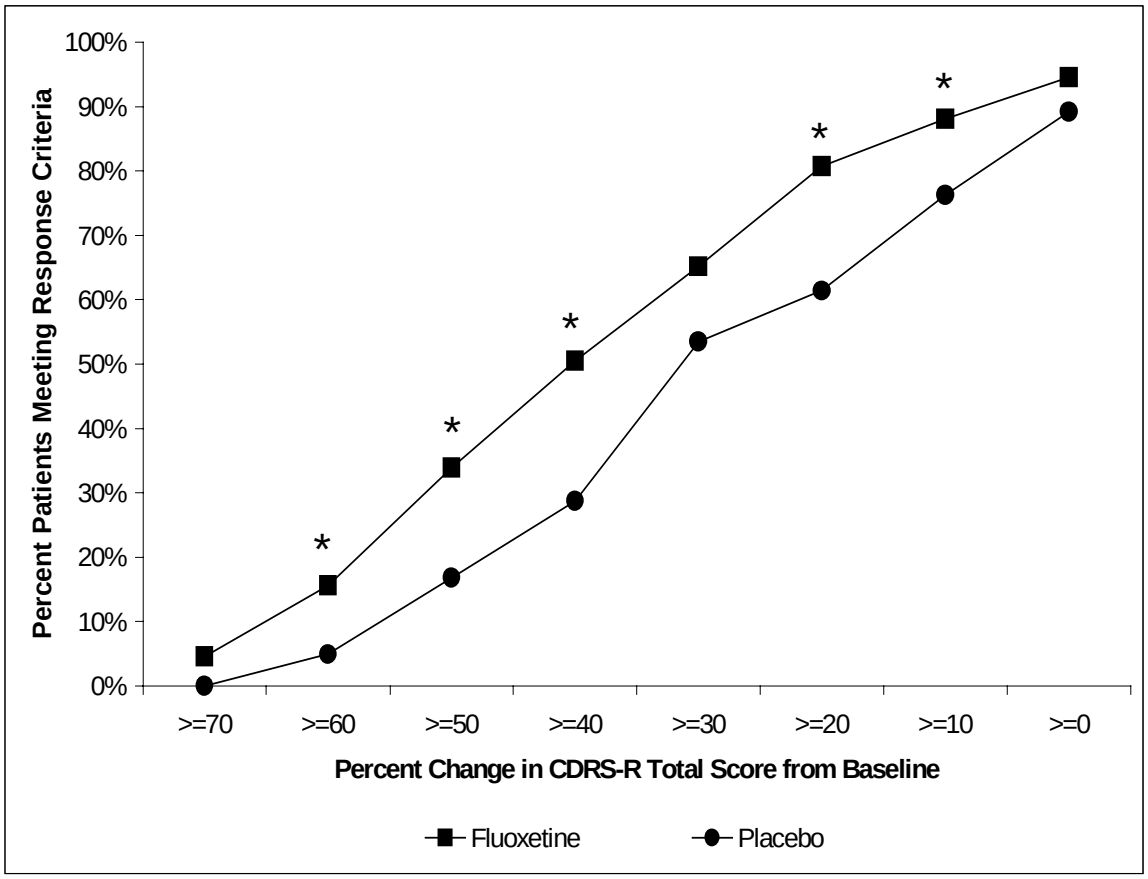
#: Stratification variable included.

Investigators 6 and 17 are pooled into Investigator 999
RMP.B1YP.JCLLIB2(EFS1JEMA)
RMP.B1YO.HCJEREP(EFS1JEMA)
XEFS0001

Figure 11.2 plots the percent of patients who met response criteria (vertical axis) against different possible response criteria (horizontal axis). This plot allows for comparison of response rates between treatment groups when different criteria for response are used. The primary comparison was response, defined as a decrease of 30% or more in CDRS-R total score from baseline to endpoint of the acute treatment phase. This plot also presents response rates for the two treatment groups when response was defined as a decrease of 10%, 20%, 40%, 50%, 60%, and 70% or greater in CDRS-R total score from baseline to endpoint of the acute treatment phase. This graph only displays patients whose change from baseline reduction was ≥0. Six fluoxetine-treated patients and 11 placebo-treated patients were not included because their CDRS-R total scores increased from baseline.

During the acute treatment phase, the fluoxetine treatment group had a consistently greater response rate than the placebo treatment group regardless of the percent change criteria evaluated. The fluoxetine treatment group had statistically significantly greater percentages of patients achieving response than the placebo treatment group for percent change criteria of 10% (p=.030), 20% (p=.002), 40% (p=.002), 50% (p=.007), and 60% (p=.013). The percent change from baseline criteria at which the differences between the fluoxetine and placebo treatment groups are the greatest occurred at the 20% and 40% change criteria. At the 20% change criteria, 81% of fluoxetine-treated patients responded

to treatment as compared with 61% of placebo-treated patients. At the 40% change criteria, 50% of fluoxetine-treated patients responded to treatment as compared with 29% of placebo-treated patients.



Data for this figure were taken from RMP.B1YSHCJE.SASPGM (CDRSRSP3.SAS).
*Statistically significant difference between treatment groups.

Figure 11.2. **Percent change distribution in CDRS-R total score for all randomized patients during the acute treatment phase (Study Period IV) of B1Y-MC-HCJE.**

11.4.2.2. Additional Analyses of CDRS-R

11.4.2.2.1. Remission

The number of patients meeting criteria for remission during the acute treatment phase is presented in Table 11.11. Remission was defined as an endpoint CDRS-R total score ≤28.

A statistically significant difference between treatment groups was observed, with twice as many fluoxetine-treated patients meeting criteria for remission as compared with placebo-treated patients. Forty-five (41%) fluoxetine-treated patients met remission criteria compared with 20 (20%) placebo-treated patients ($p<.01$).

Table 11.11. CDRS-R Total Score
Number of Patients Meeting Criteria for Remission
All Randomized Patients
Acute Treatment Phase (Study Period IV)
B1Y-MC-HCJE

```
Protocol: B1Y-MC-HCJE
Outcome Variable: REMISSION - SCORE <=28
Stratification Variable: INVESTIGATOR (number of strata = 14)

                                                NO                YES
   Therapy                  N              n        %         n        %
-- ------------------    -------        ------ ----------  ------ ----------
A. Flx 20                  109            64      58.7       45      41.3
B. Placebo                 101            81      80.2       20      19.8

COMPARISON OF TREATMENT GROUPS

STATISTICS                            VALUE      P-VALUE
------------------------------    ----------- -----------
Fisher's exact test                                <0.01
   (2-tailed)
Pearson's chi-square test              11.3       <0.01
   df=1
# Cochran-Mantel-Haenszel              12.0       <0.01
   general association test
   df=1

#: Stratification variable included.


Investigators 6 and 17 are pooled into Investigator 999
RMP.B1YP.JCLLIB2(EFS1JEME)
RMP.B1YO.HCJEREP(EFS1JEME)
XEFS0001
```

11.4.2.2.2. Mean Change from Baseline to Endpoint

Table 11.12 presents a summary of the mean change from baseline to endpoint for CDRS-R total and subtotal scores during the acute treatment phase.

A statistically significant difference between treatment groups was observed, with fluoxetine-treated patients experiencing a mean reduction in CDRS-R total score of 22 points, while placebo-treated patients experienced a mean reduction of 15 points ($p<.001$).

Statistically significant differences between treatment groups were also observed in all four CDRS-R subtotal scores (Mood, Somatic, Subjective, and Behavior), with fluoxetine-treated patients consistently exhibiting greater reductions compared with placebo-treated patients.

In addition, the 17 individual items of the CDRS-R were analyzed for change from baseline and are summarized in Table 14.2 (see Section 14.2.1.1). Fluoxetine-treated patients experienced statistically significantly greater improvement on 8 of the 17 items as compared with placebo-treated patients. These items included fun (2), social withdrawal (3), physical complaints (7), irritability (8), self-esteem (10), depressed (11),

depressed affect (15), and speech (16). Eight of the remaining items favored fluoxetine, although the results were not statistically significant.

Table 11.12. **CDRS-R Scores**
Change from Baseline to Endpoint
All Randomized Patients
Acute Treatment Phase (Study Periods III-IV)
B1Y-MC-HCJE

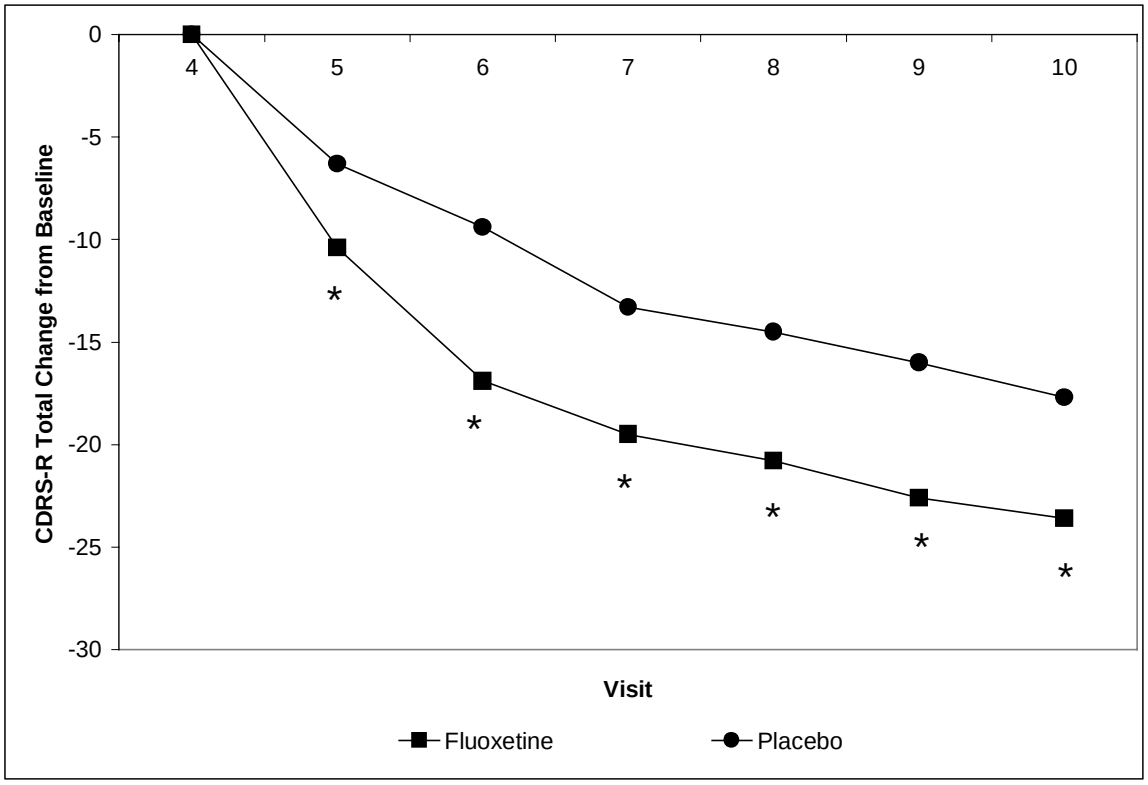
Variable	Therapy	n	Baseline Mean	Baseline SD	Endpoint Mean	Endpoint SD	Change Mean	Change SD	p-Value *1
TOTAL	Flx 20	109	57.1	9.9	35.1	13.5	-22.1	14.4	<.001
	Placebo	105	55.1	11.8	40.2	13.5	-14.9	13.3	
MOOD SUBTOTAL	Flx 20	109	15.9	4.0	9.4	4.7	-6.6	5.3	.002
	Placebo	105	15.4	4.8	11.2	5.0	-4.3	5.4	
SOMATIC SUBTOTAL	Flx 20	109	17.2	4.5	10.7	4.2	-6.5	5.2	.004
	Placebo	105	17.0	4.3	12.6	4.9	-4.5	4.8	
SUBJECTIVE SUBTOTAL	Flx 20	109	11.1	3.0	7.2	2.9	-3.9	3.6	.026
	Placebo	105	10.8	3.3	7.9	2.5	-2.9	3.1	
BEHAVIOR SUBTOTAL	Flx 20	109	12.9	2.9	7.8	4.0	-5.1	3.7	<.001
	Placebo	105	11.9	3.2	8.6	3.7	-3.3	3.7	

*1 Type III Sums of Squares from an analysis of variance (ANOVA): PROC GLM model=treatment.
RMP.B1YP.JCLLIB2(LAS3JEAA)
RMP.B1YO.HCJEREP(LAS3JEAA)

11.4.2.2.3. By-Visit Analyses

Figure 11.3 displays the mean endpoint for the CDRS-R total score for both treatment groups by visit (observed cases) during the acute treatment phase.

Fluoxetine-treated patients consistently demonstrated a greater reduction in CDRS-R total score from baseline compared with placebo-treated patients throughout the acute treatment phase. These differences were statistically significant at all visits from Visits 5 through 10 (see Section 14.2.3.2.3.). Additional detail about the visitwise and repeated measures analyses of the acute and subchronic treatment phases are presented in Section 14.2.3.2.4.



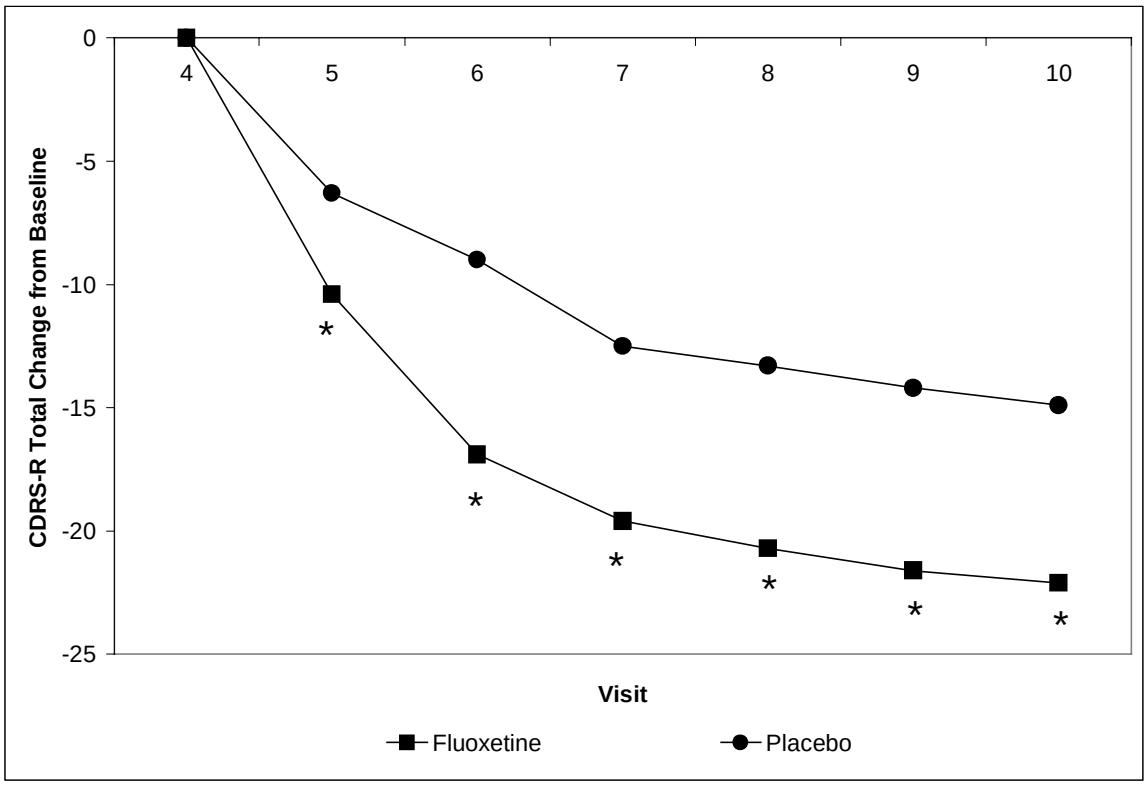
Data for this figure were taken from RMP.B1YO.HCJEREP (PRCNJEAQ).
*Statistically significant difference between treatment groups.

Figure 11.3. CDRS-R total score versus visit (observed cases) by treatment group for the acute treatment phase (Study Periods III-IV) of B1Y-MC-HCJE.

Figure 11.4 displays the mean endpoint CDRS-R total score for both treatment groups by visit using LOCF analysis for the acute treatment phase. For the LOCF analysis, all patients' last available measure was carried forward for analysis at each visit.

As seen in the observed cases analysis, the LOCF analysis indicates that fluoxetine-treated patients had statistically significantly greater improvement in CDRS-R total scores compared with placebo-treated patients starting at Visit 5 and persisting

throughout the acute treatment phase (Visit 10) (see Section 14.2.3.2.3.). Fluoxetine-treated patients demonstrated consistently greater decreases from baseline to endpoint compared with placebo-treated patients.



Data for this figure taken from RMP.B1YO.HCJEREP (PRCNJEAR).
*Statistically significant difference between treatment groups.

Figure 11.4. CDRS-R total score versus visit (LOCF) by treatment group for the acute treatment phase (Study Periods III-IV) of B1Y-MC-HCJE.

Additional detail about the visitwise and repeated measures analyses of the acute and subchronic treatment phases are presented in Section 14.2.3.2.4.

11.4.2.3. Secondary Efficacy Measures

Secondary analyses were conducted for CGI-Improvement endpoint scores, response based on CGI-Improvement scores, and recovery based on CDRS-R total and CGI-Improvement scores. These analyses are presented in Tables 11.13, 11.14, and 11.15, respectively.

The CGI-Improvement scale measures total improvement in direct comparison to the patient's condition at baseline. A statistically significant difference between treatment groups was observed with respect to this measure, with fluoxetine-treated patients having lower endpoint scores than placebo-treated patients (p=.025). CGI-Improvement scores were also used to determine response, defined as a score of 1 (very much improved) or 2

(much improved) at the endpoint of the acute treatment phase. A statistically significant difference between treatment groups was also observed on this measure, with a greater number of fluoxetine-treated patients meeting criteria for response compared with placebo-treated patients (p=.028).

Recovery, defined as a CDRS-R total score ≤28 combined with an endpoint CGI-Improvement score of 1 (very much improved) or 2 (much improved) at the endpoint of the acute treatment phase, was also evaluated. A statistically significant difference between treatment groups was again observed, with a greater number of fluoxetine-treated patients meeting criteria for recovery compared with placebo-treated patients (p<.01).

Table 11.13. CGI-Improvement Score
Endpoint Analysis
All Randomized Patients
Acute Treatment Phase (Study Periods III-IV)
B1Y-MC-HCJE

Variable	Flx 20 (N=109)	Placebo (N=110)	Total (N=219)	p-Value
CGI-Improvement Score				
No. Patients	109	106	215	.025**
Mean	2.50	2.86	2.67	
Median	2.00	3.00	3.00	
Standard Dev.	1.29	1.06	1.19	
Minimum	1.00	1.00	1.00	
Maximum	7.00	6.00	7.00	

RMP.B1YP.JCLLIB2(DES1JEAJ)
RMP.B1YO.HCJEREP(DES1JEAJ)
RMP.SAS.B1YM.USM037
B1Y98032
** Means are analyzed using a Type III Sum of Squares analysis of variance (ANOVA): PROC GLM model=treatment.
XDES0001

Table 11.14. CGI-Improvement Score
Number of Patients Meeting Criteria for Response
All Randomized Patients
Acute Treatment Phase (Study Periods III-IV)
B1Y-MC-HCJE

Protocol: B1Y-MC-HCJE
Outcome Variable: RESPONSE - SCORE = 1 OR 2
Stratification Variable: INVESTIGATOR (number of strata = 14)

		NO		YES	
Therapy	N	n	%	n	%
A. Flx	109	52	47.7	57	52.3
B. Placebo	106	67	63.2	39	36.8

COMPARISON OF TREATMENT GROUPS

STATISTICS	VALUE	P-VALUE
Fisher's exact test (2-tailed)		0.028
Pearson's chi-square test df=1	5.2	0.022
# Cochran-Mantel-Haenszel general association test df=1	5.2	0.023

#: Stratification variable included.

Investigators 6 and 17 are pooled into Investigator 999
RMP.B1YP.JCLLIB2(EFS1JEMF)
RMP.B1YO.HCJEREP(EFS1JEMF)
XEFS0001

Table 11.15. CDRS-R Total and CGI-Improvement Scores
Number of Patients Meeting Criteria for Recovery
All Randomized Patients
Acute Treatment Phase (Study Period IV)
B1Y-MC-HCJE

Protocol: B1Y-MC-HCJE
Outcome Variable: RECOVERY - CDRS-R <=28 AND CGI-IMPROVEMENT = 1 OR 2
Stratification Variable: INVESTIGATOR (number of strata = 14)

		NO		YES	
Therapy	N	n	%	n	%
A. Flx 20	109	66	60.6	43	39.4
B. Placebo	101	81	80.2	20	19.8

COMPARISON OF TREATMENT GROUPS

STATISTICS	VALUE	P-VALUE
Fisher's exact test (2-tailed)		<0.01
Pearson's chi-square test df=1	9.6	<0.01
# Cochran-Mantel-Haenszel general association test df=1	11.0	<0.01

#: Stratification variable included.

Investigators 6 and 17 are pooled into Investigator 999
RMP.B1YP.JCLLIB2(EFS1JEAC)
RMP.B1YO.HCJEREP(EFS1JEAC)
XEFS0001

11.4.2.4. Subgroup Analyses

11.4.2.4.1. CDRS-R Total Response

Subgroup analyses were performed to examine the consistency of treatment effect over subgroups of various demographic populations during the acute treatment phase. The subgroups examined included age category (8 to <13 years, 13 to <18 years), gender (female, male), and family history of depression (positive, negative). For this study, a decision was made to use age rather than pubertal status to delineate children from adolescents because of FDA Guidances in effect at the time this study was designed. Consequently, children were defined as patients aged 8 to <13 years old and adolescents as patients aged 13 to <18 years old.

The number of patients meeting response criteria (based on CDRS-R total score) during the acute treatment phase was examined by the three subgroups (see Table 11.16). Response was defined as a reduction in CDRS-R total score of at least 30% from baseline (Visit 4) to endpoint (last of Visits 6 through 10). This analysis includes all patients who were treated at least 1 week with fluoxetine 20 mg/day.

The Breslow-Day test for homogeneity of odds ratios was not statistically significant for any of the strata examined. There were no statistically significant differences between treatment groups for age, gender, or family history of depression.

Table 11.16. CDRS-R Total Score
Number of Patients Meeting Criteria for Response
Efficacy Subgroup Analysis, All Randomized Patients
Acute Treatment Period (Study Period IV)
B1Y-MC-HCJE

		Fluoxetine			Placebo				Between Group
Subgroup of Interest	Subgroup	N	n	%	N	n	%	Homogeneity of Odds Ratio p-Value[a]	Comparison Within Subgroup p-Value[b]
Age	8 to <13	61	42	69	55	30	55	.629	.128
	13 to <18	48	29	60	46	24	52		.533
Gender	Female	54	39	72	48	30	63	.897	.397
	Male	55	32	58	53	24	45		.248
Family History of Depression	Yes	61	42	69	57	34	60	.809	.339
	No	41	26	63	34	17	50		.348

Data were taken from RMP.B1YO.HCJEREP (EFS1JEMI).
[a]The homogeneity of odds ratio p-Value is taken from the Breslow-Day test.
[b]The between group comparison p-Value is taken from the Fisher's Exact test.

11.4.2.4.2. CDRS-R Total Score

Table 11.17 summarizes the ANOVA of the change from baseline to endpoint for the CDRS-R total score for the three different strata during the acute treatment phase. A statistical model was fit with the strata main effect, treatment, and the interaction between strata and treatment. In addition, an ANOVA was performed within each subgroup comparing the two treatment groups. The gender category showed a statistically significant (p=.031) effect, with female patients showing a greater response than male patients.

Fluoxetine-treated patients consistently showed a numerically greater response as compared with placebo-treated patients across all subgroups. These findings were statistically significant for all subgroups, except for adolescents.

Table 11.17. CDRS-R Total Score
Change from Baseline to Endpoint
Efficacy Subgroup Analysis, All Randomized Patients
Acute Treatment Phase (Study Periods III-IV)
B1Y-MC-HCJE

Subgroup of Interest	Therapy by Subgroup Interaction[a]	Subgroup Main Effect	Subgroup	Therapy	Baseline N	Baseline Mean	Baseline SD	Change Mean	Change SD	Therapy p-Value[a]
Age (years)	.371	.613	8 to <13	Flx	61	55.2	9.0	-22.4	14.2	<.001
				Placebo	59	53.0	11.9	-13.7	12.7	
			13 to <18	Flx	48	59.6	10.5	-21.6	14.8	.083
				Placebo	46	57.9	11.1	-16.4	14.0	
Gender	.632	.031	Female	Flx	54	58.8	10.3	-24.6	14.3	.003
				Placebo	50	57.1	11.9	-16.6	12.6	
			Male	Flx	55	55.5	9.3	-19.6	14.2	.023
				Placebo	55	53.3	11.4	-13.4	13.8	
Family History of Depression	.493	.745	Yes	Flx	61	56.6	9.4	-22.2	13.4	.015
				Placebo	59	55.5	12.1	-16.3	12.8	
			No	Flx	41	59.2	10.4	-23.0	16.2	.015
				Placebo	36	56.9	11.4	-14.3	14.2	

Data for this table were taken from RMP.B1YSHCJE.SASPGM (EFFMOD).
[a]Type III Sum of Squares used.
PROC GLM model = therapy for the therapy p-value within stratum.
PROC GLM model = therapy, subgroup, and therapy by subgroup for interaction and subgroup p-values.
Abbreviations: Flx = fluoxetine; SD = Standard deviation.

11.4.2.4.3. CGI-Improvement Score

Table 11.18 summarizes the ANOVA of the endpoint CGI-Improvement score for the three different strata during the acute treatment phase. The subgroup based on family history of depression showed a statistically significant effect; patients with a positive family history of depression showed lower endpoint scores than patients with a negative family history of depression (p=.026).

Fluoxetine-treated patients consistently showed a numerically greater response as compared with placebo-treated patients across all subgroups. These responses were statistically significant for female patients (p=.019) and patients with a positive family history of depression (p=.007).

Table 11.18. CGI-Improvement Score
Endpoint Analysis
Efficacy Subgroup Analysis, All Randomized Patients
Acute Treatment Phase (Study Periods III-IV)
B1Y-MC-HCJE

Subgroup of Interest	Therapy by Subgroup Interaction[a]	Subgroup Main Effect	Subgroup	Therapy	Endpoint N	Endpoint Mean	Endpoint SD	Therapy p-Value[a]
Age (years)	.959	.919	8 to <13	Flx	61	2.49	1.46	.126
				Placebo	59	2.85	1.03	
			13 to <18	Flx	48	2.50	1.05	.094
				Placebo	47	2.87	1.10	
Gender	.379	.072	Female	Flx	54	2.28	1.05	.019
				Placebo	50	2.78	1.09	
			Male	Flx	55	2.71	1.46	.361
				Placebo	56	2.93	1.02	
Family History of Depression	.290	.026	Yes	Flx	61	2.26	1.06	.007
				Placebo	59	2.80	1.06	
			No	Flx	41	2.83	1.51	.575
				Placebo	37	3.00	1.11	

Data for this table were taken from RMP.B1YSHCJE.SASPGM (CGIMOD).
[a]Type III Sum of Squares used.
PROC GLM model = therapy for the therapy p-value within subgroups.
PROC GLM model = therapy, subgroup, and therapy by strata for interaction and subgroup p-values.
Abbreviations: Flx = fluoxetine; SD = Standard deviation.

11.4.2.5. Additional Secondary Efficacy Endpoints

The mean change from baseline scores were compared between treatment groups for the CGI-Severity, BDI total, CDI total, MADRS total, HAMA total, and GAF (Current Functioning). These results are presented in Table 11.19. The sample sizes for the BDI and CDI are small because the BDI was only administered to adolescents (ages 13 to <18) and the CDI was only administered to children (ages 8 to <13).

Changes in CGI-Severity scores were statistically significantly different between the two treatment groups, with fluoxetine-treated patients experiencing greater reductions in the severity of their illness compared with placebo-treated patients ($p<.001$). Although the MADRS has not been validated for use in children and adolescents, a statistically significant difference between treatment groups was also observed with respect to this measure. Fluoxetine-treated patients demonstrated greater reductions in MADRS scores compared with placebo-treated patients ($p=.023$).

Fluoxetine-treated patients demonstrated greater numerical reductions in the change from baseline for HAMA total and GAF (Current Functioning) scores compared with placebo-treated patients; however, the differences were not statistically significant.

Placebo-treated patients exhibited greater numerical reductions in the change from baseline for CDI and BDI total scores compared with fluoxetine-treated patients. The difference between treatment groups was not statistically significant.

By-patient listings for CGI-Severity, BDI total, CDI total, MADRS total, HAMA total, and GAF (Current Functioning) scores are located in Appendix 16.2.7.

Table 11.19. **Secondary Efficacy Variables**
Change from Baseline to Endpoint
All Randomized Patients
Acute Treatment Phase (Study Periods III-IV)
B1Y-MC-HCJE

Variable	Therapy	n	Baseline Mean	Baseline SD	Endpoint Mean	Endpoint SD	Change Mean	Change SD	p-Value *1
CGI Severity	Flx 20	109	4.5	0.6	2.9	1.2	-1.6	1.3	<.001
	Placebo	106	4.4	0.6	3.4	1.1	-1.0	1.1	
BDI Total	Flx 20	46	15.5	11.1	10.9	11.8	-4.6	8.2	.700
	Placebo	38	16.6	11.6	11.3	9.3	-5.3	7.8	
CDI Total	Flx 20	56	9.2	8.3	6.8	9.1	-2.4	9.0	.822
	Placebo	53	8.4	9.3	5.6	5.4	-2.8	6.8	
MADRS Total	Flx 20	109	21.6	7.5	11.2	9.0	-10.4	9.4	.023
	Placebo	105	21.5	8.3	13.9	8.2	-7.6	8.4	
HAMA Total	Flx 20	106	10.2	5.2	5.4	4.7	-4.8	5.2	.115
	Placebo	94	11.0	5.8	7.4	5.2	-3.7	5.2	
GAF: Current Functioning	Flx 20	104	53.3	6.7	64.8	12.4	11.5	11.7	.176
	Placebo	86	54.6	7.1	63.9	9.8	9.3	10.3	

* 1 Type III Sums of Squares from an analysis of variance (ANOVA): PROC GLM model=treatment.
RMP.B1YP.JCLLIB2(LAS3JEAC)
RMP.B1YO.HCJEREP(PRCNJEAC)

11.4.3. Analysis of Patients Not Responding to Acute Treatment (Study Period V)

At the end of Study Period IV, all patients were classified as responders (30% or greater decrease in CDRS-R total score) or non-responders (<30% decrease in CDRS-R total score). Placebo-treated patients remained on placebo. Fluoxetine-treated patients who met response criteria continued to receive fluoxetine 20 mg/day. Fluoxetine-treated patients who did not meet response criteria (n=29) were rerandomized (1:1) at Visit 10 to either remain on fluoxetine 20 mg/day or to increase dose to fluoxetine 40 mg/day. Four weeks later (at Visit 12), patients who did not respond to fluoxetine 40 mg/day (based on CGI-Improvement score) were allowed to further increase dose to fluoxetine 60 mg/day for the remainder of Study Period V.

All analyses of nonresponders in Study Period V (Visits 10 through 15) compared the variable of interest between the fluoxetine 20 mg/day treatment group (n=15) and the fluoxetine 40 mg/day and 60 mg/day treatment groups combined (n=14). These analyses evaluated the effectiveness of increasing dose in patients not responding to acute treatment with fluoxetine 20 mg/day.

Table 11.20 summarizes the number of patients meeting criteria for response (based on CDRS-R total score) for all nonresponders during Study Period V. This analysis includes a total of 28 patients. One patient treated with fluoxetine 20 mg/day was not included in the analyses of CDRS-R because the patient did not have postbaseline data for this study period. Twice as many patients in the fluoxetine 40 or 60 mg/day treatment group (10 of 14, 71%) met protocol-specific response criteria when compared with patients in the 20 mg/day treatment group (5 of 14, 36%). The difference between treatment groups was clinically relevant, although this finding did not achieve statistical significance (p=.128).

Table 11.20. CDRS-R Total Score
Number of Patients Meeting Criteria for Response
All Nonresponders with Study Period V Data
Study Period V, B1Y-MC-HCJE

```
Protocol: B1Y-MC-HCJE
Outcome Variable: RESPONSE-30% REDUCTION FROM BASELINE
Stratification Variable: INVESTIGATOR (number of strata = 12)

                                                NO                YES
   Therapy                  N             n        %         n        %
-- ------------------    -------       ------ ----------  ------ ----------
A. Flx 20                   14             9      64.3        5      35.7
B. Flx40/60                 14             4      28.6       10      71.4

COMPARISON OF TREATMENT GROUPS

STATISTICS                            VALUE      P-VALUE
------------------------------    ----------- -----------
Fisher's exact test                                0.128
   (2-tailed)
Pearson's chi-square test             3.590       0.058
   df=1
$# Cochran-Mantel-Haenszel            2.513       0.113
   general association test
   df=1

#: Stratification variable included.
$: Based on TABLE Scores.


Investigators 6 and 17 are pooled into Investigator 999
RMP.B1YP.JCLLIB2(EFS1JEAG)
RMP.B1YO.HCJEREP(EFS1JEAG)
XEFS0001
```

The mean change from baseline to endpoint for CDRS-R total, BDI total, CDI total, and CGI-Severity scores for all nonresponders during Study Period V are summarized in Table 11.21.

Nonresponding patients who had their dose increased to fluoxetine 40 or 60 mg/day achieved much greater reductions in CDRS-R total scores from baseline to endpoint (-9.4 points) as compared with nonresponding patients who remained on fluoxetine 20 mg/day (1.5 points). Once again, this finding was clinically relevant, although it was not statistically significant (p=.099).

The mean change from baseline to endpoint results for the BDI total and CGI-Severity scores also showed greater reductions for the fluoxetine 40 to 60 mg/day treatment group compared with the fluoxetine 20 mg/day treatment group. None of these differences were statistically significant.

The CDI total score increased from baseline for both treatment groups, with the fluoxetine 40 to 60 mg/day treatment group exhibiting a greater increase compared with the fluoxetine 20 mg/day treatment group. No statistically significant difference between treatment groups was observed.

Table 11.21. **Efficacy Scores**
Change from Study Period V Baseline to Endpoint
All Nonresponders with Study Period V Data
Study Period V, B1Y-MC-HCJE

Variable	Therapy	n	Baseline Mean	Baseline SD	Endpoint Mean	Endpoint SD	Change Mean	Change SD	p-Value *1
CDRS-R Total	Flx 20	14	42.7	9.6	41.2	15.5	-1.5	13.7	.099
	Flx40/60	14	46.9	12.7	37.4	13.2	-9.4	10.6	
BDI Total	Flx 20	4	3.0	2.9	1.0	0.8	-2.0	2.7	.337
	Flx40/60	9	20.1	12.3	14.1	12.2	-6.0	7.6	
CDI Total	Flx 20	10	7.7	8.6	9.3	14.6	1.6	7.8	.611
	Flx40/60	5	3.6	3.8	7.4	7.2	3.8	7.4	
CGI Severity	Flx 20	14	3.6	0.8	3.4	1.1	-0.2	1.1	.401
	Flx40/60	14	3.9	0.8	3.4	1.0	-0.6	1.1	

*1 Type III Sums of Squares from analysis of variance (ANOVA): PROC GLM model=treatment
RMP.B1YP.JCLLIB2(LAS3JEAP)
RMP.B1YO.HCJEREP(LAS3JEAP)

Table 11.22 presents CGI-Improvement endpoint scores for all nonresponders during Study Period V. Patients in the fluoxetine 40 to 60 mg/day treatment group exhibited a numerically lower endpoint score (2.8), indicating greater improvement, compared with patients in the fluoxetine 20 mg/day treatment group (3.3). The difference between treatment groups was not statistically significant.

Table 11.22. CGI-Improvement Score Endpoint Analysis All Nonresponders with Study Period V Data Study Period V, B1Y-MC-HCJE

Variable	Flx 20 (N=15)	Flx40/60 (N=14)	Total (N=29)	p-Value
CGI-Improvement Score				
No. Patients	14	14	28	.303**
Mean	3.29	2.79	3.04	
Median	3.00	2.50	3.00	
Standard Dev.	1.49	0.97	1.26	
Minimum	1.00	2.00	1.00	
Maximum	5.00	5.00	5.00	

RMP.B1YP.JCLLIB2(DES1JEAE)
RMP.B1YO.HCJEREP(DES1JEAE)
** Means are analyzed using a Type III Sum of Squares analysis of variance (ANOVA): PROC GLM model=treatment.
XDES0001

11.4.4. Statistical/Analytical Issues

Please refer to Sections 9.7.1 and Appendix 16.1.6 for further details regarding statistical methodology.

11.4.4.1. Adjustments for Covariates

All analyses presented only included treatment in the model. All primary and secondary analyses are presented in a summary table (see Table 14.34), including ranked analyses of the endpoints. Alternative statistical models that include covariates were also analyzed and are presented in Section 14.2.4. Tables 14.35 through 14.37 present these alternative models. Table 14.35 presents the results of ANOVA with investigator, age group (children/adolescents), gender, and treatment-by-investigator in the model for all continuous outcome measurements. In general, the investigator-by-treatment interaction was not significant; therefore, in Table 14.36, the results of the analyses excluding the investigator-by-treatment term are presented.

The conclusions from the primary analysis (with treatment in the model) did not differ from conclusions made when analyzing the data while adjusting for the covariates; that is, when treatment was statistically significant using the primary model, it was also statistically significant using the alternative model. There were two instances when

statistical significance was not obtained for the primary model but was obtained for the secondary model. For the subchronic treatment phase, there was not a statistically significant difference between treatment groups for either CDRS-R Mood subtotal (p=.055) or CDI (p=.068); however, there were statistically significant differences when including covariates of investigator, age group, and gender (CDRS-R Mood subtotal p=.025, CDI p=.012). Generally, both covariates of gender and age group were not statistically significant. Table 14.37 presents another alternative model with treatment and investigator in the model. Again, conclusions did not differ substantially compared with the primary analysis.

11.4.4.2. Handling of Dropouts or Missing Data

For the majority of analyses, the endpoint or change to endpoint (the last available measure from the postbaseline visit period) was analyzed. All patients were included in the analysis unless there was no baseline score or the patient dropped out prior to recording of a postbaseline score.

11.4.4.3. Interim Analyses and Data Monitoring

In order to provide as much long-term data as possible, an interim analysis was performed after all patients completed the 19-week subchronic treatment phase (end of Study Period V), rather than after all patients completed the 9-week acute treatment phase (end of Study Period IV) as planned. A data monitoring board (DMB) was formed to review this data. The DMB decided to maintain blinding except for those individuals involved in the preparation of this clinical study report and those necessary for strategic planning. Data for patients who completed Study Period V are considered final. As the relapse prevention phase (Study Period VI) is ongoing, data for this treatment phase will be presented in a separate clinical study report. The blinding plan and DMB information are presented in Appendix 16.1.14.

11.4.4.4. Multicenter Studies

A total of 19 investigators were recruited for this study. Four investigators never randomized patients. Investigator 6 did not randomize any patients to fluoxetine treatment and only randomized 1 patient to placebo treatment. As specified in the protocol, investigators who did not randomize patients into one or more treatment groups were to be pooled for statistical analysis purposes. Since no other investigator experienced this situation, Investigator 6 was pooled with the next lowest enroller, Investigator 17. As a result of this pooling, all by-investigator analyses include 14 investigators. All by-investigator analyses are presented in Sections 14.2.1.2 and 14.2.3.6. All analyses showed similar results across the investigators.

11.4.4.5. Multiple Comparisons/Multiplicity

Two treatment groups were analyzed in this study. No adjustments were made to the p-values for multiple comparisons.

11.4.4.6. Use of an "Efficacy Subset" of Patients

All analyses were performed on an intent-to-treat population. Nine patients were not included in the primary analysis due to missing a postbaseline measurement. Details about these patients are presented in Appendix 16.2.4. Empty Not totally, see p2536

11.4.5. Tabulation of Individual Response Data

By-patient data listings for all efficacy measures are located in Appendix 16.2.7. Empty

11.4.6. By-Patient Displays

No additional by-patient displays were evaluated.

11.4.7. Efficacy Conclusions

The primary efficacy objective of Study B1Y-MC-HCJE was to evaluate the efficacy of fluoxetine 20 mg/day versus placebo during the acute treatment (9 weeks) of MDD in child and adolescent outpatients. An important secondary objective was the comparison of different dosing strategies in patients who did not respond to acute treatment with fluoxetine 20 mg/day. Another secondary objective was an evaluation of the efficacy of fluoxetine 20 to 60 mg/day versus placebo during subchronic treatment (19 weeks). This summary will address the efficacy findings from these study objectives. It will not address the findings from a final important secondary objective, the ongoing study of relapse prevention (Study Period VI). These analyses will be presented in a separate clinical study report.

As MDD is difficult to diagnose properly in children and adolescents, patients in this study were extensively evaluated on three separate occasions by three experienced clinicians during a 2-week baseline assessment period (Study Period I). This comprehensive evaluation ensured that patients met DSM-IV criteria for MDD. Comorbid psychiatric diagnoses were identified through the use of structured and semi-structured interviews.

A total of 219 patients were randomized to treatment, with 109 patients receiving fluoxetine treatment and 110 patients receiving placebo treatment. Randomization was stratified to achieve treatment groups that were balanced for gender and age. The mean age was 12.7 years and the mean age of onset of MDD was 10.3 years. The patients randomized to treatment were predominantly Caucasian (82%). The mean CDRS-R total score at baseline was 57.1 for fluoxetine-treated patients and 55.4 for placebo-treated patients (p=.231), indicating that patients in both treatment groups had moderate to severe depression.

The primary efficacy outcome measure for this study was the CDRS-R, a 17-item investigator-administered questionnaire that is modeled after the Hamilton Depression Rating Scale, a frequently used investigator-rated instrument assessing depression severity in adult depression clinical trials (Hamilton 1960). The primary efficacy

analysis was a comparison of response rates between fluoxetine-treated and placebo-treated patients during acute treatment (9 weeks). Response was defined as a reduction of 30% or more from baseline CDRS-R total score. While the definition of response was based on sound scientific rationale, no standard measure for response exists for pediatric patients.

Table 11.23 summarizes the categorical efficacy results for the acute and subchronic treatment phases. The continuous efficacy results for both treatment phases are summarized in Table 11.24.

Table 11.23 Categorical Efficacy Analyses All Randomized Patients B1Y-MC-HCJE

	Acute Treatment (Study Periods III-IV)			Subchronic Treatment (Study Periods III-V)		
Measure	Flx 20 (%)	Placebo (%)	p-Value[a]	Flx 20-60 (%)	Placebo (%)	p-Value[a]
CDRS-R Total Response[b]	65	54	.093	75	60	.026
CDRS-R Total Remission[c]	41	20	<.01	51	46	.493
CGI-Improvement Response[d]	52	37	.028	63	52	.099
Recovery Rate[e]	39	20	<.01	51	46	.493

Data for this table were taken from RMP.B1YO.HCJEREP (EFS1JEMA), RMP.B1YO.HCJEREP (EFS1JEMB), RMP.B1YO.HCJEREP (EFS1JEME), RMP.B1YO.HCJEREP (EFS1JEAA), RMP.B1YO.HCJEREP (EFS1JEMF), RMP.B1YO.HCJEREP (EFS1JEAB), RMP.B1YO.HCJEREP (EFS1JEAC), and RMP.B1YO.HCJEREP (EFS1JEAD).

[a]Fisher's exact test.

[b]Response- 30% or greater reduction in CDRS-R total score from baseline to endpoint.

[c]Remission- endpoint CDRS-R total score ≤28.

[d]CGI-Improvement Response- endpoint score of 1 (very much improved) or 2 (much improved).

[e]Recovery- CDRS-R total score ≤28 combined with an endpoint CGI-Improvement score of 1 (very much improved) or 2 (much improved).

Abbreviations: CDRS-R = Children's Depression Rating Scale- Revised; CGI = Clinical Global Impression; Flx = fluoxetine.

Table 11.24. Continuous Efficacy Analyses All Randomized Patients B1Y-MC-HCJE

Measure	Acute Treatment (Study Periods III-IV) p-Value	Subchronic Treatment (Study Periods III-V) p-Value
CDRS-R Total Mean Change	<.001	.021
CDRS-R Mood Subtotal Mean Change	.002	.055
CDRS-R Somatic Subtotal Mean Change	.004	.181
CDRS-R Subjective Subtotal Mean Change	.026	.078
CDRS-R Behavior Subtotal Mean Change	<.001	.011
CGI-Improvement Endpoint Score	.025	.323
CGI-Severity Mean Change	<.001	.025
BDI Total Mean Change	.700	1.00
CDI Total Mean Change	.822	.068
MADRS Total Mean Change	.023	.212
HAMA Total Mean Change	.115	.669
GAF: Current Functioning Mean Change	.176	.803

Data for this table were taken from RMP.B1YO.HCJEREP (LAS3JEAA), RMP.B1YO.HCJEREP (LAS3JEAB), RMP.B1YO.HCJEREP (DES1JEAJ), RMP.B1YO.HCJEREP (DES1JEAG), RMP.B1YO.HCJEREP (PRCNJEAC), and RMP.B1YO.HCJEREP (PRCNJEAD).

Abbreviations: BDI = Beck Depression Inventory; CDI = Children's Depression Inventory; CDRS-R = Children's Depression Rating Scale-Revised; CGI = Clinical Global Impression; GAF = Global Assessment of Functioning; HAMA = Hamilton Anxiety Rating Scale; MADRS = Montgomery-Asberg Depression Rating Scale.

During acute treatment, 65% of fluoxetine-treated patients met response criteria (30% decrease in CDRS-R total) as compared with 54% of placebo-treated patients. Although numerically greater for fluoxetine-treated patients, these findings were not statistically significant (p=.093). It should be noted, however, that statistically significantly more fluoxetine-treated patients had decreases in CDRS-R total score of 20%, 40%, 50%, and 60% from baseline as compared with placebo-treated patients.

The effectiveness of fluoxetine in the acute treatment of MDD in children and adolescents is supported by a wide range of categorical and continuous analyses. Fluoxetine-treated patients demonstrated statistically significantly greater improvement on mean change from baseline to endpoint for the CDRS-R total score as well as for all four CDRS-R subtotal scores as compared with placebo-treated patients. Statistically significantly more fluoxetine-treated patients met protocol-defined criteria for both remission and recovery as compared with placebo-treated patients. Statistically significantly greater improvement was also observed in fluoxetine-treated patients for the investigator-rated MADRS total score mean change, CGI-Improvement endpoint score, and CGI-Severity mean change score as compared with placebo-treated patients. Results of subgroup analyses showed no clinically significant treatment differences among subgroups based on age, gender, or family history of depression. These results provide

strong support for the efficacy of fluoxetine 20 mg/day in the acute treatment of MDD in children and adolescents.

The efficacy of fluoxetine in the treatment of children and adolescents who did not respond to fluoxetine 20 mg/day was also evaluated. Examination of the 29 patients who did not respond to acute treatment shows that twice as many patients (10 of 14, 71%) who received fluoxetine 40 or 60 mg/day met protocol response criteria as compared with patients who remained at fluoxetine 20 mg/day (5 of 14, 36%) after 10 additional weeks of treatment. The CDRS-R total mean change scores for patients receiving the higher doses of fluoxetine was considerably greater (-9.4) than those observed for nonresponders continuing on 20 mg/day (-1.5), indicating that patients who were rerandomized to dose titration experienced substantial clinical benefit. Patients treated with the higher doses also showed strong numerical trends on CDRS-R total, CGI-Severity, BDI total, and CGI-Improvement scores in comparison with patients maintained at 20 mg/day. Statistical significance was not achieved on any of these measures; however, the sample sizes were small. The magnitude of the observed changes indicate that these data are clinically relevant and support dose escalation to achieve efficacy in children and adolescents who do not respond to acute treatment with fluoxetine 20 mg/day.

During the subchronic treatment phase, statistically significantly more fluoxetine-treated patients met protocol-defined response criteria as compared with placebo-treated patients. In addition, statistically significant changes in favor of fluoxetine treatment for the mean change in CDRS-R total score were seen during subchronic treatment. Numerically, although not statistically significantly, more fluoxetine-treated than placebo-treated patients met criteria for remission and recovery. Additional analyses of efficacy during subchronic treatment also showed numerical, although not statistically significant, trends in favor of fluoxetine treatment as compared with placebo treatment. During the subchronic treatment phase, the analyses comparing patients who received fluoxetine 20 to 60 mg/day versus patients who received placebo included nonresponders who were maintained on 20 mg/day, making it difficult to fully evaluate the impact of longer-term treatment. In spite of this limitation, these data support the efficacy of fluoxetine 20 to 60 mg/day in the subchronic treatment of MDD in children and adolescents.

In summary, the data presented in this clinical study report strongly support the efficacy of fluoxetine 20 mg/day in the acute treatment of MDD in children and adolescents, ages 8 to 18 years. In addition, the data indicate that dose escalation to fluoxetine 40 mg/day, then 60 mg/day is effective in those children and adolescents who do not respond to fluoxetine 20 mg/day during acute treatment. These data also support the efficacy of fluoxetine 20 to 60 mg/day for longer-term, subchronic treatment of MDD in children and adolescents.

11.5. Pharmacokinetic Results

11.5.1. Patient Demographics

The demographic characteristics of patients included in the pharmacokinetic analyses are presented in Table 11.25. Pharmacokinetic blood samples were obtained at baseline prior to dosing (Visit 1), and at Visits 10 and 15 (or discontinuation) during the subchronic treatment phase. Patients included in the pharmacokinetic dataset were treated with fluoxetine 20 mg/day; patients that titrated to 40 or 60 mg/day were not included in this dataset. Because pharmacokinetic samples were collected at Visit 10, 9 weeks after initiation of study medication, fluoxetine and norfluoxetine had reached steady-state concentrations in the plasma. The pharmacokinetic dataset consisted of 94 pediatric patients. Fifty-two patients were categorized as children (mean age 10.8 years) and 42 patients were categorized as adolescents (mean age 15.1 years). Children had an average weight of 49.2 kg, while adolescents had an average weight of 68.6 kg. The mean body mass index (BMI) was similar between the two groups. There were an equal number of males and females in the overall population. The gender distribution was also similar within the child and adolescent groups. Eighty-five patients were Caucasians; the remaining 9 patients were of African, Hispanic, or East/Southeast Asian origin.

Table 11.25. Patient Demographics Pharmacokinetic Dataset B1Y-MC-HCJE

Demographic	Category	Subcategory	N	Mean	SD	Range
Age (years)	Overall	-	94	12.8	2.5	8-17
	Children	-	52	10.8	1.3	8-12
	Adolescents	-	42	15.1	1.3	13-17
Ethnic Origin	Overall	Caucasian	85	-	-	-
		Other	9	-	-	-
	Children	Caucasian	49	-	-	-
		Other	3	-	-	-
	Adolescents	Caucasian	36	-	-	-
		Other	6	-	-	-
Gender	Overall	Male	47	-	-	-
		Female	47	-	-	-
	Children	Male	28	-	-	-
		Female	24	-	-	-
	Adolescents	Male	19	-	-	-
		Female	23	-	-	-
Weight (kg)	Overall	-	93	57.7	18.4	24-103
	Children	-	52	49.2	16.0	24-102
	Adolescents	-	41[a]	68.6	15.4	34-103
Height (cm)	Overall	-	93	155.8	14.3	124-188
	Children	-	52	146.9	11.0	124-188
	Adolescents	-	41[a]	167.2	8.9	135-188
Body Mass Index (kg/m^2)[b]	Overall	-	93	23.4	5.7	15-40
	Children	-	52	22.5	5.7	15-39
	Adolescents	-	41[a]	24.6	5.7	16-40

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[a]Patient 419 did not have body weight or height data available.

[b]Body Mass Index = Weight (kg)/ [Height (cm) / 100]^2

Abbreviations: SD = standard deviation.

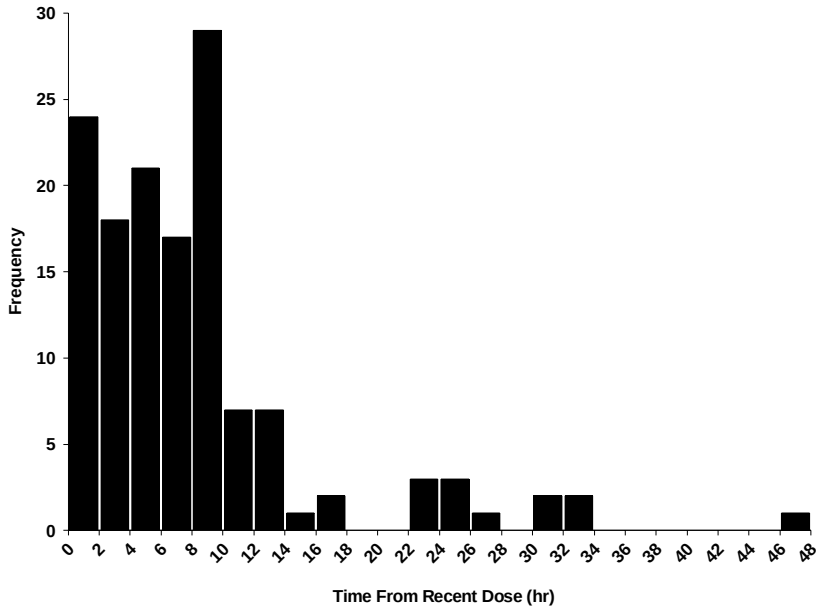
11.5.2. Plasma Sample Collection

The majority (53%) of patients contributed a single blood sample to the pharmacokinetic dataset. The remaining 47% of patients provided two blood samples.

Pharmacokinetic blood samples were collected under steady-state conditions. Site personnel collected pharmacokinetic blood samples within the 24-hour dosing interval for

fluoxetine. In general, maximal fluoxetine concentrations (C_{max}) occur approximately 6 to 8 hours after dosing and maximal norfluoxtine concentrations occur approximately 10 to 24 hours after dosing with fluoxetine. It is known that the concentrations of fluoxetine and norfluoxetine fluctuate little over a 24-hour dosing interval once steady-state has been achieved.

Figure 11.5 presents the time distribution of blood samples collected within the 24-hour dosing interval. The majority of samples (approximately 80%) obtained from this population were collected within 10 hours of dosing. The histogram indicates that the majority of the plasma concentrations were collected around the time of peak fluoxetine concentration.



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Source of Data: \\proton\proton.grp\pkregsub\fluoxtne\hcje\3_working\working4.xls\tfds histo

Figure 11.5. **Histogram illustrating the number of samples post-fluoxetine dose (fluoxetine/norfluoxetine plasma concentrations) included in the pharmacokinetic dataset for the subchronic treatment phase of B1Y-MC-HCJE.**

11.5.3. Observed Concentrations

For pediatric patients randomized to receive fluoxetine 20 mg/day, the overall mean steady-state plasma concentrations of fluoxetine and norfluoxetine were 117 ng/mL and 144 ng/mL, respectively (Table 11.26). The between-patient variability in fluoxetine and norfluoxetine concentrations was high. The mean fluoxetine concentration in children was approximately 2-fold higher than that observed in adolescents; similarly, the mean

norfluoxetine concentration in children was 1.5-fold higher than that observed in adolescents. Female patients had similar mean fluoxetine concentrations compared with male patients; both child and adolescent female patients had similar mean fluoxetine concentrations compared with their male counterparts.

Table 11.26. Observed Fluoxetine and Norfluoxetine Concentrations at Steady-State After Dosing with Fluoxetine 20 mg/day Subchronic Treatment Phase (Study Periods III-V) B1Y-MC-HCJE

Category	N	Mean (ng/mL)	SD	%CV	Range (ng/mL)
Fluoxetine					
All patients	138	116.6	73.7	63.2	3 - 435
Children	79	144.8	76.4	52.8	16 - 435
Adolescents	59	78.8	49.4	62.7	3 - 199
Gender					
Male	66	115.0	59.9	52.1	21 - 246
Female	72	118.0	84.9	71.9	3 - 435
Children					
Male	41	144.5	53.2	36.8	24 - 246
Female	38	145.2	96.2	66.3	16 - 435
Adolescents					
Male	25	66.6	32.7	49	21 - 157
Female	34	87.7	57.6	65.7	3 - 199
Norfluoxetine					
All patients	138	144.1	58.9	40.9	32 - 344
Children	79	167.2	59.6	35.7	47 - 344
Adolescents	59	113.1	41.4	36.6	32 - 227
Gender					
Male	66	143.1	61.9	43.2	42 - 293
Female	72	144.9	56.5	38.9	32 - 344
Children					
Male	41	168.9	62.1	36.8	59 - 293
Female	38	165.3	57.6	34.9	47 - 344
Adolescents					
Male	25	100.9	30.9	30.6	42 - 175
Female	34	122.1	46	37.7	32 - 227

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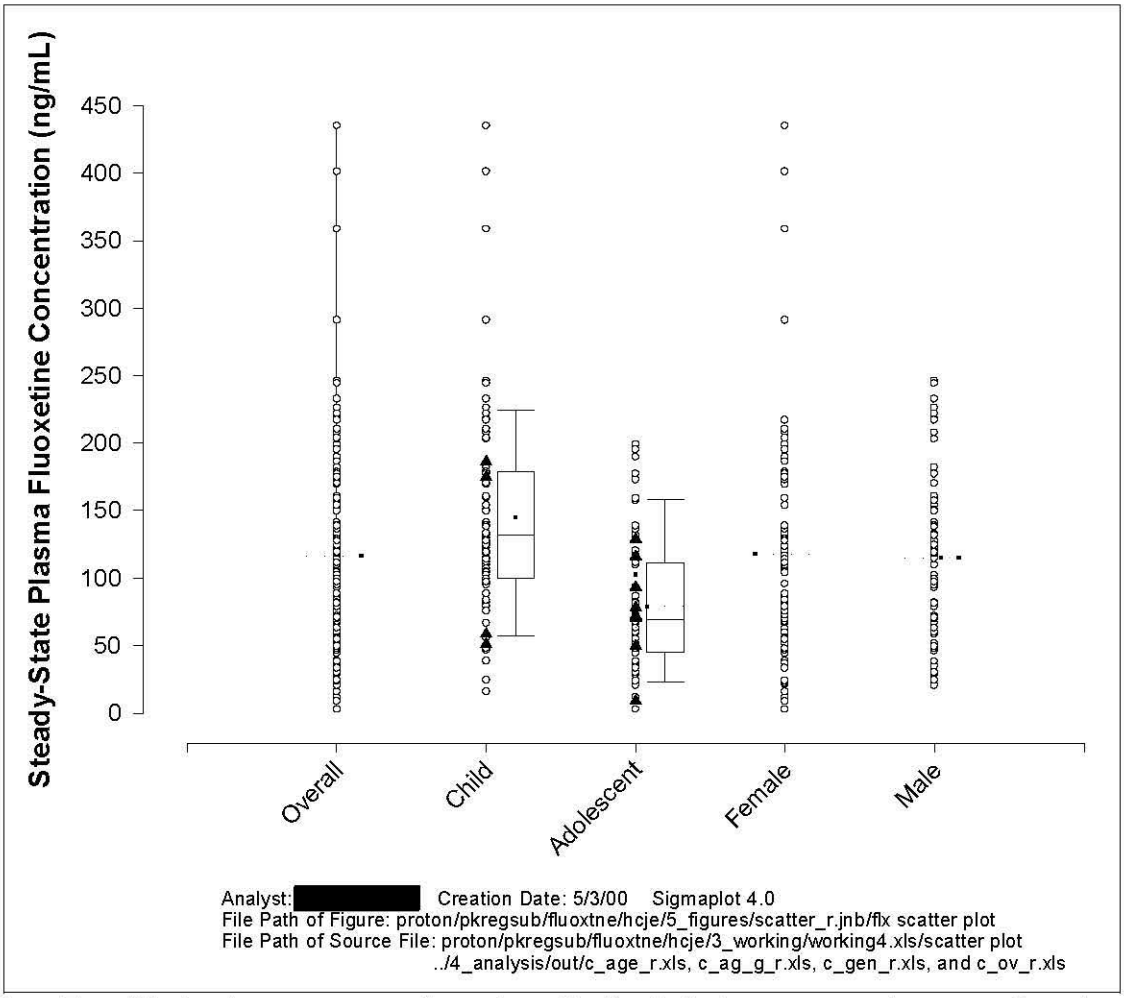
WinNONLIN table generator \\proton\proton.grp\pkregsub\fluoxtne\hcje\4_analysis\2_out\c_age.xls, c_age_gn.xls, c_gen.xls, and c_ov.xls.
Abbreviations: CV = coefficient of variation; SD = standard deviation.

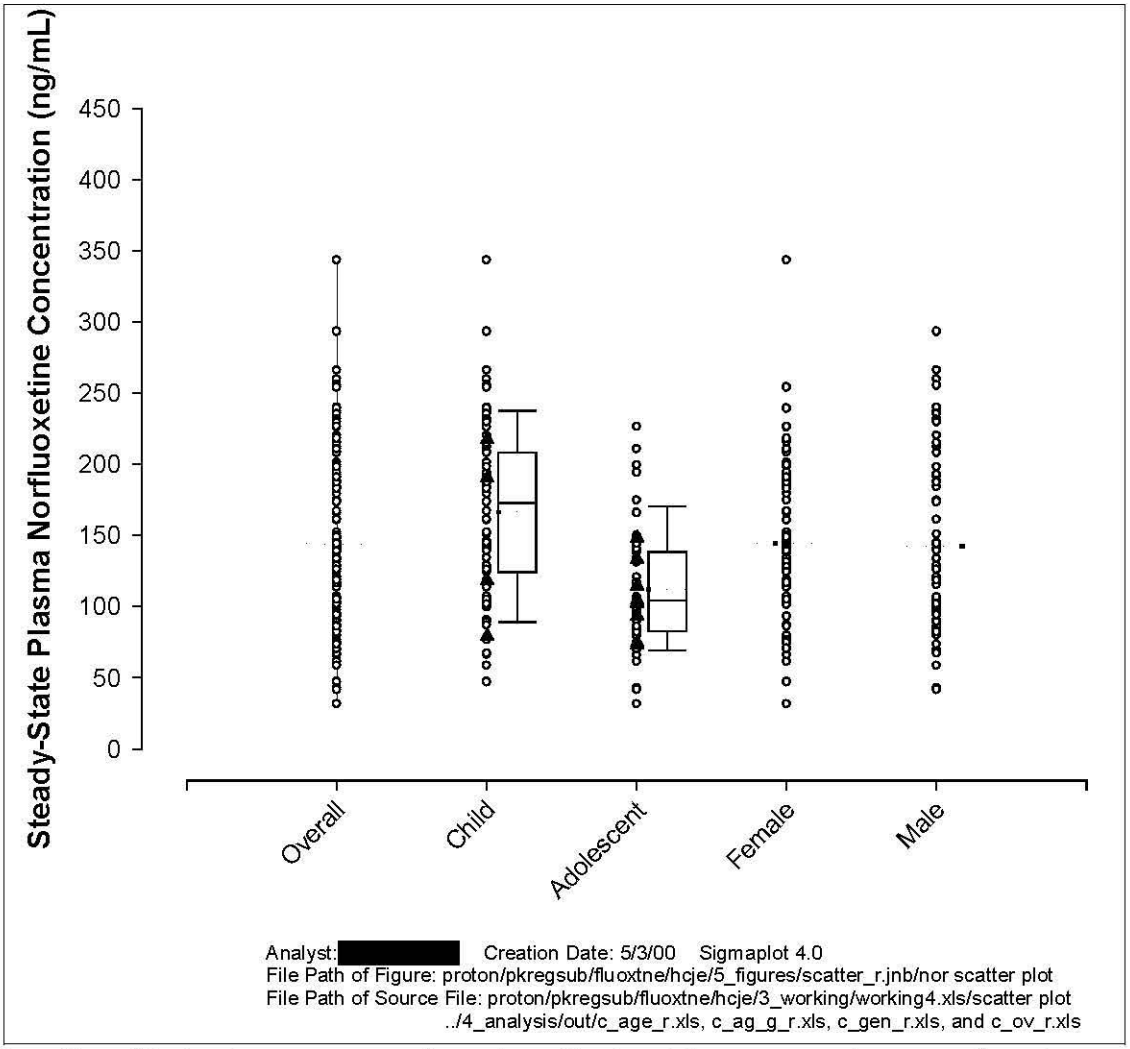
The distribution of the individual observed steady-state concentrations for fluoxetine and norfluoxetine are illustrated in Figures 11.6 and 11.7, respectively. Mean fluoxetine and norfluoxetine concentrations were higher in children than in adolescents. As illustrated,

3 female children (4 observations) had fluoxetine and norfluoxetine concentrations >250 ng/mL. The 9 non-Caucasians had concentrations typical of their respective subgroups (child or adolescent).



Note: The solid triangles represent non-Caucasians. The line in the box represents the average for each subgroup. The solid line in each box and whisker plot represents the median (50th); the whiskers extend to the 5th and 95th percentiles. Data points outside the whiskers may represent potential outliers.

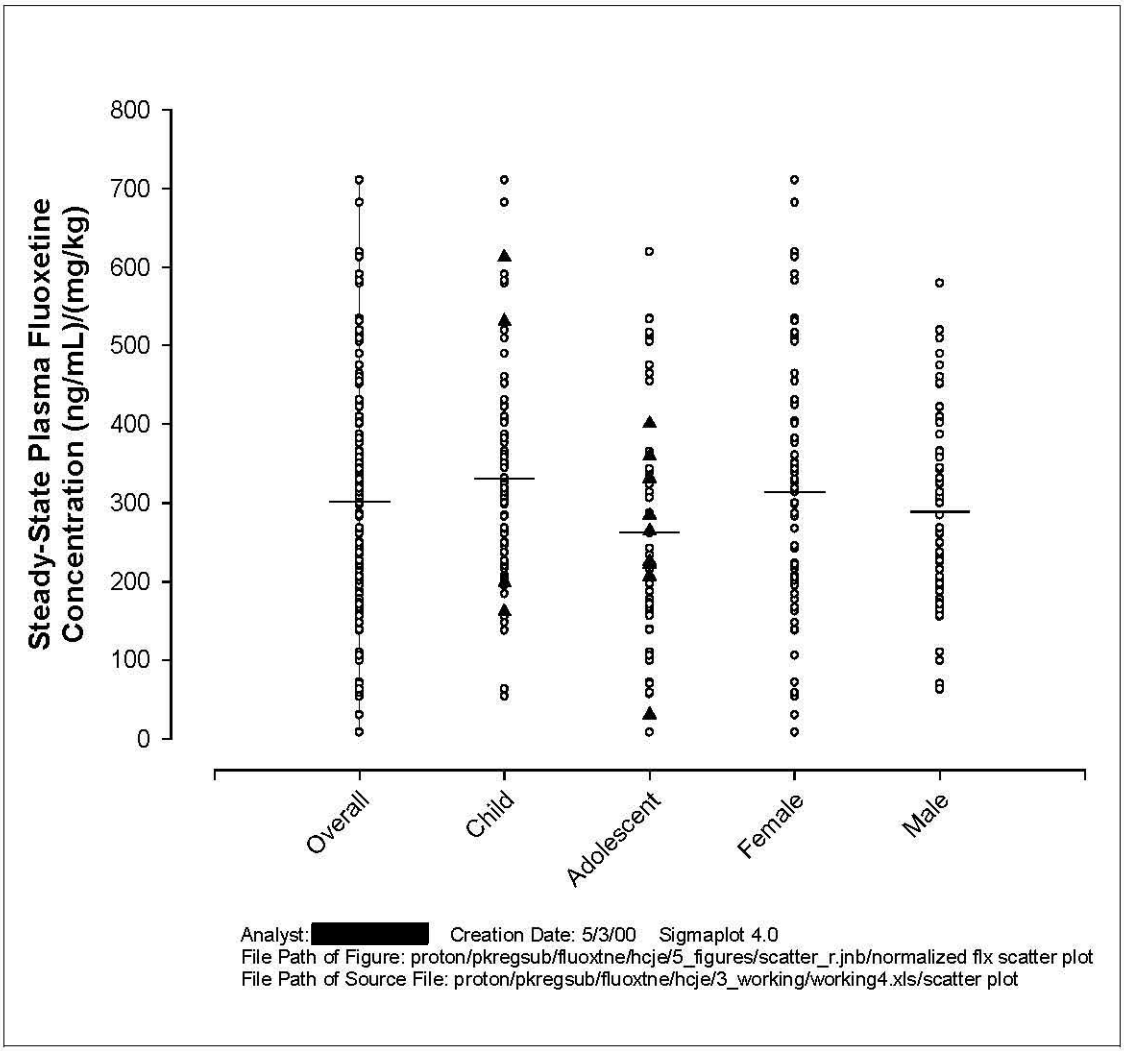
Figure 11.6. Observed steady-state fluoxetine concentrations for individual patients after fluoxetine 20 mg/day during the subchronic treatment phase (Study Periods IV-V) of B1Y-MC-HCJE.



Note: The solid triangles represent non-Caucasians. The dotted line represents the average for each subgroup. The solid line in each box and whisker plot represents the median (50th); the whiskers extend to the 5th and 95th percentiles. Data points outside the whiskers may represent potential outliers.

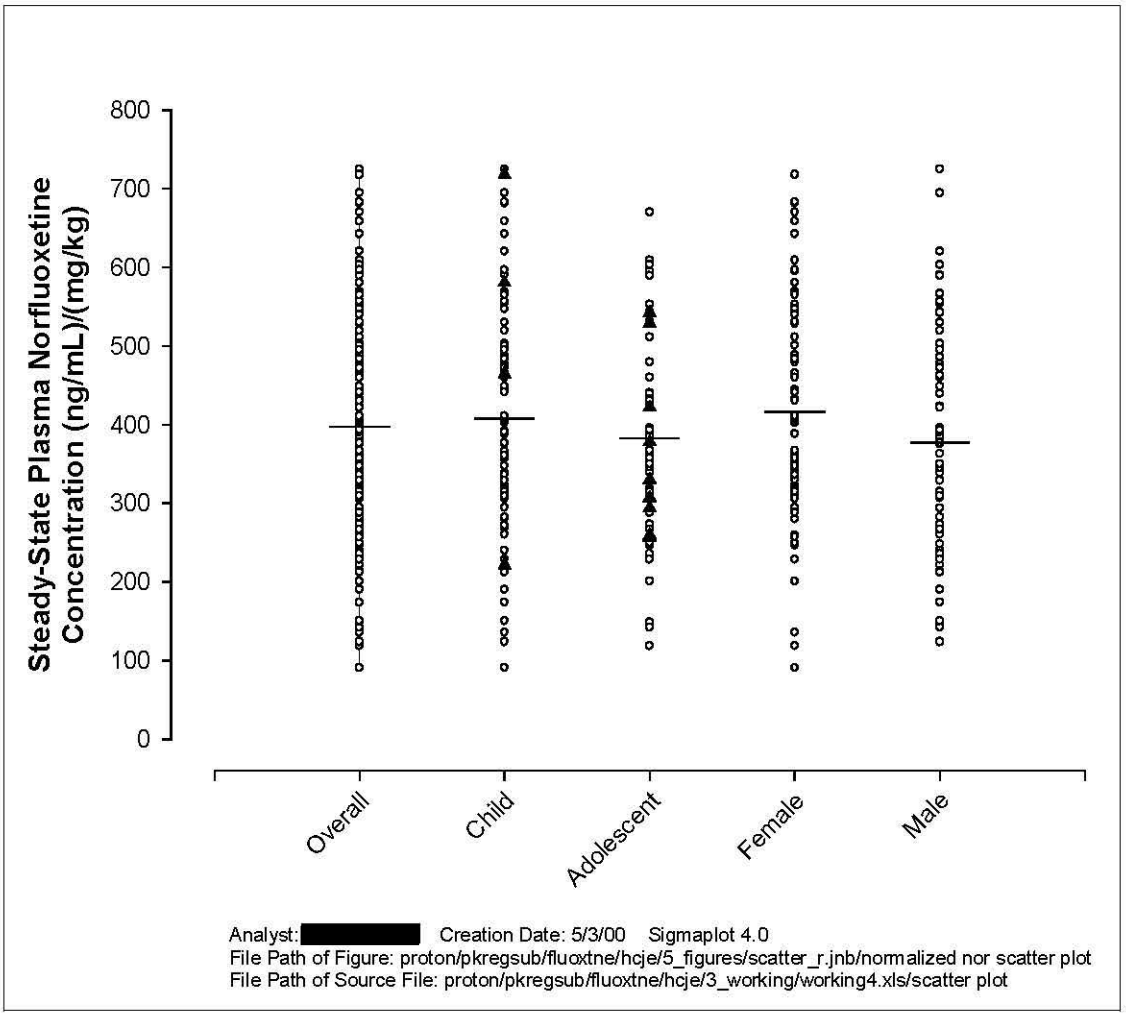
Figure 11.7. Observed steady-state norfluoxetine concentrations for individual patients after fluoxetine 20 mg/day during the subchronic treatment phase (Study Periods IV-V) of B1Y-MC-HCJE.

Normalizing the observed fluoxetine and norfluoxetine concentrations by body weight suggests that the exposures in children are comparable to those observed in adolescents (Figures 11.8 and 11.9). The average normalized fluoxetine concentrations at steady-state in children and adolescents were 331 and 262 (ng/mL)/(mg/kg), respectively. Normalized norfluoxetine concentrations were 408 and 382 (ng/mL)/(mg/kg) for children and adolescents, respectively. Thus, body weight explains a portion of the variability in observed fluoxetine and norfluoxetine plasma concentrations.



Note: Data from patient 419 was not normalized by body weight. The solid triangles represent non-Caucasians.

Figure 11.8. **Dose-weight normalized steady-state fluoxetine concentrations for individual patients after fluoxetine 20 mg/day during the subchronic treatment phase (Study Periods IV-V) of B1Y-MC-HCJE.**



Note: Data from patient 419 was not normalized by body weight. The solid triangles represent non-Caucasians.

Figure 11.9. **Dose-weight normalized steady-state norfluoxetine concentrations for individual patients after fluoxetine 20 mg/day during the subchronic treatment phase (Study Periods IV-V) of B1Y-MC-HCJE.**

11.5.4. Discussion

Children had higher plasma fluoxetine and norfluoxetine concentrations compared with adolescents. Previous results (Study B1Y-MC-HCIU: Population Pharmacokinetic Analyses of Fluoxetine in Pediatric Patients) indicated that including body weight, body mass index, and age significantly improved the population pharmacokinetic model. The between-patient variability in both oral clearance and volume of distribution was decreased by almost 45% after accounting for these patient factors (covariates). Although age and body mass index both significantly decreased the between-patient variability in both clearance and volume of distribution, body weight had the strongest effect on these parameters. Normalizing the observed steady-state concentrations by

body weight resulted in similar exposures between children and adolescents. Approximately 50% of the variability in clearance remained unexplained. These differences between children and adolescents could be due to random unexplained patient effects.

By Visit 8 of Study B1Y-MC-HCJE, patients had received 4 weeks of fixed dosing with fluoxetine 20 mg/day, a sufficient time interval for attainment of steady-state plasma fluoxetine concentrations (fluoxetine half-life = 4 to 6 days). The half-life for norfluoxetine (4 to 16 days) is longer than that for fluoxetine; therefore, patients may not have achieved steady-state concentrations of norfluoxetine when samples were obtained.

11.5.5. Conclusions

The mean observed fluoxetine plasma concentrations in children were 2-fold higher than those observed in adolescents, and the mean observed norfluoxetine plasma concentration in children were 1.5-fold higher than those observed in adolescents. Differences between fluoxetine and norfluoxetine plasma concentrations in children and adolescents can be principally attributed to differences in body weight.

12. Safety Evaluation

The safety of fluoxetine versus placebo in pediatric patients diagnosed with MDD was evaluated in all 219 randomized patients in this study. At baseline, a medical history, including psychiatric history and evaluation of secondary conditions, and a physical examination were performed. An electrocardiogram (ECG), height, and weight were collected at baseline (Visit 1) and Visit 15 (or discontinuation). Adverse events and vital signs, including sitting blood pressure and heart rate, were monitored at each visit during the study. Adverse events were recorded at each visit, regardless of potential causality, through indirect questioning (non-solicited) and using a standardized interviewer-elicited format (the Side-Effects Checklist). Clinical laboratory tests, including hematology, clinical chemistry, thyroid function tests, and urinalysis were performed at baseline (Visit 1) and Visit 15 (or discontinuation).

12.1. Extent of Exposure

The duration of study drug exposure for all randomized patients during the acute and subchronic treatment phases is presented in Table 12.1. The mean exposure to treatment for all randomized patients reflects the differences in the number and timing of patient discontinuations between treatment groups.

During the acute treatment phase, fluoxetine-treated patients were exposed to study drug for an average of 61 ± 12 days (range from 16 to 74 days), while placebo-treated patients were exposed to study drug for an average of 54 ± 18 days (range from 0 to 81 days). Patient 1139 (placebo) discontinued the study after randomization at Visit 4 due to patient decision. This patient never ingested any study medication.

During the subchronic treatment phase, fluoxetine-treated patients were exposed to study drug for an average of 106 ± 38 days (range from 16 to 152 days), while placebo-treated patients were exposed to study drug for an average of 91 ± 47 days (range from 0 to 149 days).

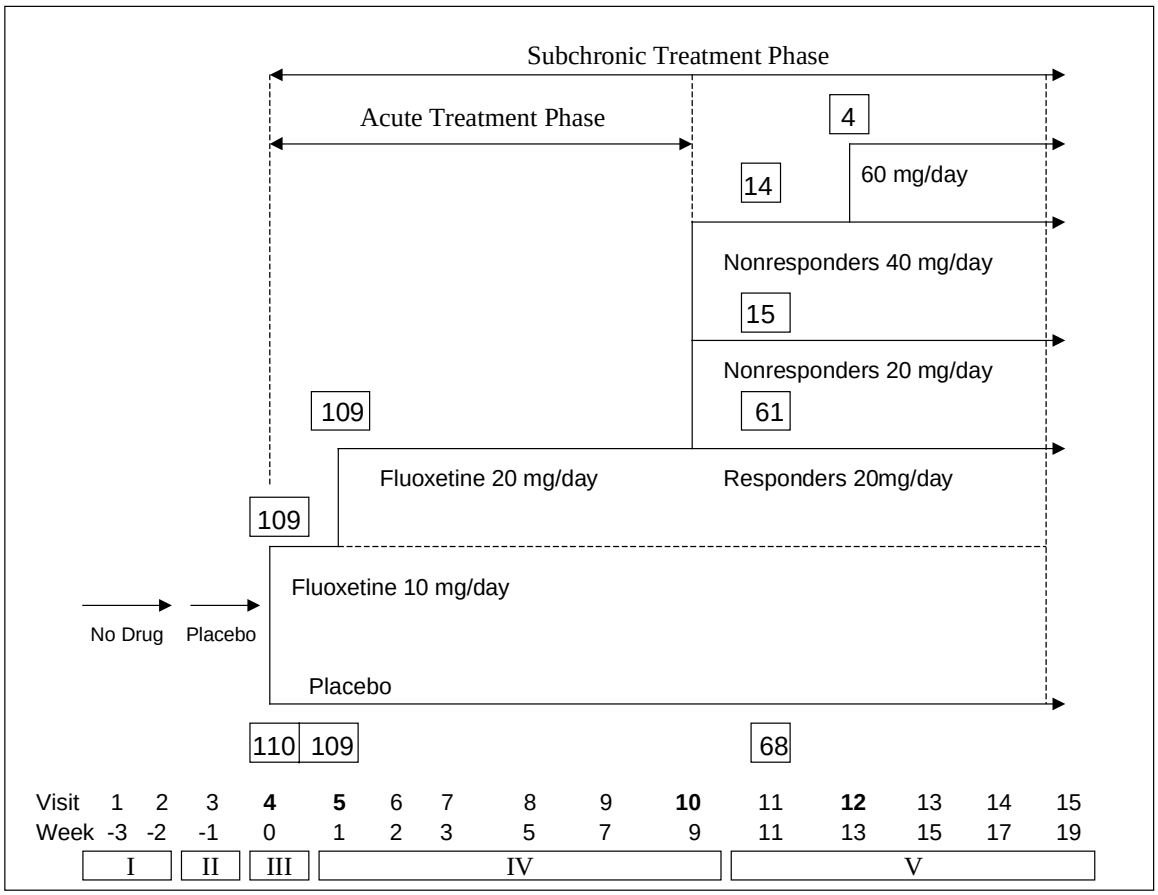
The patient disposition listing indicates the number of days each patient was exposed to treatment (see Appendix 16.2.2).

Table 12.1. Duration of Study Drug Exposure
All Randomized Patients
Acute and Subchronic Treatment Phases
Study Periods III-IV and III-V, B1Y-MC-HCJE

Variable	Flx (N=109)	Placebo (N=110)
Drug Exposure(Period III-IV)		
No. Patients	109	109
Mean	60.5	53.5
Median	63.0	62.0
Standard Dev.	11.6	18.3
Minimum	16.0	0.0
Maximum	74.0	81.0
Drug Exposure(Period III-V)		
No. Patients	109	109
Mean	105.9	91.4
Median	119.0	114.0
Standard Dev.	38.2	47.4
Minimum	16.0	0.0
Maximum	152.0	149.0

RMP.B1YP.JCLLIB2(DES1JEAF)
RMP.B1YO.HCJEREP(DES1JEAF)
XDES0001

Figure 12.1 is a graphical representation of the numbers of patients at the various dosing levels during the study. At Visit 4, 109 patients were randomized to fluoxetine and 110 patients were randomized to placebo. Fluoxetine-treated patients received 10 mg/day for Study Period III (1 week) and 20 mg/day for Study Period IV (8 weeks). Patients were allowed to decrease dose to fluoxetine 10 mg/day for non-tolerability; however, there were no patients that did so. At the beginning of Study Period V (Visit 10), response to treatment was evaluated. Placebo-treated patients remained on placebo regardless of their response to treatment. Sixty-one fluoxetine-treated patients had responded to acute treatment and continued taking 20 mg/day. Of the 29 fluoxetine-treated patients who did not respond to treatment, 15 were rerandomized to fluoxetine 20 mg/day and 14 were rerandomized to fluoxetine 40 mg/day. After 4 weeks of continued treatment (Visit 12), response to treatment was re-evaluated in patients receiving fluoxetine 40 mg/day. Due to insufficient response at the 40 mg/day dose, 4 patients had their dose increased to fluoxetine 60 mg/day.



Data for this figure were taken from: RMP.B1YSHCJE.SASPGM (DOSING), RMP.B1YO.HCJEREP (RDS2JEKB).

Figure 12.1. **Study dose for all randomized patients during acute and subchronic treatment phases (Study Periods III-V) of B1Y-MC-HCJE.**

12.2. Adverse Events

An adverse event was defined as any undesirable experience (or unanticipated benefit) that occurred after informed consent for the study had been obtained.

Adverse events were collected via two methods. Patients were questioned about the occurrence of adverse events in a non-directed manner at the beginning of each visit. These events are referred to as non-solicited adverse events. The Side-Effects Checklist was completed after collection of non-solicited adverse events. Patients were asked if they had experienced trouble with specific symptoms on the Checklist since their last visit. Patients responded with the choices “not at all,” “just a little,” “pretty much,” “very much,” or “don’t know.” An event was considered to be treatment-emergent if it was present at baseline and worsened as defined by an increase in severity for non-solicited events or an increase in score on the Checklist at any postbaseline visit or if the event was

a new occurrence after baseline. The following sections detail the analyses of treatment-emergent non-solicited and solicited adverse events.

Adverse events were examined for the acute treatment phase (Study Periods III through IV), the subchronic treatment phase (Study Periods III through V), and for the double-blind nonresponder rerandomization period (Study Period V).

Analyses of adverse events for all patients entering Study Period V and all subgroup analyses are presented in Sections 14.3.1.3 and 14.3.2, respectively. Adverse events were analyzed by maximum severity (for treatment-emergent non-solicited adverse events) and by body system and maximum intensity (for treatment-emergent solicited adverse events), in Section 14.3.1.

12.2.1. Brief Summary of Adverse Events

Treatment-emergent adverse events were collected through spontaneous reporting (non-solicited adverse events) and through the use of a structured adverse event questionnaire (solicited adverse events).

For treatment-emergent non-solicited adverse events, 94 (86%) fluoxetine-treated and 80 (73%) placebo-treated patients reported at least one event during the 9-week acute treatment phase (p=.019). One hundred one (93%) fluoxetine-treated patients and 87 (79%) placebo-treated patients reported at least one treatment-emergent non-solicited adverse event during the 19-week subchronic treatment phase (p=.006), which was inclusive of all events captured during acute treatment. During both the acute and subchronic treatment phases, headache was the only event reported statistically significantly more often by fluoxetine-treated patients compared with placebo-treated patients.

For treatment-emergent solicited adverse events, 105 (96%) fluoxetine-treated patients and 100 (91%) placebo-treated patients reported at least one event during the acute treatment phase (p=.165). One hundred seven (98%) fluoxetine-treated patients and 101 (92%) placebo-treated patients reported at least one treatment-emergent solicited adverse event during the subchronic treatment phase (p=.059), which was inclusive of all events captured during acute treatment. During both acute and subchronic treatment, no solicited adverse events were reported statistically significantly more often by fluoxetine-treated patients as compared with placebo-treated patients.

No patients died during Study Periods I through V. Nine serious adverse events occurred in 9 patients (3 not randomized, 2 fluoxetine-treated, 4 placebo-treated). Serious adverse events led to the discontinuation of 5 patients (1 not randomized, 1 fluoxetine-treated, 3 placebo-treated). Three of the nine serious adverse events occurred during the diagnostic evaluation and placebo washout periods of the study, prior to randomization to study treatment. The remaining six serious adverse events occurred during double-blind treatment in 2 fluoxetine-treated (one each for suicidal ideation and swollen

tonsils/tonsillectomy) and 4 placebo-treated patients (one each for abdominal pain/appendicitis, kidney infection, self-mutilatory behavior, and aggressive behavior).

A total of 23 patients discontinued due to adverse events including the 5 patients discontinued due to serious adverse events, during Study Periods I through V (1 not randomized, 11 fluoxetine-treated, 11 placebo-treated). No individual event that led to discontinuation occurred in more than 1 fluoxetine-treated patient.

12.2.2. Display and Analysis of Adverse Events

12.2.2.1. Acute Treatment Phase (Study Periods III-IV)

12.2.2.1.1. Non-Solicited Events

Treatment-emergent non-solicited adverse events that occurred during the acute treatment phase are summarized in Table 12.2.

Ninety-four (86%) fluoxetine-treated patients reported at least one treatment-emergent non-solicited adverse event compared with 80 (73%) placebo-treated patients (p=.019). There were no statistically significant differences between the two treatment groups in the number of patients reporting specific treatment-emergent non-solicited adverse events, with the exception of headache (p=.017), with fluoxetine-treated patients experiencing a higher incidence (30%) than placebo-treated patients (16%).

Treatment-emergent non-solicited adverse events were also analyzed by body system (see Table 14.38, Section 14.3.1.1.1) and by maximum severity (see Table 14.39, Section 14.3.1.1.2). The majority of reported treatment-emergent non-solicited adverse events were mild or moderate in severity. There were no statistically significant differences between treatment groups in the incidence of treatment-emergent non-solicited adverse events classified as severe.

Table 12.2. **Treatment-Emergent Non-Solicited Adverse Events**
Incidence by Decreasing Frequency (Ordered by Fluoxetine)
All Randomized Patients
Acute Treatment Phase (Study Periods III-IV)
B1Y-MC-HCJE

Event Classification	Flx 20 (N=109) n (%)	Placebo (N=110) n (%)	Total (N=219) n (%)	p-Value*
PATIENTS WITH >= 1 TESS	94 (86.2)	80 (72.7)	174 (79.5)	.019
PATIENTS WITH NO TESS	15 (13.8)	30 (27.3)	45 (20.5)	.019
HEADACHE	33 (30.3)	18 (16.4)	51 (23.3)	.017
RHINITIS	24 (22.0)	21 (19.1)	45 (20.5)	.619
ABDOMINAL PAIN	17 (15.6)	16 (14.5)	33 (15.1)	.852
PHARYNGITIS	16 (14.7)	9 (8.2)	25 (11.4)	.143
ACCIDENTAL INJURY	13 (11.9)	8 (7.3)	21 (9.6)	.261
DIARRHEA	11 (10.1)	11 (10.0)	22 (10.0)	1.00
DIZZINESS	10 (9.2)	4 (3.6)	14 (6.4)	.106
RASH	10 (9.2)	4 (3.6)	14 (6.4)	.106
ANOREXIA	9 (8.3)	6 (5.5)	15 (6.8)	.437
COUGH INCREASED	9 (8.3)	7 (6.4)	16 (7.3)	.615
NAUSEA	9 (8.3)	8 (7.3)	17 (7.8)	.806
NERVOUSNESS	9 (8.3)	6 (5.5)	15 (6.8)	.437
ASTHENIA	8 (7.3)	6 (5.5)	14 (6.4)	.594
PAIN	8 (7.3)	9 (8.2)	17 (7.8)	1.00
VOMITING	8 (7.3)	8 (7.3)	16 (7.3)	1.00
FEVER	7 (6.4)	5 (4.5)	12 (5.5)	.569
ABNORMAL DREAMS	6 (5.5)	3 (2.7)	9 (4.1)	.332
EPISTAXIS	5 (4.6)	1 (0.9)	6 (2.7)	.119
DRY MOUTH	4 (3.7)	5 (4.5)	9 (4.1)	1.00
DYSMENORRHEA	4 (3.7)	3 (2.7)	7 (3.2)	.721
EAR PAIN	4 (3.7)	3 (2.7)	7 (3.2)	.721
FLU SYNDROME	4 (3.7)	3 (2.7)	7 (3.2)	.721
INSOMNIA	4 (3.7)	5 (4.5)	9 (4.1)	1.00
PRURITUS	4 (3.7)	5 (4.5)	9 (4.1)	1.00
AGITATION	3 (2.8)	0	3 (1.4)	.122
BACK PAIN	3 (2.8)	5 (4.5)	8 (3.7)	.721
CHEST PAIN	3 (2.8)	2 (1.8)	5 (2.3)	.683
CONSTIPATION	3 (2.8)	2 (1.8)	5 (2.3)	.683
DYSPEPSIA	3 (2.8)	4 (3.6)	7 (3.2)	1.00
ECCHYMOSIS	3 (2.8)	2 (1.8)	5 (2.3)	.683
NECK PAIN	3 (2.8)	0	3 (1.4)	.122
SINUSITIS	3 (2.8)	2 (1.8)	5 (2.3)	.683
SOMNOLENCE	3 (2.8)	3 (2.7)	6 (2.7)	1.00
TREMOR	3 (2.8)	0	3 (1.4)	.122
AKATHISIA	2 (1.8)	0	2 (0.9)	.247
ALLERGIC REACTION	2 (1.8)	2 (1.8)	4 (1.8)	1.00
ANXIETY	2 (1.8)	0	2 (0.9)	.247
ASTHMA	2 (1.8)	0	2 (0.9)	.247
CHILLS	2 (1.8)	0	2 (0.9)	.247

RMP.B1YP.JCLLIB2(AES2JEKS)
RMP.B1YO.HCJEREP(AES2JEKS)
* Frequencies are analyzed using a Fisher's Exact test.
XAES0002

Table 12.2. **Treatment-Emergent Non-Solicited Adverse Events Incidence by Decreasing Frequency (Ordered by Fluoxetine) All Randomized Patients Acute Treatment Phase (Study Periods III-IV) B1Y-MC-HCJE (continued)**

Event Classification	Flx 20 (N=109) n	(%)	Placebo (N=110) n	(%)	Total (N=219) n	(%)	p-Value*
DEPRESSION	2	(1.8)	1	(0.9)	3	(1.4)	.622
DRY SKIN	2	(1.8)	1	(0.9)	3	(1.4)	.622
EYE DISORDER	2	(1.8)	0		2	(0.9)	.247
GASTROENTERITIS	2	(1.8)	0		2	(0.9)	.247
HOSTILITY	2	(1.8)	5	(4.5)	7	(3.2)	.446
HYPERKINESIA	2	(1.8)	0		2	(0.9)	.247
INFECTION	2	(1.8)	2	(1.8)	4	(1.8)	1.00
OTITIS EXTERNA	2	(1.8)	1	(0.9)	3	(1.4)	.622
PERSONALITY DISORDER	2	(1.8)	1	(0.9)	3	(1.4)	.622
PHOTOSENSITIVITY REACTION	2	(1.8)	0		2	(0.9)	.247
SLEEP DISORDER	2	(1.8)	0		2	(0.9)	.247
SPEECH DISORDER	2	(1.8)	2	(1.8)	4	(1.8)	1.00
THIRST	2	(1.8)	2	(1.8)	4	(1.8)	1.00
WEIGHT LOSS	2	(1.8)	1	(0.9)	3	(1.4)	.622
ACUTE BRAIN SYNDROME	1	(0.9)	0		1	(0.5)	.498
APATHY	1	(0.9)	0		1	(0.5)	.498
BRONCHITIS	1	(0.9)	0		1	(0.5)	.498
BUCCOGLOSSAL SYNDROME	1	(0.9)	0		1	(0.5)	.498
CONTACT DERMATITIS	1	(0.9)	0		1	(0.5)	.498
DELUSIONS	1	(0.9)	0		1	(0.5)	.498
DYSPHAGIA	1	(0.9)	1	(0.9)	2	(0.9)	1.00
DYSPNEA	1	(0.9)	0		1	(0.5)	.498
EAR DISORDER	1	(0.9)	1	(0.9)	2	(0.9)	1.00
EMOTIONAL LABILITY	1	(0.9)	0		1	(0.5)	.498
ENDOMETRIAL HYPERPLASIA	1	(0.9)	0		1	(0.5)	.498
EUPHORIA	1	(0.9)	0		1	(0.5)	.498
EYE PAIN	1	(0.9)	0		1	(0.5)	.498
FECAL INCONTINENCE	1	(0.9)	0		1	(0.5)	.498
FLATULENCE	1	(0.9)	0		1	(0.5)	.498
FUNGAL DERMATITIS	1	(0.9)	1	(0.9)	2	(0.9)	1.00
HALLUCINATIONS	1	(0.9)	0		1	(0.5)	.498
HEPATITIS NONSPECIFIC	1	(0.9)	0		1	(0.5)	.498
HEPATOMEGALY	1	(0.9)	0		1	(0.5)	.498
HERPES SIMPLEX	1	(0.9)	0		1	(0.5)	.498
HYPERTONIA	1	(0.9)	1	(0.9)	2	(0.9)	1.00
HYPOTENSION	1	(0.9)	0		1	(0.5)	.498
JOINT DISORDER	1	(0.9)	0		1	(0.5)	.498
LEG CRAMPS	1	(0.9)	1	(0.9)	2	(0.9)	1.00
LUNG DISORDER	1	(0.9)	0		1	(0.5)	.498
MACULOPAPULAR RASH	1	(0.9)	1	(0.9)	2	(0.9)	1.00
MANIC REACTION	1	(0.9)	0		1	(0.5)	.498

RMP.B1YP.JCLLIB2(AES2JEKS)
RMP.B1YO.HCJEREP(AES2JEKS)
* Frequencies are analyzed using a Fisher's Exact test.
XAES0002

Table 12.2. **Treatment-Emergent Non-Solicited Adverse Events Incidence by Decreasing Frequency (Ordered by Fluoxetine) All Randomized Patients Acute Treatment Phase (Study Periods III-IV) B1Y-MC-HCJE (continued)**

Event Classification	Flx 20 (N=109) n	(%)	Placebo (N=110) n	(%)	Total (N=219) n	(%)	p-Value*
MIGRAINE	1	(0.9)	1	(0.9)	2	(0.9)	1.00
MYALGIA	1	(0.9)	5	(4.5)	6	(2.7)	.212
NEUROSIS	1	(0.9)	0		1	(0.5)	.498
OVERDOSE	1	(0.9)	0		1	(0.5)	.498
PALPITATION	1	(0.9)	1	(0.9)	2	(0.9)	1.00
PNEUMONIA	1	(0.9)	0		1	(0.5)	.498
SURGICAL PROCEDURE	1	(0.9)	1	(0.9)	2	(0.9)	1.00
SWEATING	1	(0.9)	0		1	(0.5)	.498
SYNCOPE	1	(0.9)	0		1	(0.5)	.498
TACHYCARDIA	1	(0.9)	0		1	(0.5)	.498
TINNITUS	1	(0.9)	0		1	(0.5)	.498
TOOTH DISORDER	1	(0.9)	0		1	(0.5)	.498
URINARY FREQUENCY	1	(0.9)	2	(1.8)	3	(1.4)	1.00
URINARY TRACT INFECTION	1	(0.9)	1	(0.9)	2	(0.9)	1.00
VASODILATATION	1	(0.9)	0		1	(0.5)	.498
YAWN	1	(0.9)	0		1	(0.5)	.498
ABDOMINAL SYNDROME ACUTE	0		1	(0.9)	1	(0.5)	1.00
ACNE	0		1	(0.9)	1	(0.5)	1.00
ALOPECIA	0		1	(0.9)	1	(0.5)	1.00
AMNESIA	0		1	(0.9)	1	(0.5)	1.00
APHTHOUS STOMATITIS	0		1	(0.9)	1	(0.5)	1.00
ARTHRALGIA	0		1	(0.9)	1	(0.5)	1.00
BRADYCARDIA	0		1	(0.9)	1	(0.5)	1.00
CYSTITIS	0		1	(0.9)	1	(0.5)	1.00
DEHYDRATION	0		2	(1.8)	2	(0.9)	.498
DYSURIA	0		1	(0.9)	1	(0.5)	1.00
FACE EDEMA	0		1	(0.9)	1	(0.5)	1.00
GASTROINTESTINAL DISORDER	0		1	(0.9)	1	(0.5)	1.00
HYPESTHESIA	0		1	(0.9)	1	(0.5)	1.00
HYPOVENTILATION	0		1	(0.9)	1	(0.5)	1.00
INCREASED APPETITE	0		3	(2.7)	3	(1.4)	.247
INTENTIONAL INJURY	0		1	(0.9)	1	(0.5)	1.00
LARYNGITIS	0		1	(0.9)	1	(0.5)	1.00
LEUKORRHEA	0		1	(0.9)	1	(0.5)	1.00
METRORRHAGIA	0		1	(0.9)	1	(0.5)	1.00
MOUTH ULCERATION	0		1	(0.9)	1	(0.5)	1.00
SKIN DISCOLORATION	0		1	(0.9)	1	(0.5)	1.00
SKIN ULCER	0		1	(0.9)	1	(0.5)	1.00
SUBCUTANEOUS NODULE	0		1	(0.9)	1	(0.5)	1.00
THINKING ABNORMAL	0		1	(0.9)	1	(0.5)	1.00
UNEXPECTED BENEFIT	0		1	(0.9)	1	(0.5)	1.00

RMP.B1YP.JCLLIB2(AES2JEKS)
RMP.B1YO.HCJEREP(AES2JEKS)
* Frequencies are analyzed using a Fisher's Exact test.
XAES0002

Table 12.2. Treatment-Emergent Non-Solicited Adverse Events Incidence by Decreasing Frequency (Ordered by Fluoxetine) All Randomized Patients Acute Treatment Phase (Study Periods III-IV) B1Y-MC-HCJE (concluded)

Event Classification	Flx 20 (N=109) n (%)	Placebo (N=110) n (%)	Total (N=219) n (%)	p-Value*
WEIGHT GAIN	0	1 (0.9)	1 (0.5)	1.00

RMP.B1YP.JCLLIB2(AES2JEKS)
RMP.B1YO.HCJEREP(AES2JEKS)
* Frequencies are analyzed using a Fisher's Exact test.
XAES0002

12.2.2.1.2. Solicited Events

The incidence of treatment-emergent solicited adverse events from the Side-Effects Checklist during the acute treatment phase is summarized in Table 12.3.

One hundred five (96%) fluoxetine-treated patients and 100 (91%) placebo-treated patients reported at least one treatment-emergent solicited adverse event (p=.165). One treatment-emergent solicited adverse event, trouble pronouncing words, was reported statistically significantly (p=.015) more often by placebo-treated patients (26%) compared with fluoxetine-treated patients (12%).

Treatment-emergent solicited adverse events were also analyzed by maximum intensity (see Table 14.40, Section 14.3.1.1.3). There were no clinically relevant differences in maximum intensity for any treatment-emergent solicited adverse event.

Table 12.3. Treatment-Emergent Solicited Adverse Events
Side-Effects Checklist
Incidence by Decreasing Frequency (Ordered by Fluoxetine)
All Randomized Patients
Acute Treatment Phase (Study Periods III-IV)
B1Y-MC-HCJE

Event Classification	Flx 20 (N=109) n (%)	Placebo (N=110) n (%)	Total (N=219) n (%)	p-Value*
PATIENTS WITH >= 1 TESS	105 (96.3)	100 (90.9)	205 (93.6)	.165
PATIENTS WITH NO TESS	4 (3.7)	10 (9.1)	14 (6.4)	.165
23. FEELING SLEEPY	52 (47.7)	47 (42.7)	99 (45.2)	.499
22. TIREDNESS	50 (45.9)	46 (41.8)	96 (43.8)	.587
15. HEADACHE	49 (45.0)	41 (37.3)	90 (41.1)	.273
26. GETTING ALONG WITH PARENTS	43 (39.4)	45 (40.9)	88 (40.2)	.891
32. PAYING ATTENTION	43 (39.4)	31 (28.2)	74 (33.8)	.088
14. COLD OR SNIFFLES	41 (37.6)	50 (45.5)	91 (41.6)	.273
31. BEING SAD	41 (37.6)	32 (29.1)	73 (33.3)	.199
29. GETTING MAD	40 (36.7)	47 (42.7)	87 (39.7)	.408
30. NOT BEING HAPPY	40 (36.7)	34 (30.9)	74 (33.8)	.394
09. BEING SICK TO YOUR STOMACH	39 (35.8)	33 (30.0)	72 (32.9)	.390
24. SLEEPING	39 (35.8)	45 (40.9)	84 (38.4)	.488

1 Treatment-Emergent = was present at baseline (Visit 4) and worsened as defined by increase in score on the side-effects checklist at any postbaseline visit (Visits 5-10) or new occurrence after baseline.
RMP.B1YP.JCLLIB2(AES2JEKI)
RMP.B1YO.HCJEREP(AES2JEKI)
* Frequencies are analyzed using a Fisher’s Exact test.
XAES0002

Table 12.3. Treatment-Emergent Solicited Adverse Events
Side-Effects Checklist
Incidence by Decreasing Frequency (Ordered by Fluoxetine)
All Randomized Patients
Acute Treatment Phase (Study Periods III-IV)
B1Y-MC-HCJE (continued)

Event Classification	Flx 20 (N=109) n (%)	Placebo (N=110) n (%)	Total (N=219) n (%)	p-Value*
28. CRYING	39 (35.8)	39 (35.5)	78 (35.6)	1.00
07. STOMACHACHES	37 (33.9)	43 (39.1)	80 (36.5)	.484
16. DIZZINESS	34 (31.2)	23 (20.9)	57 (26.0)	.092
27. GETTING ALONG WITH KIDS	33 (30.3)	31 (28.2)	64 (29.2)	.768
03. DRY MOUTH AND LIPS	32 (29.4)	38 (34.5)	70 (32.0)	.469
01. EATING	31 (28.4)	35 (31.8)	66 (30.1)	.659
21. SITTING STILL	30 (27.5)	42 (38.2)	72 (32.9)	.114
08. MUSCLE CRAMPS	27 (24.8)	34 (30.9)	61 (27.9)	.366
12. ITCHY OR SCRATCHY SKIN	27 (24.8)	32 (29.1)	59 (26.9)	.543
25. BAD DREAMS	27 (24.8)	27 (24.5)	54 (24.7)	1.00
06. DIARRHEA	22 (20.2)	19 (17.3)	41 (18.7)	.607
18. SHAKINESS	21 (19.3)	23 (20.9)	44 (20.1)	.866
13. RASHES	17 (15.6)	18 (16.4)	35 (16.0)	1.00

1 Treatment-Emergent = was present at baseline (Visit 4) and worsened as defined by increase in score on the side-effects checklist at any postbaseline visit (Visits 5-10) or new occurrence after baseline.
RMP.B1YP.JCLLIB2(AES2JEKI)
RMP.B1YO.HCJEREP(AES2JEKI)
* Frequencies are analyzed using a Fisher’s Exact test.
XAES0002

Table 12.3. Treatment-Emergent Solicited Adverse Events
Side-Effects Checklist
Incidence by Decreasing Frequency (Ordered by Fluoxetine)
All Randomized Patients
Acute Treatment Phase (Study Periods III-IV)
B1Y-MC-HCJE (concluded)

Event Classification	Flx 20 (N=109) n (%)	Placebo (N=110) n (%)	Total (N=219) n (%)	p-Value*
17. PLAYING SPORTS	17 (15.6)	20 (18.2)	37 (16.9)	.719
02. DRINKING	14 (12.8)	20 (18.2)	34 (15.5)	.351
19. PRONOUNCING WORDS	13 (11.9)	28 (25.5)	41 (18.7)	.015
20. DOING THINGS WITH YOUR HANDS	13 (11.9)	19 (17.3)	32 (14.6)	.339
04. WETNESS IN MOUTH	10 (9.2)	19 (17.3)	29 (13.2)	.110
11. URINATING	10 (9.2)	12 (10.9)	22 (10.0)	.823
05. CONSTIPATION	9 (8.3)	10 (9.1)	19 (8.7)	1.00
10. WETTING THE BED	3 (2.8)	5 (4.5)	8 (3.7)	.721

1 Treatment-Emergent = was present at baseline (Visit 4) and worsened as defined by increase in score on the side-effects checklist at any postbaseline visit (Visits 5-10) or new occurrence after baseline.
RMP.B1YP.JCLLIB2(AES2JEKI)
RMP.B1YO.HCJEREP(AES2JEKI)
* Frequencies are analyzed using a Fisher's Exact test.
XAES0002

12.2.2.2. Subchronic Treatment Phase (Study Periods III-V)

12.2.2.2.1. Non-Solicited Adverse Events

Treatment-emergent non-solicited adverse events that occurred during the subchronic treatment phase are summarized in Table 12.4.

One hundred one (93%) fluoxetine-treated patients reported at least one treatment-emergent non-solicited adverse event compared with 87 (79%) placebo-treated patients (p=.006). Fluoxetine-treated patients reported more headaches than placebo-treated patients (p=.014). No other event occurred in statistically significantly different percentages of patients in the two treatment groups.

Treatment-emergent non-solicited adverse events were also examined by body system (see Table 14.41, Section 14.3.1.2.1) and by maximum severity (see Table 14.42, Section 14.3.1.2.2). The majority of reported treatment-emergent non-solicited adverse events were mild or moderate in severity. There were no statistically significant differences between treatment groups in the incidence of treatment-emergent non-solicited adverse events classified as severe.

Table 12.4. Treatment-Emergent Non-Solicited Adverse Events Incidence by Decreasing Frequency (Ordered by Fluoxetine) All Randomized Patients Subchronic Treatment Phase (Study Periods III-V) B1Y-MC-HCJE

Event Classification	Flx (N=109) n (%)	Placebo (N=110) n (%)	Total (N=219) n (%)	p-Value*
PATIENTS WITH >= 1 TESS	101 (92.7)	87 (79.1)	188 (85.8)	.006
PATIENTS WITH NO TESS	8 (7.3)	23 (20.9)	31 (14.2)	.006
HEADACHE	37 (33.9)	21 (19.1)	58 (26.5)	.014
RHINITIS	34 (31.2)	29 (26.4)	63 (28.8)	.458
ABDOMINAL PAIN	22 (20.2)	22 (20.0)	44 (20.1)	1.00
PHARYNGITIS	21 (19.3)	14 (12.7)	35 (16.0)	.202
ACCIDENTAL INJURY	19 (17.4)	10 (9.1)	29 (13.2)	.076
COUGH INCREASED	16 (14.7)	9 (8.2)	25 (11.4)	.143
DIARRHEA	14 (12.8)	13 (11.8)	27 (12.3)	.840
RASH	13 (11.9)	10 (9.1)	23 (10.5)	.517
DIZZINESS	11 (10.1)	8 (7.3)	19 (8.7)	.483
NERVOUSNESS	11 (10.1)	6 (5.5)	17 (7.8)	.218
VOMITING	11 (10.1)	12 (10.9)	23 (10.5)	1.00
ANOREXIA	10 (9.2)	9 (8.2)	19 (8.7)	.815
ASTHENIA	10 (9.2)	7 (6.4)	17 (7.8)	.462
FEVER	10 (9.2)	8 (7.3)	18 (8.2)	.632
PAIN	10 (9.2)	12 (10.9)	22 (10.0)	.823
NAUSEA	9 (8.3)	11 (10.0)	20 (9.1)	.815
ABNORMAL DREAMS	7 (6.4)	3 (2.7)	10 (4.6)	.215
BACK PAIN	6 (5.5)	5 (4.5)	11 (5.0)	.768
DRY MOUTH	6 (5.5)	6 (5.5)	12 (5.5)	1.00
EAR PAIN	6 (5.5)	3 (2.7)	9 (4.1)	.332
INSOMNIA	6 (5.5)	5 (4.5)	11 (5.0)	.768
PRURITUS	6 (5.5)	6 (5.5)	12 (5.5)	1.00
EPISTAXIS	5 (4.6)	2 (1.8)	7 (3.2)	.280
HOSTILITY	5 (4.6)	5 (4.5)	10 (4.6)	1.00
INFECTION	5 (4.6)	5 (4.5)	10 (4.6)	1.00
PERSONALITY DISORDER	5 (4.6)	2 (1.8)	7 (3.2)	.280
SOMNOLENCE	5 (4.6)	4 (3.6)	9 (4.1)	.748
AGITATION	4 (3.7)	0	4 (1.8)	.060
ALLERGIC REACTION	4 (3.7)	2 (1.8)	6 (2.7)	.446
DYSMENORRHEA	4 (3.7)	4 (3.6)	8 (3.7)	1.00
DYSPEPSIA	4 (3.7)	5 (4.5)	9 (4.1)	1.00
ECCHYMOSIS	4 (3.7)	2 (1.8)	6 (2.7)	.446
FLU SYNDROME	4 (3.7)	3 (2.7)	7 (3.2)	.721
HYPERKINESIA	4 (3.7)	1 (0.9)	5 (2.3)	.212
PHOTOSENSITIVITY REACTION	4 (3.7)	1 (0.9)	5 (2.3)	.212
SINUSITIS	4 (3.7)	2 (1.8)	6 (2.7)	.446
AKATHISIA	3 (2.8)	0	3 (1.4)	.122
ASTHMA	3 (2.8)	0	3 (1.4)	.122
CHEST PAIN	3 (2.8)	2 (1.8)	5 (2.3)	.683

RMP.B1YP.JCLLIB2(AES2JEKL)
RMP.B1YO.HCJEREP(AES2JEKL)
* Frequencies are analyzed using a Fisher's Exact test.
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Table 12.4. Treatment-Emergent Non-Solicited Adverse Events Incidence by Decreasing Frequency (Ordered by Fluoxetine) All Randomized Patients Subchronic Treatment Phase (Study Periods III-V) B1Y-MC-HCJE (continued)

Event Classification	Flx (N=109) n	(%)	Placebo (N=110) n	(%)	Total (N=219) n	(%)	p-Value*
CONSTIPATION	3	(2.8)	6	(5.5)	9	(4.1)	.499
CONTACT DERMATITIS	3	(2.8)	0		3	(1.4)	.122
DEPRESSION	3	(2.8)	2	(1.8)	5	(2.3)	.683
MYALGIA	3	(2.8)	6	(5.5)	9	(4.1)	.499
NECK PAIN	3	(2.8)	1	(0.9)	4	(1.8)	.369
SPEECH DISORDER	3	(2.8)	2	(1.8)	5	(2.3)	.683
TREMOR	3	(2.8)	1	(0.9)	4	(1.8)	.369
ACUTE BRAIN SYNDROME	2	(1.8)	0		2	(0.9)	.247
ANXIETY	2	(1.8)	0		2	(0.9)	.247
BRONCHITIS	2	(1.8)	2	(1.8)	4	(1.8)	1.00
CHILLS	2	(1.8)	1	(0.9)	3	(1.4)	.622
DRY SKIN	2	(1.8)	3	(2.7)	5	(2.3)	1.00
EAR DISORDER	2	(1.8)	1	(0.9)	3	(1.4)	.622
EUPHORIA	2	(1.8)	0		2	(0.9)	.247
EYE DISORDER	2	(1.8)	0		2	(0.9)	.247
GASTROENTERITIS	2	(1.8)	0		2	(0.9)	.247
INCREASED APPETITE	2	(1.8)	3	(2.7)	5	(2.3)	1.00
NECK RIGIDITY	2	(1.8)	1	(0.9)	3	(1.4)	.622
OTITIS EXTERNA	2	(1.8)	1	(0.9)	3	(1.4)	.622
SLEEP DISORDER	2	(1.8)	0		2	(0.9)	.247
SURGICAL PROCEDURE	2	(1.8)	2	(1.8)	4	(1.8)	1.00
SWEATING	2	(1.8)	0		2	(0.9)	.247
THINKING ABNORMAL	2	(1.8)	1	(0.9)	3	(1.4)	.622
THIRST	2	(1.8)	2	(1.8)	4	(1.8)	1.00
TOOTH DISORDER	2	(1.8)	0		2	(0.9)	.247
WEIGHT LOSS	2	(1.8)	1	(0.9)	3	(1.4)	.622
YAWN	2	(1.8)	0		2	(0.9)	.247
AMBLYOPIA	1	(0.9)	0		1	(0.5)	.498
AMNESIA	1	(0.9)	1	(0.9)	2	(0.9)	1.00
ANEMIA	1	(0.9)	0		1	(0.5)	.498
APATHY	1	(0.9)	0		1	(0.5)	.498
BRADYCARDIA	1	(0.9)	1	(0.9)	2	(0.9)	1.00
BUCCOGLOSSAL SYNDROME	1	(0.9)	0		1	(0.5)	.498
CARDIOVASCULAR DISORDER	1	(0.9)	0		1	(0.5)	.498
DELUSIONS	1	(0.9)	0		1	(0.5)	.498
DYSPHAGIA	1	(0.9)	1	(0.9)	2	(0.9)	1.00
DYSPNEA	1	(0.9)	0		1	(0.5)	.498
EMOTIONAL LABILITY	1	(0.9)	0		1	(0.5)	.498
ENDOCRINE DISORDER	1	(0.9)	0		1	(0.5)	.498
ENDOMETRIAL HYPERPLASIA	1	(0.9)	0		1	(0.5)	.498
EYE PAIN	1	(0.9)	0		1	(0.5)	.498

RMP.B1YP.JCLLIB2(AES2JEKL)
RMP.B1YO.HCJEREP(AES2JEKL)
* Frequencies are analyzed using a Fisher's Exact test.
XAES0002

Table 12.4. Treatment-Emergent Non-Solicited Adverse Events Incidence by Decreasing Frequency (Ordered by Fluoxetine) All Randomized Patients Subchronic Treatment Phase (Study Periods III-V) B1Y-MC-HCJE (continued)

Event Classification	Flx (N=109) n	(%)	Placebo (N=110) n	(%)	Total (N=219) n	(%)	p-Value*
FECAL INCONTINENCE	1	(0.9)	0		1	(0.5)	.498
FLATULENCE	1	(0.9)	0		1	(0.5)	.498
FUNGAL DERMATITIS	1	(0.9)	1	(0.9)	2	(0.9)	1.00
GASTROINTESTINAL DISORDER	1	(0.9)	1	(0.9)	2	(0.9)	1.00
HALLUCINATIONS	1	(0.9)	0		1	(0.5)	.498
HEPATITIS NONSPECIFIC	1	(0.9)	0		1	(0.5)	.498
HEPATOMEGALY	1	(0.9)	1	(0.9)	2	(0.9)	1.00
HERPES SIMPLEX	1	(0.9)	0		1	(0.5)	.498
HYPERCHOLESTEREMIA	1	(0.9)	0		1	(0.5)	.498
HYPERTONIA	1	(0.9)	1	(0.9)	2	(0.9)	1.00
HYPOTENSION	1	(0.9)	0		1	(0.5)	.498
INCREASED SALIVATION	1	(0.9)	1	(0.9)	2	(0.9)	1.00
INTENTIONAL INJURY	1	(0.9)	1	(0.9)	2	(0.9)	1.00
JOINT DISORDER	1	(0.9)	0		1	(0.5)	.498
LARYNGITIS	1	(0.9)	1	(0.9)	2	(0.9)	1.00
LEG CRAMPS	1	(0.9)	3	(2.7)	4	(1.8)	.622
LEUKOPENIA	1	(0.9)	0		1	(0.5)	.498
LUNG DISORDER	1	(0.9)	0		1	(0.5)	.498
LYMPHADENOPATHY	1	(0.9)	1	(0.9)	2	(0.9)	1.00
MACULOPAPULAR RASH	1	(0.9)	1	(0.9)	2	(0.9)	1.00
MANIC REACTION	1	(0.9)	0		1	(0.5)	.498
MIGRAINE	1	(0.9)	1	(0.9)	2	(0.9)	1.00
NEUROSIS	1	(0.9)	0		1	(0.5)	.498
OTITIS MEDIA	1	(0.9)	0		1	(0.5)	.498
OVERDOSE	1	(0.9)	1	(0.9)	2	(0.9)	1.00
PALPITATION	1	(0.9)	1	(0.9)	2	(0.9)	1.00
PNEUMONIA	1	(0.9)	0		1	(0.5)	.498
RECTAL HEMORRHAGE	1	(0.9)	0		1	(0.5)	.498
SINUS BRADYCARDIA	1	(0.9)	0		1	(0.5)	.498
SYNCOPE	1	(0.9)	0		1	(0.5)	.498
TACHYCARDIA	1	(0.9)	0		1	(0.5)	.498
THYROID DISORDER	1	(0.9)	0		1	(0.5)	.498
TINNITUS	1	(0.9)	0		1	(0.5)	.498
ULCERATIVE STOMATITIS	1	(0.9)	0		1	(0.5)	.498
URINARY FREQUENCY	1	(0.9)	2	(1.8)	3	(1.4)	1.00
URINARY TRACT INFECTION	1	(0.9)	1	(0.9)	2	(0.9)	1.00
VASODILATATION	1	(0.9)	0		1	(0.5)	.498
VESICULOBULLOUS RASH	1	(0.9)	0		1	(0.5)	.498
ABDOMINAL SYNDROME ACUTE	0		1	(0.9)	1	(0.5)	1.00
ACNE	0		1	(0.9)	1	(0.5)	1.00
ALOPECIA	0		1	(0.9)	1	(0.5)	1.00

RMP.B1YP.JCLLIB2(AES2JEKL)
RMP.B1YO.HCJEREP(AES2JEKL)
* Frequencies are analyzed using a Fisher's Exact test.
XAES0002

Table 12.4. Treatment-Emergent Non-Solicited Adverse Events Incidence by Decreasing Frequency (Ordered by Fluoxetine) All Randomized Patients Subchronic Treatment Phase (Study Periods III-V) B1Y-MC-HCJE (concluded)

Event Classification	Flx (N=109) n (%)	Placebo (N=110) n (%)	Total (N=219) n (%)	p-Value*
APHTHOUS STOMATITIS	0	1 (0.9)	1 (0.5)	1.00
ARTHRALGIA	0	1 (0.9)	1 (0.5)	1.00
BILIRUBINURIA	0	1 (0.9)	1 (0.5)	1.00
CYSTITIS	0	1 (0.9)	1 (0.5)	1.00
DEHYDRATION	0	2 (1.8)	2 (0.9)	.498
DYSURIA	0	1 (0.9)	1 (0.5)	1.00
FACE EDEMA	0	1 (0.9)	1 (0.5)	1.00
HYPESTHESIA	0	1 (0.9)	1 (0.5)	1.00
HYPOVENTILATION	0	1 (0.9)	1 (0.5)	1.00
LEUKORRHEA	0	1 (0.9)	1 (0.5)	1.00
LYMPHOCYTOSIS	0	1 (0.9)	1 (0.5)	1.00
MENORRHAGIA	0	1 (0.9)	1 (0.5)	1.00
METRORRHAGIA	0	1 (0.9)	1 (0.5)	1.00
MOUTH ULCERATION	0	1 (0.9)	1 (0.5)	1.00
PUSTULAR RASH	0	1 (0.9)	1 (0.5)	1.00
SKIN DISCOLORATION	0	1 (0.9)	1 (0.5)	1.00
SKIN ULCER	0	1 (0.9)	1 (0.5)	1.00
SPLENOMEGALY	0	1 (0.9)	1 (0.5)	1.00
SUBCUTANEOUS NODULE	0	1 (0.9)	1 (0.5)	1.00
UNEXPECTED BENEFIT	0	1 (0.9)	1 (0.5)	1.00
VERTIGO	0	1 (0.9)	1 (0.5)	1.00
WEIGHT GAIN	0	1 (0.9)	1 (0.5)	1.00

RMP.B1YP.JCLLIB2(AES2JEKL)
RMP.B1YO.HCJEREP(AES2JEKL)
* Frequencies are analyzed using a Fisher's Exact test.
XAES0002

12.2.2.2.2. Solicited Events

The incidence of treatment-emergent solicited adverse events from the Side-Effects Checklist during the subchronic treatment phase is summarized in Table 12.5.

One hundred seven (98%) fluoxetine-treated patients and 101 (92%) placebo-treated patients reported at least one treatment-emergent solicited adverse event (p=.059). During subchronic treatment, the adverse event trouble pronouncing words occurred statistically more often in placebo-treated patients as compared with fluoxetine-treated patients (p=.025). In addition, placebo-treated patients experienced significantly more events of wetness in mouth as compared with fluoxetine-treated patients (p=.026). No other event occurred statistically significantly more often between the two treatment groups.

For the primary analysis of the Side-Effects Checklist, the intensity score of "don't know = 4" was set to "not at all = 0." Treatment-emergent solicited adverse events were also evaluated using a more conservative method of determining treatment-emergence. In this analysis, the intensity score of "don't know = 4" was set to "missing." "Missing"

values for a known event were then assumed to have an intensity score based on whether the event occurred at baseline or postbaseline. Baseline events were assigned an intensity score of 1 and postbaseline events were assigned an intensity score of 3. Treatment-emergence for these events was determined using these values. This additional analysis of the Side-Effects Checklist is presented in Table 14.43 (see Section 14.3.1.2.3). One hundred eight (99%) fluoxetine-treated patients reported treatment-emergent solicited adverse events as compared with 102 (93%) placebo-treated patients (p=.035). Placebo-treated patients reported statistically significantly more events of trouble pronouncing words (p=.027) and wetness in mouth (p=.011). These results are similar to those seen using the primary analysis of the Side-Effects Checklist (see Table 12.5).

Treatment-emergent solicited adverse events were also examined by maximum intensity (see Table 14.44, Section 14.3.1.2.4). There were no clinically relevant differences in maximum intensity for any treatment-emergent solicited adverse event.

Table 12.5. **Treatment-Emergent Solicited Adverse Events**
Side-Effects Checklist
Incidence by Decreasing Frequency (Ordered by Fluoxetine)
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE

Event Classification	Flx (N=109) n (%)	Placebo (N=110) n (%)	Total (N=219) n (%)	p-Value*
PATIENTS WITH >= 1 TESS	107 (98.2)	101 (91.8)	208 (95.0)	.059
PATIENTS WITH NO TESS	2 (1.8)	9 (8.2)	11 (5.0)	.059
15. HEADACHE	57 (52.3)	44 (40.0)	101 (46.1)	.079
23. FEELING SLEEPY	56 (51.4)	49 (44.5)	105 (47.9)	.345
22. TIREDNESS	55 (50.5)	48 (43.6)	103 (47.0)	.345
14. COLD OR SNIFFLES	51 (46.8)	56 (50.9)	107 (48.9)	.590
26. GETTING ALONG WITH PARENTS	51 (46.8)	48 (43.6)	99 (45.2)	.685
07. STOMACHACHES	48 (44.0)	49 (44.5)	97 (44.3)	1.00
28. CRYING	47 (43.1)	44 (40.0)	91 (41.6)	.682
31. BEING SAD	47 (43.1)	36 (32.7)	83 (37.9)	.127
32. PAYING ATTENTION	47 (43.1)	37 (33.6)	84 (38.4)	.166
24. SLEEPING	45 (41.3)	50 (45.5)	95 (43.4)	.586
29. GETTING MAD	45 (41.3)	51 (46.4)	96 (43.8)	.497

1 Treatment-Emergent = was present at baseline (Visit 4) and worsened as defined by increase in score on the side-effects checklist at any postbaseline visit (Visits 5-15) or new occurrence after baseline.
RMP.B1YP.JCLLIB2(AES2JEKK)
RMP.B1YO.HCJEREP(AES2JEKK)
* Frequencies are analyzed using a Fisher’s Exact test.
XAES0002

Table 12.5. Treatment-Emergent Solicited Adverse Events
Side-Effects Checklist
Incidence by Decreasing Frequency (Ordered by Fluoxetine)
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE (continued)

Event Classification	Flx (N=109) n (%)	Placebo (N=110) n (%)	Total (N=219) n (%)	p-Value*
09. BEING SICK TO YOUR STOMACH	44 (40.4)	39 (35.5)	83 (37.9)	.488
30. NOT BEING HAPPY	44 (40.4)	39 (35.5)	83 (37.9)	.488
16. DIZZINESS	38 (34.9)	32 (29.1)	70 (32.0)	.387
08. MUSCLE CRAMPS	35 (32.1)	42 (38.2)	77 (35.2)	.396
01. EATING	34 (31.2)	39 (35.5)	73 (33.3)	.567
03. DRY MOUTH AND LIPS	34 (31.2)	42 (38.2)	76 (34.7)	.321
21. SITTING STILL	34 (31.2)	43 (39.1)	77 (35.2)	.258
27. GETTING ALONG WITH KIDS	34 (31.2)	33 (30.0)	67 (30.6)	.884
12. ITCHY OR SCRATCHY SKIN	32 (29.4)	36 (32.7)	68 (31.1)	.662
25. BAD DREAMS	30 (27.5)	35 (31.8)	65 (29.7)	.555
06. DIARRHEA	28 (25.7)	23 (20.9)	51 (23.3)	.428
18. SHAKINESS	26 (23.9)	24 (21.8)	50 (22.8)	.750
17. PLAYING SPORTS	19 (17.4)	21 (19.1)	40 (18.3)	.861

1 Treatment-Emergent = was present at baseline (Visit 4) and worsened as defined by increase in score on the side-effects checklist at any postbaseline visit (Visits 5-15) or new occurrence after baseline.
RMP.B1YP.JCLLIB2(AES2JEKK)
RMP.B1YO.HCJEREP(AES2JEKK)
* Frequencies are analyzed using a Fisher’s Exact test.
XAES0002

Table 12.5. Treatment-Emergent Solicited Adverse Events
Side-Effects Checklist
Incidence by Decreasing Frequency (Ordered by Fluoxetine)
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE (concluded)

Event Classification	Flx (N=109) n (%)	Placebo (N=110) n (%)	Total (N=219) n (%)	p-Value*
13. RASHES	18 (16.5)	25 (22.7)	43 (19.6)	.308
19. PRONOUNCING WORDS	18 (16.5)	33 (30.0)	51 (23.3)	.025
02. DRINKING	16 (14.7)	21 (19.1)	37 (16.9)	.471
20. DOING THINGS WITH YOUR HANDS	15 (13.8)	25 (22.7)	40 (18.3)	.115
04. WETNESS IN MOUTH	11 (10.1)	24 (21.8)	35 (16.0)	.026
05. CONSTIPATION	11 (10.1)	14 (12.7)	25 (11.4)	.672
11. URINATING	10 (9.2)	13 (11.8)	23 (10.5)	.660
10. WETTING THE BED	3 (2.8)	5 (4.5)	8 (3.7)	.721

1 Treatment-Emergent = was present at baseline (Visit 4) and worsened as defined by increase in score on the side-effects checklist at any postbaseline visit (Visits 5-15) or new occurrence after baseline.
RMP.B1YP.JCLLIB2(AES2JEKK)
RMP.B1YO.HCJEREP(AES2JEKK)
* Frequencies are analyzed using a Fisher's Exact test.
XAES0002

12.2.2.3. Adverse Events in Nonresponders Following Rerandomization

Comparisons were made between the fluoxetine 20 mg/day treatment group (n=15) and the 40 mg/day and 60 mg/day treatment groups combined (n=14). When determining treatment-emergent events for these analyses, baseline was defined as Visits 4 through 10.

12.2.2.3.1. Non-Solicited Events

Table 12.6 summarizes the treatment-emergent non-solicited adverse events reported by all nonresponders during Study Period V.

Seven (47%) patients in the fluoxetine 20 mg/day treatment group reported at least one treatment-emergent non-solicited adverse event compared with 9 (64%) patients in the fluoxetine 40 to 60 mg/day treatment group (p=.462). There were no statistically significant differences between the two treatment groups in the incidence of any treatment-emergent non-solicited adverse event.

Table 12.6. Treatment-Emergent Non-Solicited Adverse Events Incidence by Decreasing Frequency (Ordered by Flx 20 mg) All Nonresponders Study Period V, B1Y-MC-HCJE

Event Classification	Flx 20 (N=15) n (%)	Flx40/60 (N=14) n (%)	Total (N=29) n (%)	p-Value*
PATIENTS WITH >= 1 TESS	7 (46.7)	9 (64.3)	16 (55.2)	.462
PATIENTS WITH NO TESS	8 (53.3)	5 (35.7)	13 (44.8)	.462
PERSONALITY DISORDER	3 (20.0)	0	3 (10.3)	.224
COUGH INCREASED	2 (13.3)	1 (7.1)	3 (10.3)	1.00
HOSTILITY	2 (13.3)	0	2 (6.9)	.483
RHINITIS	2 (13.3)	2 (14.3)	4 (13.8)	1.00
DIARRHEA	1 (6.7)	0	1 (3.4)	1.00
EAR PAIN	1 (6.7)	0	1 (3.4)	1.00
EUPHORIA	1 (6.7)	0	1 (3.4)	1.00
FEVER	1 (6.7)	1 (7.1)	2 (6.9)	1.00
INSOMNIA	1 (6.7)	0	1 (3.4)	1.00
LYMPHADENOPATHY	1 (6.7)	0	1 (3.4)	1.00
SOMNOLENCE	1 (6.7)	1 (7.1)	2 (6.9)	1.00
SPEECH DISORDER	1 (6.7)	0	1 (3.4)	1.00
THINKING ABNORMAL	1 (6.7)	0	1 (3.4)	1.00
ABDOMINAL PAIN	0	2 (14.3)	2 (6.9)	.224
ABNORMAL DREAMS	0	1 (7.1)	1 (3.4)	.483
ACCIDENTAL INJURY	0	3 (21.4)	3 (10.3)	.100
AMBLYOPIA	0	1 (7.1)	1 (3.4)	.483
BACK PAIN	0	1 (7.1)	1 (3.4)	.483
BRONCHITIS	0	1 (7.1)	1 (3.4)	.483
CONTACT DERMATITIS	0	1 (7.1)	1 (3.4)	.483
DIZZINESS	0	1 (7.1)	1 (3.4)	.483
DRY MOUTH	0	2 (14.3)	2 (6.9)	.224
INCREASED SALIVATION	0	1 (7.1)	1 (3.4)	.483
INFECTION	0	2 (14.3)	2 (6.9)	.224
INTENTIONAL INJURY	0	1 (7.1)	1 (3.4)	.483
NECK RIGIDITY	0	2 (14.3)	2 (6.9)	.224
NERVOUSNESS	0	1 (7.1)	1 (3.4)	.483
PAIN	0	2 (14.3)	2 (6.9)	.224
PHARYNGITIS	0	2 (14.3)	2 (6.9)	.224
PRURITUS	0	1 (7.1)	1 (3.4)	.483
RASH	0	1 (7.1)	1 (3.4)	.483
SINUS BRADYCARDIA	0	1 (7.1)	1 (3.4)	.483
SINUSITIS	0	1 (7.1)	1 (3.4)	.483
ULCERATIVE STOMATITIS	0	1 (7.1)	1 (3.4)	.483
VOMITING	0	1 (7.1)	1 (3.4)	.483

RMP.B1YP.JCLLIB2(AES2JEKN)
RMP.B1YO.HCJEREP(AES2JEKN)
* Frequencies are analyzed using a Fisher's Exact test.
XAES0002

12.2.2.3.2. Solicited Events

Table 12.7 summarizes the treatment-emergent solicited adverse events from the Side-Effects Checklist reported by all nonresponders during Study Period V.

Eight (53%) patients in the fluoxetine 20 mg/day treatment group reported at least one treatment-emergent solicited adverse event compared with 11 (79%) patients in the fluoxetine 40 to 60 mg/day treatment group (p=.245). There were no statistically

significant differences between the two treatment groups in the incidence of any treatment-emergent solicited adverse event.

Table 12.7. Treatment-Emergent Solicited Adverse Events
Side Effects Checklist
Incidence by Decreasing Frequency (Ordered by Flx 20 mg)
All Nonresponders
Study Period V, B1Y-MC-HCJE

Event Classification	Flx 20 (N=15) n (%)	Flx40/60 (N=14) n (%)	Total (N=29) n (%)	p-Value*
PATIENTS WITH >= 1 TESS	8 (53.3)	11 (78.6)	19 (65.5)	.245
PATIENTS WITH NO TESS	7 (46.7)	3 (21.4)	10 (34.5)	.245
07. STOMACHACHES	2 (13.3)	3 (21.4)	5 (17.2)	.651
14. COLD OR SNIFFLES	2 (13.3)	3 (21.4)	5 (17.2)	.651
23. FEELING SLEEPY	2 (13.3)	2 (14.3)	4 (13.8)	1.00
24. SLEEPING	2 (13.3)	2 (14.3)	4 (13.8)	1.00
28. CRYING	2 (13.3)	1 (7.1)	3 (10.3)	1.00
01. EATING	1 (6.7)	1 (7.1)	2 (6.9)	1.00
06. DIARRHEA	1 (6.7)	0	1 (3.4)	1.00
08. MUSCLE CRAMPS	1 (6.7)	3 (21.4)	4 (13.8)	.330
09. BEING SICK TO YOUR STOMACH	1 (6.7)	1 (7.1)	2 (6.9)	1.00
15. HEADACHE	1 (6.7)	3 (21.4)	4 (13.8)	.330
18. SHAKINESS	1 (6.7)	1 (7.1)	2 (6.9)	1.00
22. TIREDNESS	1 (6.7)	2 (14.3)	3 (10.3)	.598
25. BAD DREAMS	1 (6.7)	1 (7.1)	2 (6.9)	1.00
29. GETTING MAD	1 (6.7)	2 (14.3)	3 (10.3)	.598
32. PAYING ATTENTION	1 (6.7)	4 (28.6)	5 (17.2)	.169
02. DRINKING	0	1 (7.1)	1 (3.4)	.483
03. DRY MOUTH AND LIPS	0	2 (14.3)	2 (6.9)	.224
04. WETNESS IN MOUTH	0	1 (7.1)	1 (3.4)	.483
12. ITCHY OR SCRATCHY SKIN	0	2 (14.3)	2 (6.9)	.224
16. DIZZINESS	0	3 (21.4)	3 (10.3)	.100
19. PRONOUNCING WORDS	0	1 (7.1)	1 (3.4)	.483
20. DOING THINGS WITH YOUR HANDS	0	1 (7.1)	1 (3.4)	.483
21. SITTING STILL	0	2 (14.3)	2 (6.9)	.224
26. GETTING ALONG WITH PARENTS	0	2 (14.3)	2 (6.9)	.224
27. GETTING ALONG WITH KIDS	0	2 (14.3)	2 (6.9)	.224
30. NOT BEING HAPPY	0	2 (14.3)	2 (6.9)	.224
31. BEING SAD	0	1 (7.1)	1 (3.4)	.483

1 Treatment-Emergent = was present at baseline (highest score for item of Visits 4-10) and
worsened as defined by increase in score on the side-effects checklist at any postbaseline
visit (Visits 11-15) or new occurrence after baseline.
RMP.B1YP.JCLLIB2(AES2JEKM)
RMP.B1YO.HCJEREP(AES2JEKM)
* Frequencies are analyzed using a Fisher's Exact test.
XAES0002

12.2.3. Listing of Adverse Events by Patient

Complete listings of all adverse events by patient are located in Appendix 16.2.1.

12.3. Deaths, Serious Adverse Events, and Nonserious Clinically Significant Adverse Events

12.3.1. Deaths

No patients died during Study Periods I through V.

12.3.2. Serious Adverse Events

Table 12.8 summarizes the serious adverse events that occurred during Study Periods I through V. Nine serious adverse events occurred in 9 patients (3 not randomized, 2 fluoxetine-treated, 4 placebo-treated). Serious adverse events led to the discontinuation of 5 patients (1 not randomized, 1 fluoxetine-treated, 3 placebo-treated).

Three serious adverse events occurred during the diagnostic evaluation and placebo washout periods of the study (Study Periods I and II), prior to randomization to study treatment. Patient 207 discontinued the study because of the serious adverse event explosive aggression. Patients 128 and 1132 discontinued the study due to clinical findings of psychotic symptoms and suicidal ideation, both of which were exclusionary according to protocol requirements. Six serious adverse events occurred during double-blind treatment, two in fluoxetine-treated patients and four in placebo-treated patients. Patient 419 (fluoxetine-treated) discontinued the study because of suicidal ideation. Patient 1609 (fluoxetine-treated) had swollen tonsils, underwent a tonsillectomy, and completed the study through Study Period V. Patients 806, 2201, and 2213 (placebo-treated) discontinued the study due to self-mutilatory behavior, aggressive behavior, and kidney infection, respectively. Patient 1656 (placebo-treated) experienced abdominal pain/appendicitis, underwent an appendectomy, and completed the study through Study Period V.

Table 12.8. Serious Adverse Events
All Randomized Patients
B1Y-MC-HCJE

Patient	Therapy	Event Classification Term	Visit Event Reported	Discontinued (Yes/No)	Visit Discontinued	Related to Study Drug	Days in Therapy at Discontinuation	Remarks
128	NR	Psychotic symptoms	1	Yes[b]	1	NA	0	Hospitalized
207	NR	Explosive aggression	1	Yes	1	NA	0	Hospitalized
1132	NR	Suicidal ideation	3	Yes[b]	3	NA	0	Hospitalized
419	Fluoxetine	Suicidal ideation	1[a]	Yes	11	Possibly	70	Hospitalized
1609	Fluoxetine	Swollen tonsils	6	No[c]	NA	No	NA	Hospitalized
806	Placebo	Self-mutilatory behavior	1[a]	Yes	8	No	37	Hospitalized
1656	Placebo	Abdominal pain/appendicitis	9	No[c]	NA	No	NA	Hospitalized
2201	Placebo	Aggressive behavior	1[a]	Yes	6	No	10	Hospitalized
2213	Placebo	Kidney infection	10	Yes	10	No	67	Hospitalized

Data were derived from RMP.B1YO.HCJEREP (AEL1JEAA), RMP.B1YO.HCJEREP (RDL1JEAA), and patient summaries.
See Appendix 16.2.2 for documentation of visit discontinued and days in therapy at discontinuation.
[a]These events were present at Visit 1 but were not serious at that time. The events became serious at a later visit and resulted in the patient's discontinuation from the study.
[b]Discontinued due to protocol requirement, not due to the event.
[c]Completed the study through Study Period V.
Abbreviations: NA = not applicable; NR = not randomized to treatment.

12.3.3. Nonserious Clinically Significant Adverse Events

A total of 23 patients discontinued due to adverse events, including the 5 patients discontinued due to serious adverse events, during Study Periods I through V (1 not randomized, 11 fluoxetine-treated, 11 placebo-treated). Patient 207 discontinued prior to randomization for the serious adverse event of explosive aggression, and therefore is not included in Tables 12.9 and 12.10. The two pts with psychosis and suicidal ideation not included either

Tables 12.9 and 12.10 present the incidence of adverse events leading to discontinuation for all randomized patients during the acute and subchronic treatment phases of the study, respectively. Fourteen patients (5 fluoxetine-treated, 9 placebo-treated) discontinued due to adverse events during the 9-week acute treatment phase (p=.408). A total of 22 randomized patients (11 fluoxetine-treated, 11 placebo-treated) discontinued during the 19-week subchronic treatment phase (p=1.00), which is inclusive of the acute treatment phase.

Table 12.9. Adverse Events Leading to Discontinuation
Incidence by Decreasing Frequency (Ordered by Fluoxetine)
All Randomized Patients
Acute Treatment Phase (Study Periods III-IV)
B1Y-MC-HCJE

Event Classification	Flx 20 (N=109) n	(%)	Placebo (N=110) n	(%)	Total (N=219) n	(%)	p-Value*
PATIENTS DISCONTINUED	5	(4.6)	9	(8.2)	14	(6.4)	.408
RASH	1	(0.9)	1	(0.9)	2	(0.9)	1.00
ABDOMINAL PAIN	0		1	(0.9)	1	(0.5)	1.00
AGITATION	1	(0.9)	0		1	(0.5)	.498
ALOPECIA	0		1	(0.9)	1	(0.5)	1.00
ANXIETY	0		1	(0.9)	1	(0.5)	1.00
CONSTIPATION	1	(0.9)	0		1	(0.5)	.498
DIZZINESS	0		1	(0.9)	1	(0.5)	1.00
HEADACHE	0		1	(0.9)	1	(0.5)	1.00
HOSTILITY	0		1	(0.9)	1	(0.5)	1.00
HYPERKINESIA	1	(0.9)	0		1	(0.5)	.498
INFECTION	0		1	(0.9)	1	(0.5)	1.00
INTENTIONAL INJURY	0		1	(0.9)	1	(0.5)	1.00
MANIC REACTION	1	(0.9)	0		1	(0.5)	.498

RMP.B1YP.JCLLIB2(AES3JEAA)
RMP.B1YO.HCJEREP(AES3JEAA)
* Frequencies are analyzed using a Fisher's Exact test.
XAES0003

Table 12.10. Adverse Events Leading to Discontinuation
Incidence by Decreasing Frequency (Ordered by Fluoxetine)
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE

Event Classification	Flx (N=109) n (%)	Placebo (N=110) n (%)	Total (N=219) n (%)	p-Value*
PATIENTS DISCONTINUED	11 (10.1)	11 (10.0)	22 (10.0)	1.00
HOSTILITY	1 (0.9)	1 (0.9)	2 (0.9)	1.00
RASH	1 (0.9)	1 (0.9)	2 (0.9)	1.00
ABDOMINAL PAIN	0	1 (0.9)	1 (0.5)	1.00
AGITATION	1 (0.9)	0	1 (0.5)	.498
ALOPECIA	0	1 (0.9)	1 (0.5)	1.00
ANXIETY	0	1 (0.9)	1 (0.5)	1.00
CONSTIPATION	1 (0.9)	0	1 (0.5)	.498
DEPRESSION	1 (0.9)	0	1 (0.5)	.498
DIZZINESS	0	1 (0.9)	1 (0.5)	1.00
ENDOMETRIAL HYPERPLASIA	1 (0.9)	0	1 (0.5)	.498
EUPHORIA	1 (0.9)	0	1 (0.5)	.498
HEADACHE	0	1 (0.9)	1 (0.5)	1.00
HYPERKINESIA	1 (0.9)	0	1 (0.5)	.498
INFECTION	0	1 (0.9)	1 (0.5)	1.00
INTENTIONAL INJURY	0	1 (0.9)	1 (0.5)	1.00
LYMPHOCYTOSIS	0	1 (0.9)	1 (0.5)	1.00
MANIC REACTION	1 (0.9)	0	1 (0.5)	.498
MIGRAINE	1 (0.9)	0	1 (0.5)	.498
NAUSEA	0	1 (0.9)	1 (0.5)	1.00
PERSONALITY DISORDER	1 (0.9)	0	1 (0.5)	.498

RMP.B1YP.JCLLIB2(AES3JEAB)
RMP.B1YO.HCJEREP(AES3JEAB)
* Frequencies are analyzed using a Fisher's Exact test.
XAES0003

12.3.4. Listing of Deaths, Serious Adverse Events, and Nonserious Clinically Significant Adverse Events

There were no deaths reported during Study Periods I through V. Table 14.59 (see Section 14.3.3) presents a patient listing of serious adverse events and adverse events leading to discontinuation.

12.3.5. Narratives of Deaths, Serious Adverse Events, and Nonserious Clinically Significant Adverse Events

There were no deaths reported during Study Periods I through V. Patient summaries for patients who had serious adverse events or had adverse events leading to discontinuation during Study Periods I through V are presented in Section 14.3.4.

12.4. Clinical Laboratory Evaluation

Clinical laboratory data (including hematology, clinical chemistry, thyroid function tests, and urinalysis) were collected at baseline (Visit 1) and Visit 15 (or discontinuation); therefore, data are analyzed for the subchronic treatment phase only.

A summary of changes in laboratory values from baseline to endpoint for all randomized patients entering Study Period V is presented in Table 14.68 (see Section 14.3.7.2).

12.4.1. Subchronic Treatment Phase (Study Periods III-V)

Table 12.11 presents a summary of the changes in laboratory values from baseline to endpoint for all randomized patients during the 19-week subchronic treatment phase.

There were statistically significant differences between treatment groups for mean changes in alkaline phosphatase and cholesterol levels. Fluoxetine-treated patients experienced a mean decrease of 34.9 U/L (SD 29.0) in alkaline phosphatase levels compared with a mean decrease of 5.1 U/L (SD 39.2) for placebo-treated patients ($p<.001$). Additional analyses of alkaline phosphatase are presented in Section 12.4.3.

Fluoxetine-treated patients experienced a mean increase of 0.1 mmol/L (SD 0.5) in cholesterol levels compared with a mean decrease of 0.1 mmol/L (SD 0.6) for placebo-treated patients ($p=.014$).

Table 12.11. **Laboratory Analysis**
Change from Baseline to Endpoint
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE

Laboratory Test Group: Complete Blood Count

Lab Test	Lab Unit	Therapy	n	Baseline Mean	Baseline SD	Change to Endpoint Mean	Change to Endpoint SD	p-Values Therapy
HCT	1	Flx	88	0.401	0.029	-0.014	0.029	.523
		Placebo	71	0.403	0.031	-0.011	0.025	
HGB	mml/L-Fe	Flx	88	8.401	0.564	-0.212	0.400	.902
		Placebo	73	8.421	0.661	-0.204	0.451	
RBC	TI/L	Flx	88	4.714	0.319	-0.122	0.244	.451
		Placebo	73	4.778	0.348	-0.095	0.202	
MCHC	mml/L-Fe	Flx	88	21.051	0.956	0.134	1.218	.681
		Placebo	71	20.969	0.944	0.052	1.266	
MCH	fmol(Fe)	Flx	88	1.791	0.108	0.004	0.063	.330
		Placebo	73	1.767	0.107	-0.006	0.060	
WBC	GI/L	Flx	88	6.794	1.925	0.230	1.783	.827
		Placebo	73	6.767	1.879	0.161	2.202	
BANDS	GI/L	Flx	88	0.000	0.000	0.003	0.027	.494
		Placebo	73	0.000	0.000	0.009	0.074	
POLYS	GI/L	Flx	88	3.751	1.498	0.211	1.471	.889
		Placebo	73	3.678	1.423	0.174	1.895	
LYMPHS	GI/L	Flx	88	2.363	0.567	-0.012	0.530	.869
		Placebo	73	2.439	0.661	-0.027	0.643	
MONOS	GI/L	Flx	88	0.442	0.173	0.018	0.169	.511
		Placebo	73	0.455	0.163	-0.002	0.221	
EOSN	GI/L	Flx	88	0.194	0.205	0.006	0.171	.854
		Placebo	73	0.150	0.119	0.002	0.104	
BASO	GI/L	Flx	88	0.045	0.020	0.003	0.027	.640
		Placebo	73	0.045	0.020	0.005	0.031	

XLAS0006

Table 12.11. Laboratory Analysis
Change from Baseline to Endpoint
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE (continued)

Laboratory Test Group: Complete Blood Count

Lab Test	Lab Unit	Therapy	n	Baseline Mean	Baseline SD	Change to Endpoint Mean	Change to Endpoint SD	p-Values Therapy
MCV	fL	Flx	88	85.170	4.305	-0.455	4.045	.945
		Placebo	71	84.394	4.856	-0.408	4.406	
PLTCT	GI/L	Flx	88	281.727	67.434	-1.239	44.353	.280
		Placebo	73	272.808	60.324	6.329	43.869	
ATLYMP	GI/L	Flx	88	0.000	0.000	0.000	0.000	.274
		Placebo	73	0.000	0.000	0.002	0.014	

XLAS0006

Table 12.11. Laboratory Analysis
Change from Baseline to Endpoint
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE (continued)

Laboratory Test Group: Blood Chemistry

Lab Test	Lab Unit	Therapy	n	Baseline Mean	Baseline SD	Change to Endpoint Mean	Change to Endpoint SD	p-Values Therapy
AST	U/L	Flx	86	25.035	8.879	-0.326	7.760	.621
		Placebo	75	25.613	6.476	-0.933	7.748	
ALT	U/L	Flx	86	19.453	14.829	-0.163	13.094	.921
		Placebo	75	20.480	8.916	-0.360	11.820	
CPK	U/L	Flx	86	126.465	79.854	15.395	80.020	.875
		Placebo	75	129.187	68.611	17.467	87.351	
ALKPH	U/L	Flx	84	221.429	93.843	-34.929	28.982	<.001
		Placebo	74	223.649	94.546	-5.081	39.230	
GGT	U/L	Flx	86	15.372	6.815	-0.895	4.574	.326
		Placebo	75	15.440	7.389	-0.067	6.079	
BUN	mmol/L	Flx	86	3.935	1.040	0.428	1.096	.232
		Placebo	75	4.217	0.948	0.219	1.106	
CREAT	umol/L	Flx	86	76.887	11.105	1.542	9.413	.618
		Placebo	75	75.317	11.007	2.239	8.104	
CALC	mmol/L	Flx	86	2.365	0.080	-0.030	0.092	.328
		Placebo	75	2.353	0.085	-0.016	0.095	
PHOS	mmol/L	Flx	83	1.486	0.206	0.000	0.187	.696
		Placebo	74	1.526	0.156	-0.012	0.189	
TPROT	g/L	Flx	86	73.709	4.270	-1.488	4.087	.136
		Placebo	75	72.507	4.394	-0.600	3.317	
ALBUM	g/L	Flx	86	42.942	2.578	-1.523	2.482	.403
		Placebo	75	42.547	2.835	-1.173	2.811	
NFGLU	mmol/L	Flx	84	4.944	0.606	0.057	0.947	.217
		Placebo	75	4.955	0.818	0.256	1.080	

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Table 12.11. Laboratory Analysis
Change from Baseline to Endpoint
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE (continued)

Laboratory Test Group: Blood Chemistry

Lab Test	Lab Unit	Therapy	n	Baseline Mean	Baseline SD	Change to Endpoint Mean	Change to Endpoint SD	p-Values Therapy
UR AC	umol/L	Flx	86	272.501	71.856	5.602	46.212	.190
		Placebo	75	264.012	70.424	14.830	42.244	
CHOL	mmol/L	Flx	86	4.384	0.867	0.087	0.536	.014
		Placebo	75	4.286	0.915	-0.127	0.550	
T.BILI	umol/L	Flx	84	7.858	3.359	-0.346	2.652	.742
		Placebo	71	8.165	3.986	-0.169	3.996	

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Table 12.11. Laboratory Analysis
Change from Baseline to Endpoint
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE (continued)

Laboratory Test Group: Electrolytes

Lab Test	Lab Unit	Therapy	n	Baseline Mean	Baseline SD	Change to Endpoint Mean	Change to Endpoint SD	p-Values Therapy
SODIUM	mmol/L	Flx	86	139.593	1.990	-0.093	2.831	.340
		Placebo	75	139.253	2.302	0.333	2.801	
POTAS	mmol/L	Flx	83	4.193	0.331	-0.059	0.375	.419
		Placebo	74	4.184	0.307	-0.009	0.391	
CHLOR	mmol/L	Flx	86	102.512	2.340	0.651	3.044	.610
		Placebo	75	102.307	2.509	0.893	2.953	
BICARB	mmol/L	Flx	86	25.609	2.065	0.438	2.372	.386
		Placebo	74	25.809	1.969	0.768	2.407	

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Table 12.11. Laboratory Analysis
Change from Baseline to Endpoint
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE (continued)

Laboratory Test Group: Thyroids

Lab Test	Lab Unit	Therapy	n	Baseline Mean	Baseline SD	Change to Endpoint Mean	Change to Endpoint SD	p-Values Therapy
T4-RIA	nmol/L	Flx	37	100.386	14.072	-2.574	13.282	.205
		Placebo	33	103.155	15.631	2.340	18.652	
TSH	mU/L	Flx	37	1.933	1.101	-0.401	1.014	.121
		Placebo	33	1.788	0.886	-0.051	0.832	
T3-TOT	nmol/L	Flx	37	1.947	0.354	-0.073	0.341	.264
		Placebo	33	1.900	0.370	0.027	0.395	
FTI	INDEX	Flx	37	2.651	0.277	-0.049	0.341	.492
		Placebo	33	2.748	0.356	0.015	0.430	
RT3U	1	Flx	37	0.341	0.027	0.005	0.017	.081
		Placebo	33	0.345	0.026	-0.002	0.020	

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Table 12.11. Laboratory Analysis
Change from Baseline to Endpoint
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE (continued)

Laboratory Test Group: Urinalysis

Lab Test	Lab Unit	Therapy	n	Baseline Mean	Baseline SD	Endpoint Mean	Change to Endpoint SD	p-Values Therapy
U-SPGR	NO UNITS	Flx	85	1.021	0.008	0.003	0.010	.588
		Placebo	75	1.024	0.007	0.003	0.008	
U-PH	U	Flx	85	5.882	0.878	0.082	1.126	.588
		Placebo	75	5.773	0.815	-0.013	1.097	

RMP.B1YP.JCLLIB2(LAS6JEAA)
RMP.B1Y0.HCJEREP(LAS6JEAA)
Note: n = Total number of patients in each treatment group having the variable in both baseline and postbaseline visits.

Note: Models:

FULL1 - Type III Sums of Squares from an analysis of variance (ANOVA): PROC GLM model=treatment.
Least-squares mean option in PROC GLM from the ANOVA using the mean square for error.

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Table 12.11. Laboratory Analysis
Change from Baseline to Endpoint
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE (concluded)

Legend of Lab Test Code Abbreviations:

Abbrev.	Description
HCT	HEMATOCRIT
HGB	HEMOGLOBIN
RBC	ERYTHROCYTE COUNT
MCHC	MEAN CELL HEMOGLOBIN CONCENTRATION (MCHC)
MCH	MEAN CELL HEMOGLOBIN (MCH)
WBC	LEUKOCYTE COUNT
BANDS	BANDS
POLYS	NEUTROPHILS, SEGMENTED
LYMPHS	LYMPHOCYTES
MONOS	MONOCYTES
EOSN	EOSINOPHILS
BASO	BASOPHILS
MCV	MEAN CELL VOLUME (MCV)
PLTCT	PLATELET COUNT
ATLYMP	LYMPHOCYTES, ATYPICAL
U-SPGR	UA-SPECIFIC GRAVITY
U-PH	UA-PH
AST	AST/SGOT
ALT	ALT/SGPT
CPK	CREATINE PHOSPHOKINASE
ALKPH	ALKALINE PHOSPHATASE
GGT	GGT (GGPT/SGGT/YGGT)
T4-RIA	THYROXINE, TOTAL-T4
TSH	THYROID STIM. HORMONE
T3-TOT	T3, TOTAL (TRIIODOTHYRONINE)
FTI	FREE THYROXINE INDEX
RT3U	T3 % UPTAKE
BUN	UREA NITROGEN
CREAT	CREATININE
CALC	CALCIUM
PHOS	INORGANIC PHOSPHORUS
SODIUM	SODIUM
POTAS	POTASSIUM
CHLOR	CHLORIDE
TPROT	TOTAL PROTEIN
ALBUM	ALBUMIN
NFGLU	GLUCOSE, NON-FASTING
UR AC	URIC ACID
CHOL	CHOLESTEROL
BICARB	BICARBONATE, HCO3
T.BILI	BILIRUBIN, TOTAL

Table 12.12 presents a summary of the changes in laboratory values from baseline to endpoint for all randomized patients who completed Study Period V. Baseline for this analysis was the last laboratory value obtained during Visits 1 through 4 and endpoint was Visit 15. A statistically significant difference between treatment groups was observed for mean change in alkaline phosphatase levels. Fluoxetine-treated patients exhibited a mean decrease of 41.1 U/L (SD 30.5) compared with a mean decrease of 2.8 U/L (SD 35.9) for placebo-treated patients (p<.001).

Table 12.12. Laboratory Analysis
Change from Baseline to Endpoint
All Randomized Patients Completing Study Period V
B1Y-MC-HCJE

Laboratory Test Group: Complete Blood Count

				-----Baseline------		Change to -----Endpoint-----		p-Values
Lab Test	Lab Unit	Therapy	n	Mean	SD	Mean	SD	Therapy
HCT	1	Flx	50	0.402	0.028	-0.015	0.029	.321
		Placebo	45	0.401	0.034	-0.010	0.024	
HGB	mml/L-Fe	Flx	50	8.410	0.480	-0.197	0.381	.944
		Placebo	45	8.428	0.683	-0.192	0.405	
RBC	TI/L	Flx	50	4.708	0.275	-0.126	0.249	.488
		Placebo	45	4.753	0.362	-0.093	0.203	
MCHC	mml/L-Fe	Flx	50	21.063	0.899	0.186	1.255	.763
		Placebo	45	21.045	0.781	0.110	1.178	
MCH	fmol(Fe)	Flx	50	1.796	0.093	0.005	0.068	.616
		Placebo	45	1.775	0.103	-0.001	0.052	
WBC	GI/L	Flx	50	6.739	1.886	0.491	1.778	.440
		Placebo	45	6.821	1.851	0.176	2.171	
BANDS	GI/L	Flx	50	0.000	0.000	0.005	0.035	.345
		Placebo	45	0.000	0.000	0.000	0.000	
POLYS	GI/L	Flx	50	3.741	1.464	0.393	1.434	.486
		Placebo	45	3.709	1.380	0.153	1.901	
LYMPHS	GI/L	Flx	50	2.348	0.588	0.016	0.552	.777
		Placebo	45	2.470	0.691	-0.019	0.652	
MONOS	GI/L	Flx	50	0.423	0.132	0.053	0.138	.403
		Placebo	45	0.449	0.154	0.025	0.185	
EOSN	GI/L	Flx	50	0.187	0.187	0.018	0.185	.972
		Placebo	45	0.146	0.114	0.017	0.091	
BASO	GI/L	Flx	50	0.042	0.017	0.005	0.030	.389
		Placebo	45	0.046	0.021	0.000	0.026	

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Table 12.12. Laboratory Analysis
Change from Baseline to Endpoint
All Randomized Patients Completing Study Period V
B1Y-MC-HCJE (continued)

Laboratory Test Group: Complete Blood Count

Lab Test	Lab Unit	Therapy	n	Baseline Mean	Baseline SD	Change to Endpoint Mean	Change to Endpoint SD	p-Values Therapy
MCV	fL	Flx	50	85.320	3.582	-0.520	3.986	.597
		Placebo	45	84.400	4.905	-0.089	3.924	
PLTCT	GI/L	Flx	50	287.200	61.329	-4.960	42.012	.337
		Placebo	45	270.489	59.245	3.200	40.083	
ATLYMP	GI/L	Flx	50	0.000	0.000	0.000	0.000	.294
		Placebo	45	0.000	0.000	0.003	0.018	

XLAS0006

Table 12.12. Laboratory Analysis
Change from Baseline to Endpoint
All Randomized Patients Completing Study Period V
B1Y-MC-HCJE (continued)

Laboratory Test Group: Blood Chemistry

Lab Test	Lab Unit	Therapy	n	Baseline Mean	Baseline SD	Change to Endpoint Mean	Change to Endpoint SD	p-Values Therapy
AST	U/L	Flx	50	25.900	10.420	-0.960	8.727	.580
		Placebo	46	26.283	7.470	-1.870	7.160	
ALT	U/L	Flx	50	20.300	17.767	-0.980	15.695	.956
		Placebo	46	21.174	9.792	-1.130	10.118	
CPK	U/L	Flx	50	135.380	90.168	7.260	83.595	.930
		Placebo	46	123.348	64.998	8.500	48.683	
ALKPH	U/L	Flx	49	218.306	97.364	-41.061	30.478	<.001
		Placebo	45	218.822	96.819	-2.800	35.888	
GGT	U/L	Flx	50	15.260	6.995	-0.980	5.097	.921
		Placebo	46	15.152	7.071	-0.891	3.401	
BUN	mmol/L	Flx	50	3.884	0.980	0.657	1.083	.114
		Placebo	46	4.261	0.938	0.310	1.039	
CREAT	umol/L	Flx	50	76.908	10.298	1.414	8.445	.678
		Placebo	46	74.371	10.799	2.114	7.947	
CALC	mmol/L	Flx	50	2.368	0.086	-0.036	0.100	.411
		Placebo	46	2.356	0.084	-0.020	0.093	
PHOS	mmol/L	Flx	48	1.479	0.202	0.006	0.176	.474
		Placebo	45	1.541	0.155	-0.020	0.174	
TPROT	g/L	Flx	50	73.780	4.032	-1.400	3.980	.404
		Placebo	46	72.652	4.634	-0.739	3.726	
ALBUM	g/L	Flx	50	43.080	2.506	-1.680	2.470	.351
		Placebo	46	42.696	2.740	-1.174	2.823	
NFGLU	mmol/L	Flx	48	4.946	0.568	0.084	0.945	.850
		Placebo	46	4.987	0.931	0.126	1.146	

XLAS0006

Table 12.12. Laboratory Analysis
Change from Baseline to Endpoint
All Randomized Patients Completing Study Period V
B1Y-MC-HCJE (continued)

Laboratory Test Group: Blood Chemistry

Lab Test	Lab Unit	Therapy	n	Baseline Mean	Baseline SD	Change to Endpoint Mean	Change to Endpoint SD	p-Values Therapy
UR AC	umol/L	Flx	50	275.273	75.419	6.186	34.806	.143
		Placebo	46	258.091	73.391	17.327	39.151	
CHOL	mmol/L	Flx	50	4.358	0.788	0.076	0.551	.180
		Placebo	46	4.309	0.890	-0.076	0.550	
T.BILI	umol/L	Flx	48	8.265	3.603	-0.428	2.721	.923
		Placebo	42	8.143	4.029	-0.489	3.255	

XLAS0006

Table 12.12. Laboratory Analysis
Change from Baseline to Endpoint
All Randomized Patients Completing Study Period V
B1Y-MC-HCJE (continued)

Laboratory Test Group: Electrolytes

Lab Test	Lab Unit	Therapy	n	Baseline Mean	Baseline SD	Change to Endpoint Mean	Change to Endpoint SD	p-Values Therapy
SODIUM	mmol/L	Flx	50	139.860	1.969	-0.280	3.143	.619
		Placebo	46	139.239	2.243	0.022	2.745	
POTAS	mmol/L	Flx	48	4.148	0.317	-0.015	0.352	.761
		Placebo	45	4.191	0.289	0.009	0.390	
CHLOR	mmol/L	Flx	50	102.760	2.264	0.700	2.964	.645
		Placebo	46	102.348	2.331	0.978	2.925	
BICARB	mmol/L	Flx	50	25.692	2.056	0.766	2.195	.620
		Placebo	45	25.816	2.004	1.007	2.514	

XLAS0006

Table 12.12. Laboratory Analysis
Change from Baseline to Endpoint
All Randomized Patients Completing Study Period V
B1Y-MC-HCJE (continued)

Laboratory Test Group: Thyroids

Lab Test	Lab Unit	Therapy	n	Baseline Mean	Baseline SD	Change to Endpoint Mean	Change to Endpoint SD	p-Values Therapy
T4-RIA	nmol/L	Flx	2	108.752	10.011	-17.375	17.291	.587
		Placebo	4	102.960	15.119	-10.296	12.478	
TSH	mU/L	Flx	2	1.465	0.658	-0.230	0.495	.856
		Placebo	4	1.815	0.500	-0.103	0.830	
T3-TOT	nmol/L	Flx	2	2.081	0.315	-0.100	0.119	.914
		Placebo	4	2.047	0.416	-0.046	0.618	
FTI	INDEX	Flx	2	2.950	0.212	-0.550	0.212	.066
		Placebo	4	2.625	0.287	-0.150	0.173	
RT3U	1	Flx	2	0.350	0.014	-0.005	0.035	.470
		Placebo	4	0.333	0.024	0.015	0.026	

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Table 12.12. Laboratory Analysis
Change from Baseline to Endpoint
All Randomized Patients Completing Study Period V
B1Y-MC-HCJE (continued)

Laboratory Test Group: Urinalysis

Lab Test	Lab Unit	Therapy	n	Baseline Mean	Baseline SD	Change to Endpoint Mean	Change to Endpoint SD	p-Values Therapy
U-SPGR	NO UNITS	Flx	48	1.021	0.009	0.004	0.009	.730
		Placebo	46	1.024	0.007	0.004	0.008	
U-PH	U	Flx	48	5.854	0.772	0.104	1.134	.634
		Placebo	46	5.739	0.801	0.000	0.966	

RMP.B1YP.JCLLIB2(LAS6JERA)
RMP.B1Y0.HCJEREP(LAS6JERA)
Note: n = Total number of patients in each treatment group having the variable in both baseline and postbaseline visits.

Note: Models:

FULL1 - Type III Sums of Squares from an analysis of variance (ANOVA): PROC GLM model=treatment.
Least-squares mean option in PROC GLM from the ANOVA using the mean square for error.

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Table 12.12. Laboratory Analysis
Change from Baseline to Endpoint
All Randomized Patients Completing Study Period V
B1Y-MC-HCJE (concluded)

Legend of Lab Test Code Abbreviations:

Abbrev.	Description
HCT	HEMATOCRIT
HGB	HEMOGLOBIN
RBC	ERYTHROCYTE COUNT
MCHC	MEAN CELL HEMOGLOBIN CONCENTRATION (MCHC)
MCH	MEAN CELL HEMOGLOBIN (MCH)
WBC	LEUKOCYTE COUNT
BANDS	BANDS
POLYS	NEUTROPHILS, SEGMENTED
LYMPHS	LYMPHOCYTES
MONOS	MONOCYTES
EOSN	EOSINOPHILS
BASO	BASOPHILS
MCV	MEAN CELL VOLUME (MCV)
PLTCT	PLATELET COUNT
ATLYMP	LYMPHOCYTES, ATYPICAL
U-SPGR	UA-SPECIFIC GRAVITY
U-PH	UA-PH
AST	AST/SGOT
ALT	ALT/SGPT
CPK	CREATINE PHOSPHOKINASE
ALKPH	ALKALINE PHOSPHATASE
GGT	GGT (GGPT/SGGT/YGGT)
T4-RIA	THYROXINE, TOTAL-T4
TSH	THYROID STIM. HORMONE
T3-TOT	T3, TOTAL (TRIIODOTHYRONINE)
FTI	FREE THYROXINE INDEX
RT3U	T3 % UPTAKE
BUN	UREA NITROGEN
CREAT	CREATININE
CALC	CALCIUM
PHOS	INORGANIC PHOSPHORUS
SODIUM	SODIUM
POTAS	POTASSIUM
CHLOR	CHLORIDE
TPROT	TOTAL PROTEIN
ALBUM	ALBUMIN
NFGLU	GLUCOSE, NON-FASTING

Legend of Lab Test Code Abbreviations:

Abbrev.	Description
UR AC	URIC ACID
CHOL	CHOLESTEROL
BICARB	BICARBONATE, HCO3
T.BILI	BILIRUBIN, TOTAL

12.4.2. Treatment-Emergent Abnormal Values

The laboratory reference ranges used in this study were established for pediatric patients by [redacted] The reference ranges used for each patient in this pediatric population are included in the by-patient listing of laboratory values contained in Appendix 16.2.8.

Laboratory values that became abnormal or went out of range during the study were evaluated. The proportion of patients with abnormal laboratory values was summarized and compared across treatment groups. The results for the subchronic treatment phase are displayed in Table 14.66 (see Section 14.3.7).

No fluoxetine-treated patients experienced an abnormally low or high alkaline phosphatase level during subchronic treatment. In the placebo treatment group, 1 (1%) placebo-treated patient experienced an abnormally low alkaline phosphatase level, while 2 (3%) placebo-treated patients experienced an abnormally high alkaline phosphatase level.

During subchronic treatment, 1 (1%) fluoxetine-treated patient experienced an abnormally low cholesterol level and 8 (10%) fluoxetine-treated patients experienced an abnormally high cholesterol level. Four (6%) placebo-treated patients experienced an abnormally low cholesterol level, while 4 (6%) placebo-treated patients experienced an abnormally high cholesterol level. There were no statistically significant differences between treatment groups in the incidence of any abnormal laboratory value.

Laboratory values that went out of range for all patients entering Study Period V are summarized in Table 14.67 (see Section 14.3.7).

12.4.3. Additional Analyses of Alkaline Phosphatase Levels

The pattern observed in the mean change from baseline to endpoint for alkaline phosphatase in pediatric patients is not similar to what has been reported in adult patients (Clinical Investigator's Brochure 1999). To investigate this further, alkaline phosphatase levels were analyzed for patients completing Study Period V and by dose (Table 12.13), by age (Table 12.14), and by serum fluoxetine/norfluoxetine concentration groups (Table 12.15).

The intent-to-treat and completers' analyses both demonstrate that fluoxetine-treated patients had statistically significantly greater decreases in alkaline phosphatase levels during subchronic treatment when compared with placebo-treated patients. Although the sample sizes were small at the higher dose levels and the difference between treatment groups was not statistically significant, the magnitude of change in alkaline phosphatase levels appears to increase with increasing fluoxetine dose.

Table 12.13. Alkaline Phosphatase Levels
Intent-to-Treat and Completers' Analyses
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE

	Intent-to-Treat Analysis				Completers' Analysis			
	N	Mean Change (U/L)	SD	p-Value	N	Mean Change (U/L)	SD	p-Value
Flx	84	-34.93	28.98	<.001	49	-41.06	30.48	<.001
Placebo	74	-5.08	39.23		45	-2.80	35.89	
Flx 20mg	71	-32.70	28.52	.219[a]	42	-38.33	30.36	.137[a]
Flx 40mg	9	-43.89	21.30		4	-44.75	21.53	
Flx 60mg	4	-54.25	46.79		3	-74.33	29.40	

Data for this table were taken from RMP.B1YO.HCJEREP (LAS6JEAA, LAS6JERA), RMP.B1YSHCJE.SASPGM (LABDOSE).
[a]This p-value compares the three fluoxetine dose levels.
Abbreviations: Flx = fluoxetine; SD = standard deviation.

For this study, a decision was made to use age rather than pubertal status to delineate children from adolescents because of FDA Guidances in effect at the time this study was designed. Consequently, children were defined as patients aged 8 to <13 years old and adolescents as patients aged 13 to <18 years old.

An analysis of alkaline phosphatase levels by age is presented in Table 12.14. Over 19 weeks of treatment with fluoxetine in this study, both children and adolescents experienced statistically significant decreases in alkaline phosphatase levels. The observed decrease was slightly larger in children than adolescents, although the difference between subgroups was not statistically significant.

Table 12.14. Alkaline Phosphatase Levels
Subgroup Analysis by Age
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE

		Baseline			Change		
Subgroup	Therapy	N	Mean (U/L)	SD	Mean (U/L)	SD	Therapy p-Value
8 to <13	Flx	48	254.0	68.5	-38.4	28.9	<.001
	Placebo	45	270.8	51.1	-3.7	46.6	
13 to <18	Flx	36	178.0	105.8	-30.3	28.8	.001
	Placebo	29	150.4	100.3	-7.2	24.2	

Data for this table were derived from RMP.B1YSHCJE.SASPGM (LABSUB).
Note: There was no therapy-by-age group interaction (p=.301) nor an overall age group effect (p=.676).
Abbreviations: Flx = fluoxetine; SD = standard deviation.

To determine if alkaline phosphatase levels decreased in accordance with total serum concentrations of fluoxetine and norfluoxetine, a correlation coefficient was calculated. The correlation coefficient was low (r=-.138) and was not statistically significant (p=.218).

In addition, patients were divided into four groups based on their total serum fluoxetine/norfluoxetine concentrations. The mean change in alkaline phosphatase levels for these four groups is presented in Table 12.15. Group 1 is the group with the lowest serum concentrations and Group 4 is the group with the highest serum concentrations. There were no statistically significant differences among the serum concentration groups with respect to mean change in alkaline phosphatase levels (p= .681).

Table 12.15. Alkaline Phosphatase Levels
Subgroup Analysis by Serum Concentration Groups
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE

Serum Concentration Group	N	Total Serum Concentration (flx+norflx) Mean (ng/ml)	SD	Change in Alkaline Phosphatase Mean (U/L)	SD
1	21	119.6	36.9	-36.1	29.9
2	18	195.7	22.5	-32.8	24.3
3	20	273.0	23.1	-31.2	28.1
4	22	480.5	180.8	-41.5	33.9

Data for this table taken from: RMP.B1YSHCJE.SASPGM (ASSAY).
Abbreviations: flx = fluoxetine; norflx = norfluoxetine; SD = standard deviation.

12.4.4. Listing of Individual Laboratory Measurements by Patient and Each Abnormal Laboratory Value

A listing of individual laboratory measurements by patient and their associated laboratory ranges is located in Appendix 16.2.8.

A listing of all patients who had an abnormal laboratory value during the study is provided in Table 14.69 (see Section 14.3.7.3).

12.5. Vital Signs, Physical Findings, and Other Observations Related to Safety

Vital signs, including sitting heart rate and blood pressure, and temperature were recorded at each visit. These data were analyzed for both the acute and subchronic treatment phases. Height, weight, and ECGs were recorded at baseline (Visit 1) and Visit 15 (or discontinuation); therefore, these data are analyzed for Visits 4 through 15 only.

12.5.1. Vital Signs

12.5.1.1. Acute Treatment Phase (Study Periods III-IV)

Table 12.16 summarizes the change in vital signs from baseline to endpoint for all randomized patients during the acute treatment phase. Fluoxetine-treated patients received 20 mg/day during this phase of the study. There were no statistically significant or clinically relevant changes in any of the vital signs examined.

The blood pressure reference ranges were established by the National Institutes of Health and are presented in Appendix 16.1.12. These reference ranges were used to determine

the incidence of out of range blood pressure measurements. Out of range blood pressure measurements for the acute treatment phase are presented in Table 14.60 (see Section 14.3.5). There were no statistically significant differences between treatment groups in the incidence of out of range systolic or diastolic blood pressure measurements.

Table 12.16. Vital Signs
Change from Baseline to Endpoint
All Randomized Patients
Acute Treatment Phase (Study Periods III-IV)
B1Y-MC-HCJE

Research Project Code: B1Y

Variables Analyzed	Therapy	n	Baseline Mean	Baseline SD	Change to Endpoint Mean	Change to Endpoint SD	p-Values Therapy (Int*1)
SI_HR	Flx 20	109	79.5	13.1	-2.3	12.6	.215
	Placebo	105	79.8	11.3	-0.1	13.0	
SI_SYSBP	Flx 20	109	109.2	10.4	0.2	9.6	.546
	Placebo	105	110.1	11.6	-0.6	10.9	
SI_DIABP	Flx 20	109	65.8	9.0	0.2	9.9	.819
	Placebo	105	65.9	8.7	0.5	8.9	
TEMP	Flx 20	109	36.6	0.4	-0.0	0.5	.947
	Placebo	105	36.6	0.5	-0.0	0.5	

RMP.B1YP.JCLLIB2(LAS6JEAB)
RMP.B1YO.HCJEREP(LAS6JEAB)
Note: n = Total number of patients in each treatment group having the variable in both baseline and postbaseline visits.

Note: Models:

FULL1 - *1 Type III Sums of Squares from an analysis of variance (ANOVA): PROC GLM model=treatment.
Least-squares mean option in PROC GLM from the ANOVA using the mean square for error.

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Table 12.16. Vital Signs
Change from Baseline to Endpoint
All Randomized Patients
Acute Treatment Phase (Study Periods III-IV)
B1Y-MC-HCJE (concluded)

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Legend of Variable Abbreviations:
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Abbrev.     Description
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SI_DIABP    Sitting Diastolic Blood Pressure/mmHg
SI_HR       Sitting Heart Rate/bpm
SI_SYSBP    Sitting Systolic Blood Pressure/mmHg
TEMP        Temperature
```

12.5.1.2. Subchronic Treatment Phase (Study Periods III-V)

Table 12.17 summarizes the change in vital signs, height, and weight from baseline to endpoint for all randomized patients during the subchronic treatment phase. Fluoxetine-treated patients received 20 to 60 mg/day during this phase of the study.

Table 12.18 presents the mean change from baseline to endpoint in vital signs for all patients completing the study through Study Period V. Baseline for this analysis was Visits 1 through 4 and endpoint was last of Visits 5 through 15.

There were no statistically significant or clinically relevant changes in heart rate, blood pressure, or temperature during the subchronic treatment phase or for all patients completing Study Period V. Changes in height and weight are discussed in Sections 12.5.1.3 and 12.5.1.4, respectively.

There were no statistically significant differences between treatment groups in the incidence of out of range systolic or diastolic blood pressure for the subchronic treatment phase (see Table 14.61) or for all randomized patients entering Study Period V (see Table 14.62).

Table 12.17. Vital Signs
Change from Baseline to Endpoint
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE

Research Project Code: B1Y

Variables Analyzed	Therapy	n	Baseline Mean	Baseline SD	Change to Endpoint Mean	Change to Endpoint SD	Therapy (Int*1) p-Values
HEIGHT	Flx	88	155.4	14.4	1.0	2.4	.008
	Placebo	75	153.5	12.0	2.0	2.7	
WEIGHT	Flx	91	56.5	19.0	1.2	2.7	.008
	Placebo	78	55.8	18.9	2.3	2.6	
SI_HR	Flx	109	79.5	13.1	-1.2	13.8	.390
	Placebo	105	79.8	11.3	0.3	11.3	
SI_SYSBP	Flx	109	109.2	10.4	0.3	10.4	.576
	Placebo	105	110.1	11.6	1.1	10.1	
SI_DIABP	Flx	109	65.8	9.0	0.3	8.8	.395
	Placebo	105	65.9	8.7	1.4	9.3	
TEMP	Flx	109	36.6	0.4	0.0	0.5	.649
	Placebo	105	36.6	0.5	-0.0	0.5	

RMP.B1YP.JCLLIB2(LAS6JEAC)
RMP.B1YO.HCJEREP(LAS6JEAC)
Note: n = Total number of patients in each treatment group having the variable in both baseline and postbaseline visits.

Note: Models:

FULL1 - *1 Type III Sums of Squares from an analysis of variance (ANOVA): PROC GLM model=treatment.
Least-squares mean option in PROC GLM from the ANOVA using the mean square for error.

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Table 12.17. Vital Signs
Change from Baseline to Endpoint
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE (concluded)

```
Legend of Variable Abbreviations:
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Abbrev.     Description
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HEIGHT      Heightcm
SI_DIABP    Sitting Diastolic Blood Pressure/mmHg
SI_HR       Sitting Heart Rate/bpm
SI_SYSBP    Sitting Systolic Blood Pressure/mmHg
TEMP        Temperature
WEIGHT      Weight/kg
```

Table 12.18. Vital Signs
Change from Baseline to Endpoint
All Patients Completing Study Period V
B1Y-MC-HCJE

Research Project Code: B1Y

Variables Analyzed	Therapy	n	Baseline Mean	Baseline SD	Change to Endpoint Mean	Change to Endpoint SD	p-Values Therapy (Int*1)
HEIGHT	Flx	51	155.0	13.0	1.1	2.3	.032
	Placebo	47	153.8	13.3	2.3	2.8	
WEIGHT	Flx	52	58.4	19.3	1.5	2.7	.021
	Placebo	49	55.3	20.9	2.7	2.5	
SI_HR	Flx	52	77.7	12.6	2.2	12.0	.850
	Placebo	49	78.8	11.8	1.7	11.3	
SI_SYSBP	Flx	52	107.4	10.4	2.5	9.5	.585
	Placebo	49	107.4	10.5	3.6	10.2	
SI_DIABP	Flx	52	66.1	9.7	1.4	8.9	.447
	Placebo	49	64.4	8.1	2.8	9.4	
TEMP	Flx	52	36.6	0.4	-0.0	0.5	.406
	Placebo	49	36.5	0.5	-0.1	0.5	

RMP.B1YP.JCLLIB2(LAS6JERB)
RMP.B1YO.HCJEREP(LAS6JERB)
Note: n = Total number of patients in each treatment group having the variable in both baseline and postbaseline visits.

Note: Models:

FULL1 - *1 Type III Sums of Squares from an analysis of variance (ANOVA): PROC GLM model=treatment.
Least-squares mean option in PROC GLM from the ANOVA using the mean square for error.

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Table 12.18. Vital Signs
Change from Baseline to Endpoint
All Patients Completing Study Period V
B1Y-MC-HCJE (concluded)

```
Legend of Variable Abbreviations:
---------------------------------

Abbrev.     Description
-------     -----------

HEIGHT      Heightcm
SI_DIABP    Sitting Diastolic Blood Pressure/mmHg
SI_HR       Sitting Heart Rate/bpm
SI_SYSBP    Sitting Systolic Blood Pressure/mmHg
TEMP        Temperature
WEIGHT      Weight/kg
```

12.5.1.3. Additional Analyses of Height

As presented in Table 12.19, statistically significant differences in height increases (p=.008) were observed between fluoxetine-treated patients (1.0 cm) as compared with placebo-treated patients (2.0 cm). There were also statistically significant differences in height increases (p=.032) between fluoxetine-treated completers (1.1 cm) as compared with placebo-treated completers (2.3 cm). There were no statistically significant differences among patients receiving different fluoxetine doses, although the sample sizes were small at the higher dose levels.

Table 12.19. Height
Change from Baseline to Endpoint
Intent-to-Treat and Completers' Analyses
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE

	Intent-to-Treat Analysis				Completers' Analysis			
	N	Mean (cm)	SD	p-Value	N	Mean (cm)	SD	p-Value
Flx	88	1.0	2.4	.008	51	1.1	2.3	.032
Placebo	75	2.0	2.7		47	2.3	2.8	
Flx 20 mg	74	0.9	2.3	.658[a]	44	1.0	2.4	.416[a]
Flx 40 mg	10	1.3	3.2		4	2.5	2.1	
Flx 60 mg	4	1.9	1.3		3	1.7	1.5	

Data for this table taken from RMP.B1YO.HCJEREP (LAS6JEAC, LAS6JERB) and RMP.B1YSHCJE.SASPGM (VITDOSE).
[a]This p-value compares among the three fluoxetine dose levels.
Abbreviations: Flx = fluoxetine; SD = standard deviation

12.5.1.4. Additional Analyses of Weight

As presented in Table 12.20, fluoxetine-treated patients gained less weight (mean increase of 1.2 kg) compared with placebo-treated patients (mean increase of 2.3 kg) over the 19-week treatment period (p=.008). In addition, fluoxetine-treated completers gained less weight (mean increase of 1.5 kg) than placebo-treated completers (mean increase of 2.7 kg) over the 19-week treatment period (p=.021). There were no statistically significant differences among patients receiving different fluoxetine doses, although the sample sizes were small at the higher dose levels.

Table 12.20. Weight
Change from Baseline to Endpoint
Intent-to-Treat and Completers' Analyses
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE

	Intent-to-Treat Analysis				Completers' Analysis			
	N	Mean (kg)	SD	p-Value	N	Mean (kg)	SD	p-Value
Flx	91	1.2	2.7	.008	52	1.5	2.7	.021
Placebo	78	2.3	2.6		49	2.7	2.5	
Flx 20mg	77	1.4	2.7	.117[a]	45	1.7	2.9	.401[a]
Flx 40mg	10	0.6	1.4		4	0.2	1.2	
Flx 60mg	4	-1.2	3.1		3	0.2	1.6	

Data for this table taken from RMP.B1YO.HCJEREP (LAS6JEAC, LAS6JERB) and RMP.B1YSHCJE.SASPGM (VITDOSE).
[a]This p-value compares among the three fluoxetine dose levels.
Abbreviations: Flx = fluoxetine; SD = standard deviation.

12.5.2. Electrocardiograms

ECGs were collected at baseline (Visit 1) and at the end of Study Period V (Visit 15) or at the time of early discontinuation; therefore, data are analyzed for longer-term, subchronic treatment. ECGs were read locally at each investigative site to determine whether there were any ECG findings that would preclude the participation of the patient in the study. All ECGs were blindly read at a central site, [redacted] In addition, [redacted] blindly read all ECGs at the conclusion of Study Period V. Data from these two blinded readings were analyzed independently of one another, are included in the database, and are included in this safety review.

No fluoxetine-treated patients had ECGs that were read at the investigator site as normal at baseline and read as abnormal at endpoint. Two placebo-treated patients (Patients 339 and 1307) had ECGs that were read at the investigator site as normal at baseline and read as abnormal at endpoint (see Appendix 16.4.4). One fluoxetine-treated patient (Patient 202) had conflicting interpretations of her postbaseline ECG. At Visit 1, the investigator at the site indicated that the ECG was acceptable and [redacted] read the ECG as normal. The patient discontinued at Visit 7 and had a second ECG performed. The investigator considered this ECG to be unacceptable, but noted in the Comments section of the CRF that the limb leads were reversed. [redacted] read the investigator's comments and reported that the ECG was probably normal. This ECG is captured as normal in the database (see Appendix 16.4.4).

12.5.2.1. Subchronic Treatment Phase (Study Periods III-V)

Tables 12.21 and 12.22 present summaries of the ECG changes from baseline to endpoint for all patients who were randomized and received treatment through Study Period V using data from [redacted] ECG readings and the [redacted] ECG readings, respectively.

The QTc interval was corrected using Bazett's and Fridericia's methods. Bazett's method divides the QT interval by the square root of the RR interval while Fridericia's method uses the same formula but with a cube root of the RR interval. To investigate which correction method was more appropriate, a regression analysis was performed on the baseline readings with corrected QT as the dependent variable and heart rate as the independent variable. The regression that provides the nearest approximation to a straight line is considered superior. For both the [redacted] and the [redacted] datasets, Fridericia's correction provided the nearest approximation to a straight line; accordingly, Fridericia's method provides the better correction.

Applying Fridericia's method (listed as QTC_FRID) to [redacted] database (see Table 12.21), the QTc interval was statistically significantly higher in fluoxetine-treated patients compared with placebo-treated patients (fluoxetine 6.95 msec, placebo 0.05 msec; p=.016). A statistically significant difference (p=.049) was also observed in increase from baseline in QTc interval for fluoxetine-treated patients (7.47 msec) as compared with placebo-treated patients (0.59 msec) using Bazett's correction (listed as QTC_INT). There were no statistically significant differences between treatment groups for any other ECG parameter.

Table 12.21. Electrocardiogram Measures [redacted]
Change from Baseline to Endpoint
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE

Research Project Code: B1Y

Variables Analyzed	Therapy	n	Baseline Mean	Baseline SD	Change to Endpoint Mean	Change to Endpoint SD	p-Values Therapy
ECGHR	Flx	88	70.557	10.099	0.250	10.276	.908
	Placebo	73	73.658	12.160	0.452	11.846	
RR_INT	Flx	88	867.045	121.145	-5.114	123.707	.882
	Placebo	73	838.767	149.554	-8.219	141.797	
PR_INT	Flx	88	140.568	17.043	-0.909	14.435	.767
	Placebo	73	142.192	18.727	-0.274	12.244	
QRS_INT	Flx	88	81.477	6.166	-0.114	8.373	.670
	Placebo	73	81.781	7.700	0.411	6.960	
QT_INT	Flx	88	368.989	24.985	5.898	25.882	.070
	Placebo	73	365.959	22.801	-1.027	21.457	
QTC_INT	Flx	88	397.722	18.164	7.474	23.096	.049
	Placebo	73	402.200	18.550	0.589	20.323	
QTC_FRID	Flx	88	387.692	16.429	6.946	20.148	.016
	Placebo	73	389.430	13.085	0.047	14.517	

RMP.B1YP.JCLLIB2(LAS6JEAI)
RMP.B1YO.HCJEREP(LAS6JEAI)
Note: n = Total number of patients in each treatment group having the variable in both baseline and postbaseline visits.

Note: Models:

FULL1 - Type III Sums of Squares from an analysis of variance (ANOVA): PROC GLM model=treatment.
Least-squares mean option in PROC GLM from the ANOVA using the mean square for error.

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Table 12.21. Electrocardiogram Measures[redacted]
Change from Baseline to Endpoint
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE (concluded)

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Legend of Variable Abbreviations:
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Abbrev.     Description
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ECGHR       ECG Heart Rate
PR_INT      PR Interval
QRS_INT     QRS Interval
QT_INT      QT Interval
QTC_FRID    QTC Interval Fridericia Method
QTC_INT     QTC Interval Bazett Method
RR_INT      RR Interval
```

As presented in Table 12.22, there were no statistically significant differences in any ECG parameter using [redacted] datatset for fluoxetine-treated patients as compared with placebo-treated patients.

Table 12.22. Electrocardiogram Measures[redacted]
Change from Baseline to Endpoint
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE

			Baseline		Change to Endpoint		
Variable	Therapy	N	Mean	SD	Mean	SD	p-Value
Heart Rate	Flx	89	71.42	10.41	-0.14	10.50	.571
	Placebo	74	74.72	12.26	0.88	12.28	
RR_Interval	Flx	89	865.28	131.61	-4.83	146.89	.847
	Placebo	74	828.92	156.22	-9.32	149.61	
PR_Interval	Flx	89	141.12	18.98	-0.23	11.77	.478
	Placebo	74	142.70	17.07	1.08	11.54	
QRS_Interval	Flx	89	81.80	8.86	1.24	7.81	.987
	Placebo	74	80.95	7.62	1.22	7.01	
QT_Interval	Flx	89	381.84	26.82	2.20	22.71	.252
	Placebo	74	377.70	29.54	-2.27	26.99	
Bazett's QTc	Flx	89	412.38	21.69	3.74	27.02	.322
	Placebo	74	417.81	24.09	-0.37	25.43	
Fridericia's QTc	Flx	89	401.69	18.97	3.20	19.76	.181
	Placebo	74	403.62	19.78	-1.00	19.92	

Data for this table were taken from \\eagle\eagle.grp\programs._g\rmp\b1ys\hcje[redacted]ECG.sas.
Abbreviations: Flx = fluoxetine; SD = standard deviation.

12.5.2.2. Treatment-Emergent Out of Range Values

ECG reference ranges are presented in Appendix 16.1.12. These reference ranges were used to determine out of range ECG intervals.

To explore possibly relevant changes in the QTc interval, out of range QTc measurements for the 19-week subchronic treatment phase are presented in Table 12.23 for [redacted] dataset. QTc measurements less than or equal to 440 msec at baseline that were greater than 440 msec at endpoint were considered out of range. Using Bazett's correction, 2 fluoxetine-treated and 2 placebo-treated patients had QTc intervals that met these criteria (p=1.000). Using Fridericia's correction, 1 fluoxetine- treated and 0 placebo-treated patients had QTc intervals that met these criteria (p=1.000). Using this correction, Patient 415 (fluoxetine-treated) had a QTc interval of 495.5 msec.

Table 12.23. Electrocardiogram Measures [redacted]
Incidence of Out of Range Measurements
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE

[redacted]

Test	Incidence Group	Fluox (Total=109) N	n	(%)	Placebo (Total=110) N	n	(%)	p-value*
Heart Rate (beats/min)	LOW	67	8	(11.9)	62	7	(11.3)	1.000
	HIGH	88	0	(0.0)	73	0	(0.0)	
PR Interval (msec)	LOW	88	0	(0.0)	73	0	(0.0)	
	HIGH	84	1	(1.2)	68	0	(0.0)	1.000
QRS Interval (msec)	LOW	88	0	(0.0)	73	0	(0.0)	
	HIGH	80	8	(10.0)	64	4	(6.3)	0.549
Bazett's QTC (msec)	HIGH	88	2	(2.3)	72	2	(2.8)	1.000
Fridericia's QTC (msec)	HIGH	88	1	(1.1)	73	0	(0.0)	1.000

* Frequencies are analyzed using a Fisher's Exact test.
Note: Total = Number of patients in the treatment group.
N = Number of patients at risk.
n = Number of patients in the Incidence Group Post Baseline.

RMP.B1YP.SASPGM(CUSTJEEA)
RMP.B1YO.HCJEREP(CUSTJEEA)

Similarly, out of range QTc measurements for 19-week subchronic treatment are presented in Table 12.24 using [redacted] dataset. Using Fridericia's correction, 1 patient in each of the two treatment groups met the criteria for out of range QTc measurement (p=1.000). Patients 1654 (fluoxetine-treated) and 1506 (placebo-treated) had QTc intervals of 456.3 and 442.2 msec, respectively.

Table 12.24. Electrocardiogram Measures [redacted] Incidence of Out of Range Measurements Subchronic Treatment Phase (Study Periods III-V) B1Y-MC-HCJE

		Fluoxetine			Placebo			
		N	n	%	N	n	%	p-Value
Heart Rate	Low	73	8	11.0	63	6	9.5	
	High	89	0	0	74	0	0	1.000
PR Interval	Low	89	0	0	74	0	0	
	High	82	2	2.4	69	0	0	.500
QRS Interval	Low	89	0	0	74	0	0	
	High	67	12	17.9	58	7	12.1	.457
Bazett's QTc	High	82	13	15.9	61	7	11.5	.627
Fridericia's QTc[a]	High	88	1	1.1	70	1	1.4	1.000

Data for this table were taken from \\eagle\eagle.grp\programs._g\rmp\b1ys\hcje[redacted]ECG ext.sas
[a]QTc measurements less than or equal to 440 msec at baseline that were greater than 440 msec at endpoint were considered out of range.

Upon evaluating [redacted] ECG dataset, one patient (Patient 415, fluoxetine-treated) was identified whose QTc interval (Fridericia's correction) exceeded 480 msec. The [redacted] analysis for this outlier was reviewed and the QTC interval (Fridericia's correction) was 422.3 msec.

Because of the magnitude of the increase in QTc interval using [redacted] dataset and the difference between the two datasets, the ECG for this patient was submitted to the [redacted] for re-reading. The second reading showed no increase in QTc interval (Fridericia's correction) from baseline to endpoint. Because of the similarities in the [redacted] reading and [redacted] re-reading, it is believed that these analyses are more accurate than the initial [redacted] reading.

12.5.2.3. Additional Analyses of QTc Intervals

Table 12.25 presents QTc change from baseline analyzed by subgroups based on age category. [redacted] dataset and Fridericia's correction were used for these analyses. There were no statistically significant differences among subgroups for change from

baseline in QTc interval. The change within the fluoxetine group for adolescents (3.92 msec) is not statistically significant; that is, a within-group test of the change from baseline to treatment did not detect that 3.92 is different from 0 (p=.230).

Table 12.25. QTc Interval (Fridericia's Method)
Change from Baseline to Endpoint[redacted]
Subgroup Analysis by Age
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE

		Baseline			Change		Therapy
Strata	Therapy	N	Mean	SD	Mean	SD	p-Value*
8 - <13	Flx	53	401.66	19.34	2.70	20.25	.785
	Placebo	46	399.52	18.77	1.58	20.67	
13 - <18	Flx	36	401.74	18.70	3.92	19.27	.058
	Placebo	28	410.35	19.86	-5.23	18.22	

Data for this table were taken from \\eagle\eagle.grp\programs._g\rmp\b1ys\hcje[redacted]ECG.sas
Abbreviations: Flx = fluoxetine; SD = standard deviation.
Note: There was no therapy-by-age group interaction (p=.211) nor an overall age group effect (p=.384).

12.6. Subgroup Analyses

Due to the length of the output from these reports, all subgroup analyses are presented in Section 14.3.2. There were no clinically significant treatment differences between subgroups based on age category, gender, or family history of depression.

12.7. Safety Conclusions

The safety of fluoxetine versus placebo in children and adolescents diagnosed with MDD was evaluated in all 219 patients randomized in this study. During Study Periods III through V, fluoxetine-treated patients were exposed to study drug for an average of 106 ± 38 days, while placebo-treated patients were exposed to study drug for an average of 91 ± 47 days.

Adverse events were examined for the acute treatment phase (Study Periods III through IV), the subchronic treatment phase (Study Periods III through V), and for the double-blind nonresponder rerandomization phase (Study Period V). Adverse events were collected spontaneously (non-solicited) and with a standard interviewer-elicited adverse event questionnaire (solicited). This summary includes serious adverse events reported at any time during Study Periods I through V.

No patients died during Study Periods I through V. Nine serious adverse events occurred in 9 patients (3 not randomized, 2 fluoxetine-treated, 4 placebo-treated). Serious adverse events led to the discontinuation of 5 patients (1 not randomized, 1 fluoxetine-treated, 3 placebo-treated). Three of the nine serious adverse events occurred during the

diagnostic evaluation and placebo washout periods of the study, prior to randomization to study treatment. The remaining six serious adverse events occurred during double-blind treatment in 2 fluoxetine-treated (one each for suicidal ideation and swollen tonsils/tonsillectomy) and 4 placebo-treated patients (one each for abdominal pain/appendicitis, kidney infection, self-mutilatory behavior, and aggressive behavior).

A total of 23 patients discontinued due to adverse events, including the 5 patients discontinued due to serious adverse events, during Study Periods I through V (1 not randomized, 11 fluoxetine-treated, 11 placebo-treated). One fluoxetine-treated patient was discontinued from the study due to the occurrence of a manic episode that the investigator attributed to study drug while blinded.

Statistically significantly more fluoxetine-treated patients reported the treatment-emergent non-solicited adverse event headache as compared with placebo-treated patients during the acute and subchronic treatment phases. No treatment-emergent non-solicited adverse event occurred statistically significantly more often in placebo-treated patients during acute or subchronic treatment.

During the acute and subchronic treatment phases, no treatment-emergent solicited adverse event from the Side-Effects Checklist occurred statistically significantly more often in fluoxetine-treated patients as compared with placebo-treated patients. The treatment-emergent solicited adverse event wetness in the mouth was reported by statistically significantly more placebo-treated patients compared with fluoxetine-treated patients during both acute and subchronic treatment. In addition, trouble pronouncing words was reported statistically significantly more often by placebo-treated patients as compared with fluoxetine-treated patients during subchronic treatment.

There were no clinically relevant treatment differences in solicited or non-solicited treatment-emergent adverse events observed among subgroups based on age category, gender, or family history of depression during acute or subchronic treatment.

All patients randomized to treatment with fluoxetine were able to tolerate the required titration to 20 mg/day during the acute treatment phase. During the subchronic treatment phase, 2 patients receiving fluoxetine 20 mg/day were discontinued from the study due to the occurrence of intolerable adverse events. Patient 401 discontinued at Visit 12 due to personality disorder and Patient 1602 discontinued at Visit 13 due to hostility. Both patients were discontinued when the investigator attempted to decrease their dose of study drug through the TriaLine system. Because the system did not allow for dose reduction lower than 20 mg/day following rerandomization, the patients were discontinued.

Laboratory values were evaluated by examining change from baseline to endpoint and also by examining those values that went out of range during the subchronic treatment phase. Statistically significant treatment differences were observed with regard to cholesterol and alkaline phosphatase levels. Cholesterol levels increased slightly from

baseline in fluoxetine-treated patients, whereas they decreased in placebo-treated patients. These findings were not considered clinically significant.

A statistically significant decrease from baseline was observed for alkaline phosphatase levels in fluoxetine-treated patients as compared with placebo-treated patients. This difference was observed in analyses of the intent-to-treat and completers' populations. Although there appears to be a dose-response relationship for alkaline phosphatase levels, the number of patients who were treated with fluoxetine 40 to 60 mg/day was too small to make a definitive statement about this relationship. However, there does not appear to be a plasma concentration relationship between alkaline phosphatase levels and combined serum concentrations of fluoxetine and norfluoxetine. It is notable that no fluoxetine-treated patient had a decrease in alkaline phosphatase levels that was outside the normal range for pediatric patients. Treatment with fluoxetine in children and adolescents appears to result in a modest decrease in alkaline phosphatase levels that does not appear to be related to plasma concentrations of fluoxetine and its active metabolite, norfluoxetine. The clinical relevance of this finding is uncertain.

Two independent, blinded analyses of ECG interval changes did not reveal clinically significant changes in any ECG parameter.

There were no statistically significant or clinically relevant differences between treatment groups with regard to changes in heart rate, blood pressure, or temperature during the acute or subchronic treatment phases. On average, fluoxetine-treated patients gained less weight as compared with placebo-treated patients during the subchronic treatment phase. Although the number of patients treated with fluoxetine doses greater than 20 mg/day is small, there is a suggestion of a dose-response relationship for weight gain; that is, children at doses of 40 mg/day or greater gain less weight than children at 20 mg/day. Whether this observation would persist with long-term treatment is unknown. Long-term data will be available following the completion of Study Period VI and will be presented in a separate clinical study report.

Fluoxetine-treated patients were found to have statistically significantly lesser increases in height as compared with placebo-treated patients during the subchronic treatment phase. The significance of this finding is uncertain, but previously completed studies of fluoxetine in the pediatric population did not indicate any statistically significant decreases in height in fluoxetine-treated patients as compared with placebo-treated patients.

The data from this study indicate that fluoxetine 20 to 60 mg/day is safe in the treatment of MDD in children and adolescents.

13. Discussion and Overall Conclusions

Study B1Y-MC-HCJE was a double-blind, placebo-controlled study evaluating the efficacy and safety of fluoxetine versus placebo in the treatment of Major Depressive Disorder (MDD) in child and adolescent outpatients. Diagnosis with MDD was determined following a rigorous 3-week diagnostic evaluation. The study consisted of three phases, an acute treatment phase (9 weeks), a subchronic treatment phase (19 weeks), and a relapse prevention phase (32 weeks). Results from the acute and subchronic phases are presented in this clinical study report. The relapse prevention phase is ongoing and the data from this phase will be presented in a future clinical study report.

Two hundred nineteen patients were randomized, with 109 patients receiving fluoxetine treatment and 110 patients receiving placebo treatment. Following randomization, fluoxetine-treated patients received 10 mg/day for one week, then were titrated up to 20 mg/day for the remainder of the 9-week acute treatment phase. Response was evaluated following the acute treatment phase. Patients responding to fluoxetine treatment remained on 20 mg/day for an additional 10 weeks. Patients not responding to fluoxetine treatment were rerandomized (1:1) to either continue receiving 20 mg/day or increase dose to 40 mg/day with an option to further titrate up to 60 mg/day. Placebo-treated patients remained on placebo.

The efficacy of fluoxetine versus placebo in the acute treatment of MDD in children and adolescents is supported by both disease-specific and global efficacy measures following 9 weeks of treatment. Sixty-five percent of patients randomized to fluoxetine responded (30% or greater decrease in CDRS-R total score) as compared with 54% of patients randomized to placebo after acute treatment (p=.093). The difference between treatment groups was not statistically significant, although significance was achieved when the percent decrease in CDRS-R total score was set at 10, 20, 40, 50, and 60%. Fluoxetine-treated patients also showed statistically significantly greater improvement as compared with placebo-treated patients on a wide range of secondary efficacy measures, including the categorical analyses of remission, response based on CGI-Improvement score, and recovery. In addition, fluoxetine-treated patients demonstrated statistically significantly greater mean changes from baseline to endpoint on CDRS-R total, CDRS-R subtotal, CGI-Severity, and MADRS scores as compared with placebo-treated patients. Statistically significantly greater improvement was also observed in fluoxetine-treated patients compared with placebo-treated patients, as measured by endpoint scores on the CGI-Improvement scale.

The efficacy of dose escalation to fluoxetine 40 to 60 mg/day in children and adolescents who did not respond to acute treatment with 20 mg/day is also supported by the results of this study. Nonresponders treated at the higher dose levels showed strong numerical trends on a wide range of measures, including CDRS-R response, CDRS-R total mean change, CGI-Severity, BDI total, and CGI-Improvement scores as compared with

nonresponders who remained on fluoxetine 20 mg/day. The differences between treatment groups did not reach statistical significance; however, sample sizes were small (n=29).

A statistically significantly greater number of fluoxetine-treated patients met CDRS-R response criteria as compared with placebo-treated patients during subchronic treatment (19 weeks). In addition, statistically significant changes in favor of fluoxetine treatment were observed in mean changes from baseline to endpoint on both the CDRS-R total and CGI-Severity scores. Numerically superior, although not statistically significant, changes in favor of fluoxetine treatment were also observed on a number of secondary efficacy measures. The analyses comparing patients who received fluoxetine 20 to 60 mg/day versus patients who received placebo during the subchronic treatment phase include nonresponders who were maintained on 20 mg/day, making it difficult to fully evaluate the impact of longer-term treatment. Nevertheless, these results provide support for the effectiveness of fluoxetine in the subchronic treatment phase.

Efficacy results for acute and subchronic treatment were similar across subgroups based on age category, gender, and family history of depression.

Evaluation of adverse event, vital sign, and laboratory data demonstrates the safety of fluoxetine 20 to 60 mg/day in children and adolescents. Adverse events were collected both spontaneously (non-solicited) and with a standard interviewer-elicited adverse event questionnaire (solicited). Only one treatment-emergent non-solicited adverse event, headache, was reported statistically significantly more often by fluoxetine-treated patients as compared with placebo-treated patients during the acute (30% fluoxetine, 16% placebo) and subchronic (34% fluoxetine, 19% placebo) treatment phases. No other adverse event (non-solicited or solicited) was reported statistically significantly more often by fluoxetine-treated patients during either treatment phase. No clinically relevant treatment differences were observed among subgroups based on age category, gender, or family history of depression.

There were no statistically significant or clinically relevant differences between treatment groups for changes in heart rate, blood pressure, or temperature. On average, fluoxetine-treated patients gained less weight and had lesser increases in height as compared with placebo-treated patients. Weight loss during acute treatment has been observed with fluoxetine in some studies of adults; however, weight loss was not sustained during longer-term treatment in adults (Clinical Investigator's Brochure 1999). Data from Study Period VI will be informative with regard to the significance of these findings.

Fluoxetine-treated patients had slightly elevated cholesterol levels ($p=.014$) and decreased alkaline phosphatase levels ($p<.001$) during subchronic treatment as compared with placebo-treated patients. The observed changes in cholesterol levels are not considered clinically relevant. The observed decreases in alkaline phosphatase levels appear to be related to fluoxetine dose, although they are not related to the combined serum concentrations of fluoxetine and norfluoxetine. Interestingly, although statistically

significant decreases in alkaline phosphatase levels were observed during 19 weeks of treatment, none of these decreases were outside of normal pediatric ranges. The clinical relevance of this finding is unclear.

Two independent, blinded analyses of ECG interval changes did not reveal clinically significant changes in any ECG parameter.

The results of this study support the safety and efficacy of fluoxetine 20 mg/day in the acute treatment of MDD in children and adolescents. LOCF analyses of mean CDRS-R total scores over time indicate that fluoxetine treatment was statistically superior to placebo treatment after only 1 week of treatment. This treatment effect persisted throughout the 19-week subchronic treatment phase. In addition, the efficacy of dose titration to fluoxetine 40 to 60 mg/day in patients who do not respond to 20 mg/day is demonstrated. These results also support the efficacy of fluoxetine 20 to 60 mg/day in the subchronic treatment of MDD in children and adolescents.

Fluoxetine 20 to 60 mg/day was found to be safe and well tolerated during acute and subchronic treatment in children and adolescents.

14. Tables, Figures, and Graphics Not Included in Other Sections

14.1. Demographic Data Summary

Additional baseline patient demographic information was collected on the Physician Checklist (see Table 14.1). No statistically significant differences were observed between treatment groups with respect to the information collected at baseline.

Table 14.1. Physician Checklist at Baseline
All Randomized Patients
B1Y-MC-HCJE

Variable	Flx 20 (N=109)	Placebo (N=110)	Total (N=219)	p-Value
Attending School				
No. Patients	109	110	219	.849*
Yes	93 (85.3)	95 (86.4)	188 (85.8)	
No	16 (14.7)	15 (13.6)	31 (14.2)	
Change to special classes/school				
No. Patients	109	110	219	.856*
Yes	18 (16.5)	17 (15.5)	35 (16.0)	
No	91 (83.5)	93 (84.5)	184 (84.0)	
School difficulties				
No. Patients	109	110	219	.643*
Yes	80 (73.4)	84 (76.4)	164 (74.9)	
No	29 (26.6)	26 (23.6)	55 (25.1)	

RMP.B1YP.JCLLIB2(DES1JEAP)
RMP.B1YO.HCJEREP(DES1JEAP)
* Frequencies are analyzed using a Fishers-Exact test.
XDES0001

Table 14.1. Physician Checklist at Baseline
All Randomized Patients
B1Y-MC-HCJE (continued)

Variable	Flx 20 (N=109)	Placebo (N=110)	Total (N=219)	p-Value
Other therapy				
No. Patients	109	110	219	.092*
Yes	12 (11.0)	22 (20.0)	34 (15.5)	
No	97 (89.0)	88 (80.0)	185 (84.5)	
Vacation				
No. Patients	109	110	219	.619*
Yes	21 (19.3)	25 (22.7)	46 (21.0)	
No	88 (80.7)	85 (77.3)	173 (79.0)	
Illness				
No. Patients	109	110	219	.594*
Yes	8 (7.3)	6 (5.5)	14 (6.4)	
No	101 (92.7)	104 (94.5)	205 (93.6)	

RMP.B1YP.JCLLIB2(DES1JEAP)
RMP.B1YO.HCJEREP(DES1JEAP)
* Frequencies are analyzed using a Fishers-Exact test.
XDES0001

Table 14.1. Physician Checklist at Baseline
All Randomized Patients
B1Y-MC-HCJE (continued)

Variable	Flx 20 (N=109)	Placebo (N=110)	Total (N=219)	p-Value
Sexual Activity				
No. Patients	109	110	219	1.00*
Yes	3 (2.8)	4 (3.6)	7 (3.2)	
No	105 (97.2)	106 (96.4)	211 (96.8)	
Unspecified	1	0	1	
Change in family mental health status				
No. Patients	109	110	219	.864*
Yes	21 (19.3)	20 (18.2)	41 (18.7)	
No	88 (80.7)	90 (81.8)	178 (81.3)	
Change in family status				
No. Patients	109	110	219	.776*
Yes	38 (34.9)	36 (32.7)	74 (33.8)	
No	71 (65.1)	74 (67.3)	145 (66.2)	

RMP.B1YP.JCLLIB2(DES1JEAP)
RMP.B1YO.HCJEREP(DES1JEAP)
* Frequencies are analyzed using a Fishers-Exact test.
XDES0001

Table 14.1. Physician Checklist at Baseline
All Randomized Patients
B1Y-MC-HCJE (continued)

Variable	Flx 20 (N=109)	Placebo (N=110)	Total (N=219)	p-Value
Family move				
No. Patients	109	110	219	.221*
Yes	16 (14.7)	24 (21.8)	40 (18.3)	
No	93 (85.3)	86 (78.2)	179 (81.7)	
Death of friend or close relative				
No. Patients	109	110	219	1.00*
Yes	18 (16.5)	19 (17.3)	37 (16.9)	
No	91 (83.5)	91 (82.7)	182 (83.1)	
Sexual abuse				
No. Patients	109	110	219	.119*
Yes	1 (0.9)	6 (5.5)	7 (3.2)	
No	108 (99.1)	104 (94.5)	212 (96.8)	

RMP.B1YP.JCLLIB2(DES1JEAP)
RMP.B1YO.HCJEREP(DES1JEAP)
* Frequencies are analyzed using a Fishers-Exact test.
XDES0001

Table 14.1. Physician Checklist at Baseline
All Randomized Patients
B1Y-MC-HCJE (concluded)

Variable	Flx 20 (N=109)	Placebo (N=110)	Total (N=219)	p-Value
Physical abuse				
No. Patients	109	110	219	1.00*
Yes	1 (0.9)	2 (1.8)	3 (1.4)	
No	108 (99.1)	108 (98.2)	216 (98.6)	
Mental abuse				
No. Patients	109	110	219	.632*
Yes	10 (9.2)	8 (7.3)	18 (8.2)	
No	99 (90.8)	102 (92.7)	201 (91.8)	

RMP.B1YP.JCLLIB2(DES1JEAP)
RMP.B1YO.HCJEREP(DES1JEAP)
* Frequencies are analyzed using a Fishers-Exact test.
XDES0001

14.2. Efficacy Data Summary

This section contains additional analyses of the CDRS-R, CGI-Efficacy Index, K-SADS-PL (Affective Disorders module), all by-investigator analyses of the scales evaluated in this study, efficacy analyses for the subchronic treatment phase, and secondary statistical models for efficacy measures.

14.2.1. Acute Treatment Phase (Study Periods III-IV)

14.2.1.1. Additional Efficacy Measures

The change in CDRS-R individual item scores from baseline to endpoint for the acute treatment phase, CGI-Efficacy Index scores, and endpoint analysis of K-SADS-PL (Affective Disorders module) scores are presented in Tables 14.2, 14.3, and 14.4, respectively.

Fluoxetine-treated patients showed statistically significantly greater improvement in 8 of the 17 CDRS-R individual items compared with placebo-treated patients.

Physicians used the CGI-Efficacy Index (shown in Figure 14.1) to rate overall therapeutic effect in conjunction with side effects for each patient. Over half of fluoxetine-treated patients (58%) had a score of 1, 2, 5, or 6, which indicated that therapeutic effects outweighed any side effects present, as compared with 40% of placebo-treated patients. Only 3% of fluoxetine-treated patients and 1% of placebo-treated patients had intolerable side effects with minimal or no efficacy, reflected as a score of 11, 12, 15, or 16. The remaining patients either experienced little change in efficacy with minimal side effects or experienced moderate efficacy but had side effects that outweighed the potential therapeutic benefit of the study drug.

Endpoint analyses of the current depression and mania questions of the K-SADS-PL (Affective Disorders module) were intended to rate each patient as to current states of depression and mania at the endpoint of the specific study period. It should be noted that there was some confusion in the interpretation of current depression by the investigators for this study. The presence of depression referred to MDD specifically; however, several investigators interpreted this as a category for all depressive disorders. No statistically significant differences were observed between treatment groups.

Table 14.2. CDRS-R Individual Item Scores
Change from Baseline to Endpoint
All Randomized Patients
Acute Treatment Phase (Study Periods III-IV)
B1Y-MC-HCJE

Research Project Code: B1Y

Variables Analyzed	Therapy	n	Baseline Mean	Baseline SD	Change to Endpoint Mean	Change to Endpoint SD	p-Values Therapy
CDRS01	Flx 20	109	4.0	1.8	-1.3	1.8	.265
	Placebo	105	3.8	1.8	-1.0	1.8	
CDRS02	Flx 20	109	4.8	1.2	-2.0	1.8	.012
	Placebo	105	4.5	1.4	-1.4	1.7	
CDRS03	Flx 20	109	4.1	1.4	-1.8	1.6	<.001
	Placebo	105	3.6	1.5	-0.9	1.6	
CDRS04	Flx 20	109	3.3	1.5	-1.4	1.7	.278
	Placebo	105	3.4	1.5	-1.1	1.6	
CDRS05	Flx 20	109	2.5	1.3	-0.7	1.4	.608
	Placebo	105	2.6	1.4	-0.6	1.6	
CDRS06	Flx 20	109	4.4	1.7	-1.9	2.2	.065
	Placebo	105	4.3	1.8	-1.3	2.0	
CDRS07	Flx 20	109	2.9	1.6	-1.2	1.7	.004
	Placebo	105	2.9	1.6	-0.6	1.6	
CDRS08	Flx 20	109	4.9	1.5	-2.1	2.0	<.001
	Placebo	105	4.7	1.5	-1.2	1.9	
CDRS09	Flx 20	109	2.4	1.4	-0.9	1.5	.975
	Placebo	105	2.5	1.5	-0.9	1.4	

RMP.B1YP.JCLLIB2(LAS6JEAF)
RMP.B1YO.HCJEREP(LAS6JEAF)
Note: n = Total number of patients in each treatment group having the variable in both baseline and postbaseline visits.
XLAS0006

Table 14.2. CDRS-R Individual Item Scores
Change from Baseline to Endpoint
All Randomized Patients
Acute Treatment Phase (Study Periods III-IV)
B1Y-MC-HCJE (continued)

Research Project Code: B1Y

Note: Models:

FULL1 - Type III Sums of Squares from an analysis of variance (ANOVA): PROC GLM model=treatment.
Least-squares mean option in PROC GLM from the ANOVA using the mean square for error.

XLAS0006

Table 14.2. CDRS-R Individual Item Scores
Change from Baseline to Endpoint
All Randomized Patients
Acute Treatment Phase (Study Periods III-IV)
B1Y-MC-HCJE (continued)

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Legend of Variable Abbreviations:
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Abbrev.     Description
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CDRS01      Schoolwork
CDRS02      Fun
CDRS03      Social Withdrawal
CDRS04      Sleep
CDRS05      Appetite
CDRS06      Fatigue
CDRS07      Phyiscal Complaints
CDRS08      Irritability
CDRS09      Guilt
```

Table 14.2. CDRS-R Individual Item Scores
Change from Baseline to Endpoint
All Randomized Patients
Acute Treatment Phase (Study Periods III-IV)
B1Y-MC-HCJE (continued)

Research Project Code: B1Y

Variables Analyzed	Therapy	n	Baseline Mean	Baseline SD	Change to Endpoint Mean	Change to Endpoint SD	p-Values Therapy
CDRS10	Flx 20	109	4.9	1.4	-1.8	1.7	.005
	Placebo	105	4.7	1.4	-1.2	1.6	
CDRS11	Flx 20	109	4.3	1.2	-1.9	1.7	.043
	Placebo	105	4.1	1.4	-1.4	1.5	
CDRS12	Flx 20	109	2.0	1.3	-0.6	1.3	.565
	Placebo	105	2.0	1.3	-0.5	1.2	
CDRS13	Flx 20	109	1.8	1.1	-0.6	1.3	.051
	Placebo	105	1.6	0.9	-0.3	1.0	
CDRS14	Flx 20	109	3.3	1.8	-1.3	1.9	.117
	Placebo	105	3.4	2.0	-0.9	2.1	
CDRS15	Flx 20	109	3.6	1.5	-1.3	1.5	.017
	Placebo	105	3.3	1.4	-0.8	1.4	
CDRS16	Flx 20	109	1.9	0.9	-0.6	0.8	.033
	Placebo	105	1.8	0.8	-0.3	0.8	
CDRS17	Flx 20	109	2.2	1.3	-0.7	1.1	.164
	Placebo	105	2.1	1.1	-0.4	1.1	

RMP.B1YP.JCLLIB2(LAS6JEAF)
RMP.B1YO.HCJEREP(LAS6JEAF)
Note: n = Total number of patients in each treatment group having the variable in both baseline and postbaseline visits.

Note: Models:

FULL1 - Type III Sums of Squares from an analysis of variance (ANOVA): PROC GLM model=treatment.
Least-squares mean option in PROC GLM from the ANOVA using the mean square for error.
XLAS0006

Table 14.2. CDRS-R Individual Item Scores
Change from Baseline to Endpoint
All Randomized Patients
Acute Treatment Phase (Study Periods III-IV)
B1Y-MC-HCJE (concluded)

```
Legend of Variable Abbreviations:
---------------------------------

Abbrev.     Description
-------     -----------

CDRS10      Self-Esteem
CDRS11      Depressed
CDRS12      Morbid Ideation
CDRS13      Suicidal
CDRS14      Weeping
CDRS15      Depressed Affect
CDRS16      Speech
CDRS17      Hypoactivity
```

Therapeutic Effect	Side Effects			
	None	Do not significantly interfere with patient's functioning	Significantly interferes with patient's functioning	Outweighs therapeutic effect
MARKED - Vast improvement. Complete or nearly complete remission of all symptoms.	01	02	03	04
MODERATE - Decided improvement. Partial remission of symptoms.	05	06	07	08
MINIMAL - Slight improvement which doesn't alter status of care of patient.	09	10	11	12
UNCHANGED OR WORSE	13	14	15	16

Table was reproduced from the Case Report Form for B1Y-MC-HCJE.

Figure 14.1. CGI-Efficacy Index scoring for B1Y-MC-HCJE.

Table 14.3. **CGI-Efficacy Index Score**
Endpoint Analysis
All Randomized Patients
Acute Treatment Phase (Study Periods III-IV)
B1Y-MC-HCJE

Variable	Flx 20 (N=109)	Placebo (N=110)	Total (N=219)
CGI-Efficacy Index Score			
No. Patients	109	106	215
01	31 (28.4)	12 (11.3)	43 (20.0)
02	3 (2.8)	2 (1.9)	5 (2.3)
03	1 (0.9)	0	1 (0.5)
05	18 (16.5)	20 (18.9)	38 (17.7)
06	11 (10.1)	8 (7.5)	19 (8.8)
07	0	3 (2.8)	3 (1.4)
08	0	1 (0.9)	1 (0.5)
09	16 (14.7)	23 (21.7)	39 (18.1)
10	6 (5.5)	9 (8.5)	15 (7.0)
11	0	1 (0.9)	1 (0.5)
13	16 (14.7)	22 (20.8)	38 (17.7)
14	4 (3.7)	5 (4.7)	9 (4.2)
15	1 (0.9)	0	1 (0.5)
16	2 (1.8)	0	2 (0.9)

RMP.B1YP.JCLLIB2(DES1JEAH)
RMP.B1YO.HCJEREP(DES1JEAH)
XDES0001

Table 14.4. K-SADS-PL
Endpoint Analysis
All Randomized Patients
Acute Treatment Phase (Study Periods III-IV)
B1Y-MC-HCJE

Variable	Flx 20 (N=109)	Placebo (N=110)	Total (N=219)	p-Value
Current Depression				
No. Patients	103	83	186	.184*
Yes	46 (44.7)	46 (55.4)	92 (49.5)	
No	57 (55.3)	37 (44.6)	94 (50.5)	
Current Mania				
No. Patients	103	83	186	.503*
Yes	2 (1.9)	0	2 (1.1)	
No	101 (98.1)	83 (100)	184 (98.9)	

RMP.B1YP.JCLLIB2(DES1JEAM)
RMP.B1YO.HCJEREP(DES1JEAM)
* Frequencies are analyzed using a Fishers-Exact test.
XDES0001

14.2.1.2. By-Investigator Analyses

There were a total of 19 investigators recruited for this study. Four investigators never randomized patients. Investigator 6 had no patients randomized to fluoxetine treatment and only 1 patient randomized to placebo treatment. As specified in the protocol, investigators with no patients randomized into one or more treatment groups were to be pooled for statistical analysis purposes. Since no other investigator experienced this situation, Investigator 6 was pooled with the next lowest enroller, Investigator 17. As a result of this pooling, all by-investigator analyses include 14 investigators.

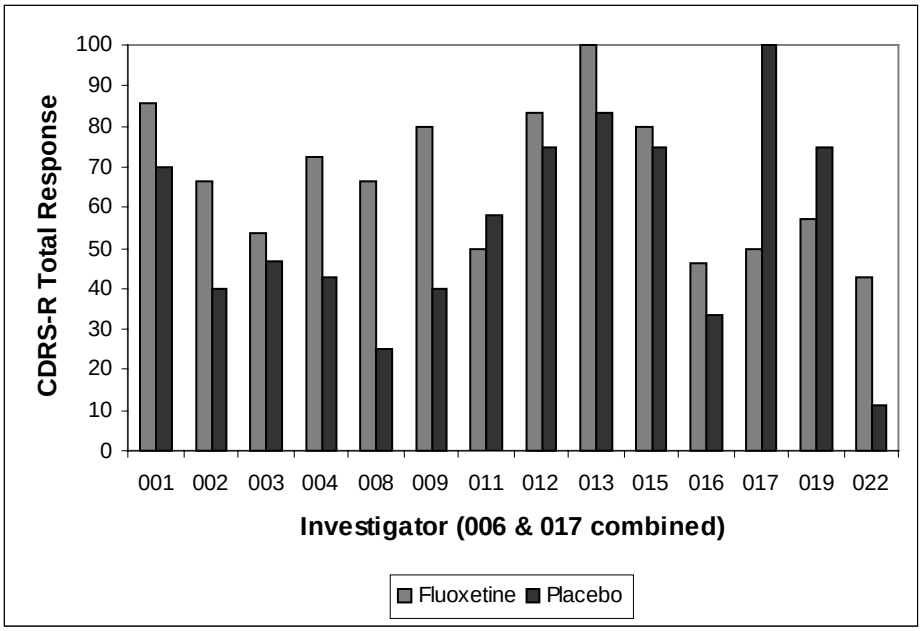
14.2.1.2.1. CDRS-R Total Response

The number of patients meeting CDRS-R total response criteria by investigator during the acute treatment phase is presented in Table 14.5. These data are presented graphically in Figure 14.2. No statistically significant differences were observed between treatment groups for any investigator.

Table 14.5. CDRS-R Total Score
Number of Patients Meeting Criteria for Response
All Randomized Patients by Investigator
Acute Treatment Phase (Study Period IV)
B1Y-MC-HCJE

			No		Yes		
Investigator	Therapy	N	n	%	n	%	p-Value[a]
Inv 1	Flx 20	14	2	14.3	12	85.7	.615
	Placebo	10	3	30.0	7	70.0	
Inv 2	Flx 20	3	1	33.3	2	66.7	1.000
	Placebo	5	3	60.0	2	40.0	
Inv 3	Flx 20	13	6	46.2	7	53.9	1.000
	Placebo	15	8	53.3	7	46.7	
Inv 4	Flx 20	11	3	27.3	8	72.7	.332
	Placebo	7	4	57.1	3	42.9	
Inv 8	Flx 20	6	2	33.3	4	66.7	.524
	Placebo	4	3	75.0	1	25.0	
Inv 9	Flx 20	5	1	20.0	4	80.0	.524
	Placebo	5	3	60.0	2	40.0	
Inv 11	Flx 20	10	5	50.0	5	50.0	1.000
	Placebo	12	5	41.7	7	58.3	
Inv 12	Flx 20	12	2	16.7	10	83.3	1.000
	Placebo	8	2	25.0	6	75.0	
Inv 13	Flx 20	1	0	0	1	100.0	1.000
	Placebo	6	1	16.7	5	83.3	
Inv 15	Flx 20	5	1	20.0	4	80.0	1.000
	Placebo	4	1	25.0	3	75.0	
Inv 16	Flx 20	13	7	53.9	6	46.2	1.000
	Placebo	6	4	66.7	2	33.3	
Inv 17	Flx 20	2	1	50.0	1	50.0	1.000
	Placebo	2	0	0	2	100	
Inv 19	Flx 20	7	3	42.9	4	57.1	.608
	Placebo	8	2	25.0	6	75.0	
Inv 22	Flx 20	7	4	57.1	3	42.9	.262
	Placebo	9	8	88.9	1	11.1	

Data for this table were derived from RMP.B1YSHCJE.SASPGM (CDRSRSP1.SAS).
[a]Fisher's Exact test (2-tail) used.
Abbreviations: Flx = fluoxetine.



Data for this figure were taken from: RMP.B1YSHCJE.SASPGM (CDRSRSP1.SAS).

Figure 14.2. **CDRS-R total score for number of patients meeting criteria for response during the acute treatment phase (Study Period IV) of B1Y-MC-HCJE for all randomized patients by investigator.**

14.2.1.2.2. Mean Change in CDRS-R Total Score from Baseline to Endpoint

By-investigator analyses of mean change from baseline to endpoint in CDRS-R total score for the acute treatment phase are presented in Table 14.6.

Fluoxetine-treated patients showed greater reductions in CDRS-R total scores as compared with placebo-treated patients for 13 of the 14 investigators. The mean change was similar for fluoxetine- and placebo-treated patients for Investigator 8. Statistically significant differences between treatment groups were observed for 2 investigators.

Table 14.6. **CDRS-R Total Score**
Change from Baseline to Endpoint
All Randomized Patients by Investigator
Acute Treatment Phase (Study Periods III-IV)
B1Y-MC-HCJE

Investigator	Therapy	n	Baseline Mean	Baseline SD	Endpoint Mean	Endpoint SD	Change Mean	Change SD	Overall p-Value *1
Inv 1	Flx 20	14	58.4	7.7	27.1	11.9	-31.3	12.5	.008
	Placebo	11	55.9	7.6	39.1	13.5	-16.8	12.1	
Inv 2	Flx 20	3	53.0	3.0	36.3	7.4	-16.7	5.5	.837
	Placebo	5	58.6	14.6	44.4	19.3	-14.2	18.9	
Inv 3	Flx 20	13	52.9	10.4	37.5	15.3	-15.4	13.0	.609
	Placebo	15	50.5	8.2	37.7	10.5	-12.8	13.3	
Inv 4	Flx 20	11	63.5	9.5	38.8	16.6	-24.7	14.5	.272
	Placebo	7	62.9	17.1	46.1	18.5	-16.7	14.7	
Inv 6	Placebo	1	43.0		60.0		17.0		
Inv 8	Flx 20	6	59.2	9.5	42.2	21.4	-17.0	23.9	.972
	Placebo	4	64.8	7.9	47.3	8.5	-17.5	15.5	
Inv 9	Flx 20	5	53.6	12.5	33.4	13.0	-20.2	4.5	.352
	Placebo	5	47.0	14.1	34.6	8.3	-12.4	17.1	
Inv 11	Flx 20	10	52.8	9.2	38.1	12.5	-14.7	10.6	.623
	Placebo	12	52.4	7.4	40.0	15.3	-12.4	10.8	

*1 Type III Sums of Squares from an analysis of variance (ANOVA): PROC GLM model=treatment.
RMP.B1YP.JCLLIB2(LAS3JEAG)
RMP.B1YO.HCJEREP(LAS3JEAG)

Table 14.6. **CDRS-R Total Score**
Change from Baseline to Endpoint
All Randomized Patients by Investigator
Acute Treatment Phase (Study Periods III-IV)
B1Y-MC-HCJE (concluded)

Investigator	Therapy	n	Baseline Mean	Baseline SD	Endpoint Mean	Endpoint SD	Change Mean	Change SD	Overall p-Value *1
Inv 12	Flx 20	12	62.3	8.1	31.8	11.9	-30.6	13.4	.174
	Placebo	8	66.5	5.5	44.5	17.4	-22.0	13.1	
Inv 13	Flx 20	1	75.0		17.0		-58.0		.043
	Placebo	7	62.6	10.9	38.4	16.3	-24.1	12.4	
Inv 15	Flx 20	5	55.4	11.4	32.0	21.4	-23.4	10.4	.416
	Placebo	4	51.8	9.8	33.3	9.0	-18.5	4.7	
Inv 16	Flx 20	13	55.3	9.1	37.8	10.5	-17.5	13.7	.386
	Placebo	6	50.7	10.7	39.2	14.2	-11.5	13.2	
Inv 17	Flx 20	2	55.0	4.2	33.5	4.9	-21.5	9.2	.758
	Placebo	2	46.0	5.7	27.5	2.1	-18.5	7.8	
Inv 19	Flx 20	7	63.6	10.9	37.0	9.7	-26.6	15.8	.293
	Placebo	8	61.9	10.9	42.3	13.6	-19.6	8.1	
Inv 22	Flx 20	7	48.1	6.6	34.3	6.1	-13.9	7.7	.151
	Placebo	10	45.1	11.5	39.5	9.2	-5.6	12.8	

*1 Type III Sums of Squares from an analysis of variance (ANOVA): PROC GLM model=treatment.
RMP.B1YP.JCLLIB2(LAS3JEAG)
RMP.B1YO.HCJEREP(LAS3JEAG)

14.2.2.1.3. CGI-Improvement Score

By-investigator analyses of mean change from baseline to endpoint in CGI-Improvement score for the acute treatment phase are presented in Table 14.7.

Fluoxetine-treated patients showed greater reductions in CGI-Improvement scores as compared with placebo-treated patients for 7 investigators. The mean change was similar for fluoxetine-treated and placebo-treated patients for 4 investigators, and placebo-treated patients demonstrated a greater reduction in CGI-Improvement score as compared with fluoxetine-treated patients for 3 investigators. Statistically significant differences between treatment groups favoring fluoxetine were observed for 2 investigators.

Table 14.7. **CGI-Improvement Score**
Endpoint Analysis
All Randomized Patients by Investigator
Acute Treatment Phase (Study Periods III-IV)
B1Y-MC-HCJE

Inv	Therapy	n	Baseline Mean	Baseline SD	Endpoint Mean	Endpoint SD	Change Mean	Change SD	Overall p-Value *1
Inv 1	Flx 20	14	.	.	1.6	1.1	.	.	.047
	Placebo	11	.	.	2.6	1.3	.	.	
Inv 2	Flx 20	3	.	.	4.0	2.6	.	.	.606
	Placebo	6	.	.	3.3	1.2	.	.	
Inv 3	Flx 20	13	.	.	2.6	1.1	.	.	.485
	Placebo	15	.	.	2.9	0.7	.	.	
Inv 4	Flx 20	11	.	.	2.6	1.6	.	.	.773
	Placebo	7	.	.	2.4	1.1	.	.	
Inv 6	Placebo	1	.	.	6.0		.	.	
Inv 8	Flx 20	6	.	.	2.0	1.5	.	.	.275
	Placebo	4	.	.	3.0	0.8	.	.	
Inv 9	Flx 20	5	.	.	2.2	0.8	.	.	1.00
	Placebo	5	.	.	2.2	1.1	.	.	
Inv 11	Flx 20	10	.	.	3.1	0.9	.	.	.866
	Placebo	12	.	.	3.2	0.9	.	.	
Inv 12	Flx 20	12	.	.	1.9	0.9	.	.	.283
	Placebo	8	.	.	2.4	0.9	.	.	

*1 Type III Sums of Squares from an analysis of variance (ANOVA): PROC GLM model=treatment.
RMP.B1YP.JCLLIB2(LAS3JEMA)
RMP.B1YO.HCJEREP(LAS3JEMA)

Table 14.7. **CGI-Improvement Score**
Endpoint Analysis
All Randomized Patients by Investigator
Acute Treatment Phase (Study Periods III-IV)
B1Y-MC-HCJE (concluded)

Inv	Therapy	n	Baseline Mean	Baseline SD	Endpoint Mean	Endpoint SD	Change Mean	Change SD	Overall p-Value *1
Inv 13	Flx 20	1	.	.	1.0		.	.	.253
	Placebo	7	.	.	2.3	1.0	.	.	
Inv 15	Flx 20	5	.	.	1.8	1.3	.	.	.584
	Placebo	4	.	.	2.3	1.0	.	.	
Inv 16	Flx 20	13	.	.	3.6	1.2	.	.	.652
	Placebo	6	.	.	3.3	1.4	.	.	
Inv 17	Flx 20	2	.	.	2.5	0.7	.	.	.423
	Placebo	2	.	.	2.0	0.0	.	.	
Inv 19	Flx 20	7	.	.	2.3	0.8	.	.	.008
	Placebo	8	.	.	3.5	0.8	.	.	
Inv 22	Flx 20	7	.	.	2.7	0.5	.	.	.247
	Placebo	10	.	.	3.1	0.7	.	.	

*1 Type III Sums of Squares from an analysis of variance (ANOVA): PROC GLM model=treatment.
RMP.B1YP.JCLLIB2(LAS3JEMA)
RMP.B1YO.HCJEREP(LAS3JEMA)

14.2.2.1.4. Change in MADRS Score from Baseline to Endpoint

By-investigator analyses of mean change from baseline to endpoint in MADRS total score for the acute treatment phase are presented in Table 14.8.

Fluoxetine-treated patients showed greater reductions in MADRS total scores as compared with placebo-treated patients for 9 investigators. The differences between treatment groups were statistically significant for 2 of these investigators. The results were similar between treatment groups for 1 investigator. Placebo-treated patients showed greater reductions in MADRS score as compared to fluoxetine-treated patients for 4 investigators.

Table 14.8. **MADRS Score**
Change from Baseline to Endpoint
All Randomized Patients by Investigator
Acute Treatment Phase (Study Periods III-IV)
B1Y-MC-HCJE

Investigator	Therapy	n	Baseline Mean	Baseline SD	Endpoint Mean	Endpoint SD	Change Mean	Change SD	Overall p-Value *1
Inv 1	Flx 20	14	27.2	4.8	7.2	9.2	-20.0	8.3	.013
	Placebo	11	27.7	5.1	16.2	8.3	-11.5	7.1	
Inv 2	Flx 20	3	23.0	3.6	10.0	6.2	-13.0	3.6	.569
	Placebo	5	26.6	9.1	16.8	12.2	-9.8	8.5	
Inv 3	Flx 20	13	21.8	7.5	16.2	11.0	-5.6	9.1	.987
	Placebo	15	18.4	5.8	12.7	6.5	-5.7	8.0	
Inv 4	Flx 20	11	21.9	9.1	12.5	9.2	-9.4	8.5	.718
	Placebo	7	24.9	9.2	14.0	8.3	-10.9	8.1	
Inv 6	Placebo	1	18.0		18.0		0.0		
Inv 8	Flx 20	6	14.8	9.2	9.3	7.7	-5.5	10.2	.361
	Placebo	4	27.5	7.2	15.5	5.0	-12.0	10.6	
Inv 9	Flx 20	5	19.4	5.4	13.0	10.6	-6.4	7.2	.633
	Placebo	5	17.8	11.4	8.8	5.5	-9.0	9.2	
Inv 11	Flx 20	10	23.4	5.0	14.1	9.9	-9.3	7.8	.763
	Placebo	12	24.3	5.7	16.1	8.8	-8.3	8.2	
Inv 12	Flx 20	12	23.8	7.9	9.4	8.3	-14.3	9.1	.348
	Placebo	8	27.0	6.8	16.8	10.1	-10.3	9.6	

RMP.B1YP.JCLLIB2(LAS3JEAL)
RMP.B1YO.HCJEREP(LAS3JEAL)

Table 14.8. **MADRS Score**
Change from Baseline to Endpoint
All Randomized Patients by Investigator
Acute Treatment Phase (Study Periods III-IV)
B1Y-MC-HCJE (concluded)

Investigator	Therapy	n	Baseline Mean	Baseline SD	Endpoint Mean	Endpoint SD	Change Mean	Change SD	Overall p-Value *1
Inv 13	Flx 20	1	33.0		0.0		-33.0		.035
	Placebo	7	24.9	6.7	13.9	9.6	-11.0	7.6	
Inv 15	Flx 20	5	20.2	6.5	7.4	10.1	-12.8	6.1	.513
	Placebo	4	17.5	3.7	7.3	5.4	-10.3	4.6	
Inv 16	Flx 20	13	19.8	5.7	11.1	6.5	-8.7	8.1	.306
	Placebo	6	18.3	2.1	13.5	6.1	-4.8	5.6	
Inv 17	Flx 20	2	23.5	0.7	13.0	5.7	-10.5	4.9	.849
	Placebo	2	17.0	7.1	5.0	1.4	-12.0	8.5	
Inv 19	Flx 20	7	19.1	10.9	12.3	6.9	-6.9	6.6	.094
	Placebo	8	18.4	8.1	18.3	7.9	-0.1	7.6	
Inv 22	Flx 20	7	14.3	4.0	9.9	10.2	-4.4	8.5	.543
	Placebo	10	10.8	7.6	9.0	7.1	-1.8	8.6	

RMP.B1YP.JCLLIB2(LAS3JEAL)
RMP.B1YO.HCJEREP(LAS3JEAL)

14.2.2.1.5. Change in CGI-Severity Score from Baseline to Endpoint

By-investigator analyses of mean change from baseline to endpoint in CGI-Severity score for the acute treatment phase are presented in Table 14.9.

Fluoxetine-treated patients showed greater reductions in CGI-Severity scores as compared with placebo-treated patients for all investigators, except for Investigator 17, for which the placebo-treated patients showed a greater reduction in CGI-Severity score as compared with fluoxetine-treated patients. A statistically significant difference between treatment groups was observed for 1 investigator.

Table 14.9. **CGI-Severity Score**
Change from Baseline to Endpoint
All Randomized Patients by Investigator
Acute Treatment Phase (Study Periods III-IV)
B1Y-MC-HCJE

Investigator	Therapy	n	Baseline Mean	Baseline SD	Endpoint Mean	Endpoint SD	Change Mean	Change SD	Overall p-Value *1
Inv 1	Flx 20	14	4.9	0.6	2.1	1.5	-2.8	1.4	.009
	Placebo	11	4.7	0.5	3.4	1.3	-1.4	1.0	
Inv 2	Flx 20	3	4.7	0.6	3.7	2.1	-1.0	2.6	.606
	Placebo	6	4.3	0.5	4.0	1.1	-0.3	1.2	
Inv 3	Flx 20	13	4.2	0.4	3.0	1.2	-1.2	1.1	.590
	Placebo	15	4.3	0.5	3.3	0.9	-1.0	1.1	
Inv 4	Flx 20	11	4.6	0.5	2.9	1.4	-1.7	1.3	.803
	Placebo	7	4.7	0.8	3.1	1.5	-1.6	1.1	
Inv 6	Placebo	1	4.0		5.0		1.0		
Inv 8	Flx 20	6	4.8	0.8	3.2	1.8	-1.7	1.9	.525
	Placebo	4	5.0	0.0	4.0	0.8	-1.0	0.8	
Inv 9	Flx 20	5	4.6	0.5	3.0	1.0	-1.6	0.5	.486
	Placebo	5	4.2	1.1	3.0	0.7	-1.2	1.1	
Inv 11	Flx 20	10	4.0	0.0	3.4	0.7	-0.6	0.7	.737
	Placebo	12	4.0	0.0	3.5	0.7	-0.5	0.7	
Inv 12	Flx 20	12	4.6	0.7	2.8	0.9	-1.8	0.9	.101
	Placebo	8	4.5	0.5	3.5	0.8	-1.0	1.1	

RMP.B1YP.JCLLIB2(LAS3JEAN)
RMP.B1YO.HCJEREP(LAS3JEAN)

Table 14.9. **CGI-Severity Score**
Change from Baseline to Endpoint
All Randomized Patients by Investigator
Acute Treatment Phase (Study Periods III-IV)
B1Y-MC-HCJE (concluded)

Investigator	Therapy	n	Baseline Mean	Baseline SD	Endpoint Mean	Endpoint SD	Change Mean	Change SD	Overall p-Value *1
Inv 13	Flx 20	1	5.0		1.0		-4.0		.184
	Placebo	7	4.6	0.5	3.0	1.6	-1.6	1.5	
Inv 15	Flx 20	5	4.6	0.5	2.0	1.7	-2.6	1.5	.197
	Placebo	4	4.0	0.0	2.8	1.3	-1.3	1.3	
Inv 16	Flx 20	13	4.7	0.5	3.5	0.8	-1.2	0.8	.308
	Placebo	6	4.3	0.5	3.7	1.0	-0.7	1.2	
Inv 17	Flx 20	2	4.0	0.0	3.5	0.7	-0.5	0.7	.423
	Placebo	2	4.0	0.0	3.0	0.0	-1.0	0.0	
Inv 19	Flx 20	7	4.6	0.5	2.9	1.2	-1.7	1.3	.051
	Placebo	8	4.3	0.5	3.8	1.2	-0.5	0.9	
Inv 22	Flx 20	7	4.1	0.4	3.1	0.7	-1.0	0.6	.830
	Placebo	10	4.2	0.6	3.3	1.1	-0.9	1.1	

RMP.B1YP.JCLLIB2(LAS3JEAN)
RMP.B1YO.HCJEREP(LAS3JEAN)

14.2.2. CDRS-R Total Response and Remission for Patients Treated at Least 5 Weeks

Table 14.10 presents CDRS-R response rates for all patients who completed at least 5 weeks of treatment, where response was defined as a patient having a reduction in CDRS-R total score of at least 30% from baseline. Seventy-eight (75%) fluoxetine-treated patients and 59 (64%) placebo-treated patients met this criterion for response. A greater number of fluoxetine-treated patients demonstrated improvement compared with placebo-treated patients; however, the difference between the two treatment groups was not statistically significant.

Table 14.10. CDRS-R Total Score
Number of Patients Meeting Criteria for Response
All Patients Treated at Least 5 Weeks
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE

```
Protocol: B1Y-MC-HCJE
Outcome Variable: RESPONSE - 30% REDUCTION FROM BASELINE
Stratification Variable: INVESTIGATOR (number of strata = 14)

                                                NO                 YES
   Therapy                  N             n        %         n        %
-- ------------------    -------       ------ ----------  ------ ----------
A. Flx                     104            26      25.0       78      75.0
B. Placebo                  92            33      35.9       59      64.1

COMPARISON OF TREATMENT GROUPS

STATISTICS                            VALUE      P-VALUE
------------------------------    ----------- -----------
Fisher's exact test                                0.119
   (2-tailed)
Pearson's chi-square test               2.7        0.098
   df=1
# Cochran-Mantel-Haenszel               2.9        0.087
   general association test
   df=1

#: Stratification variable included.


Investigators 6 and 17 are pooled into Investigator 999
RMP.B1YP.JCLLIB2(EFS1JEAE)
RMP.B1YO.HCJEREP(EFS1JEAE)
XEFS0001
```

Table 14.11 presents CDRS-R remission rates for all patients who completed at least 5 weeks of treatment, where remission was defined as a patient having a CDRS-R total score of ≤28 at endpoint. A greater number of fluoxetine-treated patients showed improvement, with 55 (53%) fluoxetine-treated patients meeting remission criterion compared with 45 (49%) placebo-treated patients. This difference between the two treatment groups was not statistically significant.

Table 14.11. CDRS-R Total Score
Number of Patients Meeting Criteria for Remission
All Patients Treated at Least 5 Weeks
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE

Protocol: B1Y-MC-HCJE
Outcome Variable: REMISSION - SCORE <=28
Stratification Variable: INVESTIGATOR (number of strata = 14)

		NO		YES	
Therapy	N	n	%	n	%
A. Flx	104	49	47.1	55	52.9
B. Placebo	92	47	51.1	45	48.9

COMPARISON OF TREATMENT FROUPS

STATISTICS	VALUE	P-VALUE
Fisher's exact test (2-tailed)		0.668
Pearson's chi-square test df=1	0.3	0.579
# Cochran-Mantel-Haenszel general association test df=1	1.0	0.325

#: Stratification variable included.

Investigators 6 and 17 are pooled into Investigator 999
RMP.B1YP.JCLLIB2(EFS1JEAF)
RMP.B1YO.HCJEREP(EFS1JEAF)
XEFS0001

14.2.3. Subchronic Treatment Phase (Study Periods III-V)

14.2.3.1. Analysis of Primary Endpoint: Patients Meeting Criteria for CDRS-R Total Response

The percentage of randomized patients meeting response criteria based on CDRS-R total score for the subchronic treatment phase is summarized in Table 14.12. This analysis includes all patients who were treated at least 1 week with fluoxetine 20 mg/day. Response was defined as a reduction in CDRS-R total score of at least 30% from baseline to endpoint.

A statistically significant difference was observed between the two treatment groups during the 19-week subchronic treatment phase. Eighty-two (75%) fluoxetine-treated patients met response criteria compared with 61 (60%) placebo-treated patients (p=.026).

Table 14.12. CDRS-R Total Score
Number of Patients Meeting Criteria for Response
All Randomized Patients
Subchronic Treatment Phase (Study Periods IV-V)
B1Y-MC-HCJE

Protocol: B1Y-MC-HCJE
Outcome Variable: RESPONSE - 30% REDUCTION FROM BASELINE
Stratification Variable: INVESTIGATOR (number of strata = 14)

		NO		YES	
Therapy	N	n	%	n	%
A. Flx	109	27	24.8	82	75.2
B. Placebo	101	40	39.6	61	60.4

Comparison of All Treatments

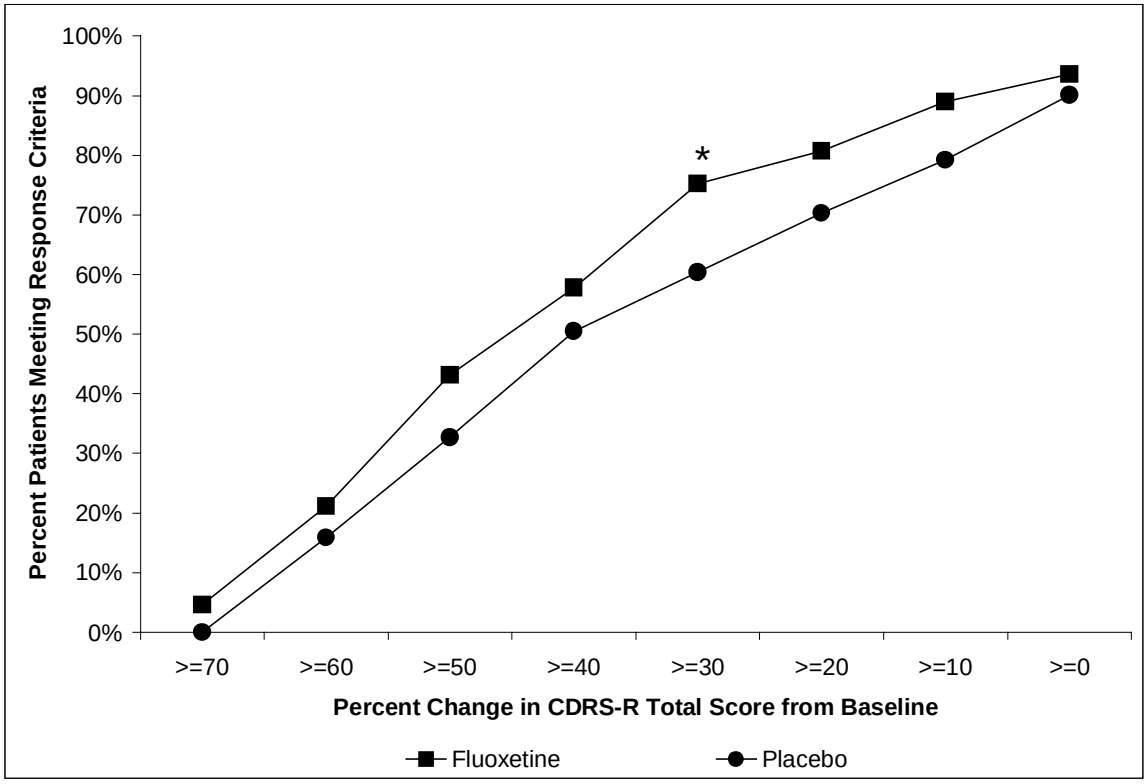
STATISTICS	P-VALUE
Fisher's exact test (2-tailed)	0.026
Pearson's chi-square test df=1	0.021
# Cochran-Mantel-Haenszel general association test df=1	0.011

#: Stratification variable included.

Investigators 6 and 17 are pooled into Investigator 999
RMP.B1YP.JCLLIB2(EFS1JEMB)
RMP.B1YO.HCJEREP(EFS1JEMB)
XEFS0001

Figure 14.3 plots the percent of patients who met the response criteria (vertical axis) against different possible response criteria (horizontal axis) during the subchronic treatment phase. This graph only displays data from patients whose change from baseline reduction was ≥0. Six fluoxetine-treated patients and 11 placebo-treated patients were not included because their CDRS-R total scores increased from baseline. During the subchronic treatment phase, the fluoxetine treatment group had a consistently greater response rate than the placebo treatment group regardless of the percent change criteria. The percent change from baseline criterion at which the differences between the fluoxetine and placebo treatment groups is the greatest occurred at the 30% change criterion (p=.026).

A complete data listing of CDRS-R total scores by patient is presented in Appendix 16.2.7.



Data for this figure were taken from RMT.B1YSHCJE.SASPGM (CDRSRSP3.SAS)
*Statistically significant difference between treatment groups.

Figure 14.3. Percent change distribution in CDRS-R total score for all randomized patients during subchronic treatment (Study Periods IV-V) of B1Y-MC-HCJE.

14.2.3.2. Additional Analyses for CDRS-R

14.2.3.2.1. Remission

The number of patients meeting criteria for remission during the subchronic treatment phase is presented in Table 14.13. Remission was defined as an endpoint CDRS-R total score ≤28.

A greater number of fluoxetine-treated patients met remission criteria, with 55 (51%) patients in the fluoxetine-treatment group meeting these criteria compared with 46 (46%) placebo-treated patients. This difference was not statistically significant (p=.493).

Table 14.13. CDRS-R Total Score
Number of Patients Meeting Criteria for Remission
All Randomized Patients
Subchronic Treatment Phase (Study Periods IV-V)
B1Y-MC-HCJE

Protocol: B1Y-MC-HCJE
Outcome Variable: REMISSION - SCORE <=28
Stratification Variable: INVESTIGATOR (number of strata = 14)

		NO		YES	
Therapy	N	n	%	n	%
A. Flx	109	54	49.5	55	50.5
B. Placebo	101	55	54.5	46	45.5

COMPARISON OF TREATMENT GROUPS

STATISTICS	VALUE	P-VALUE
Fisher's exact test (2-tailed)		0.493
Pearson's chi-square test df=1	0.5	0.476
# Cochran-Mantel-Haenszel general association test df=1	1.2	0.275

#: Stratification variable included.

Investigators 6 and 17 are pooled into Investigator 999
RMP.B1YP.JCLLIB2(EFS1JEAA)
RMP.B1YO.HCJEREP(EFS1JEAA)
XEFS0001

14.2.3.2.2. Mean Change from Baseline to Endpoint

Table 14.14 presents a summary of the mean change from baseline to endpoint for CDRS-R total and subtotal scores during the subchronic treatment phase.

The treatment effect was statistically significant for the CDRS-R total score during this treatment phase, with fluoxetine-treated patients showing greater reductions than placebo-treated patients. Fluoxetine-treated patients experienced a mean reduction of 23 points, while placebo-treated patients experienced a mean reduction of 19 points (p=.021).

The mean change was numerically greater in fluoxetine-treated patients compared with placebo-treated patients for all four subtotal scores; however, the treatment effect was statistically significant only for the Behavior subtotal (p=.011).

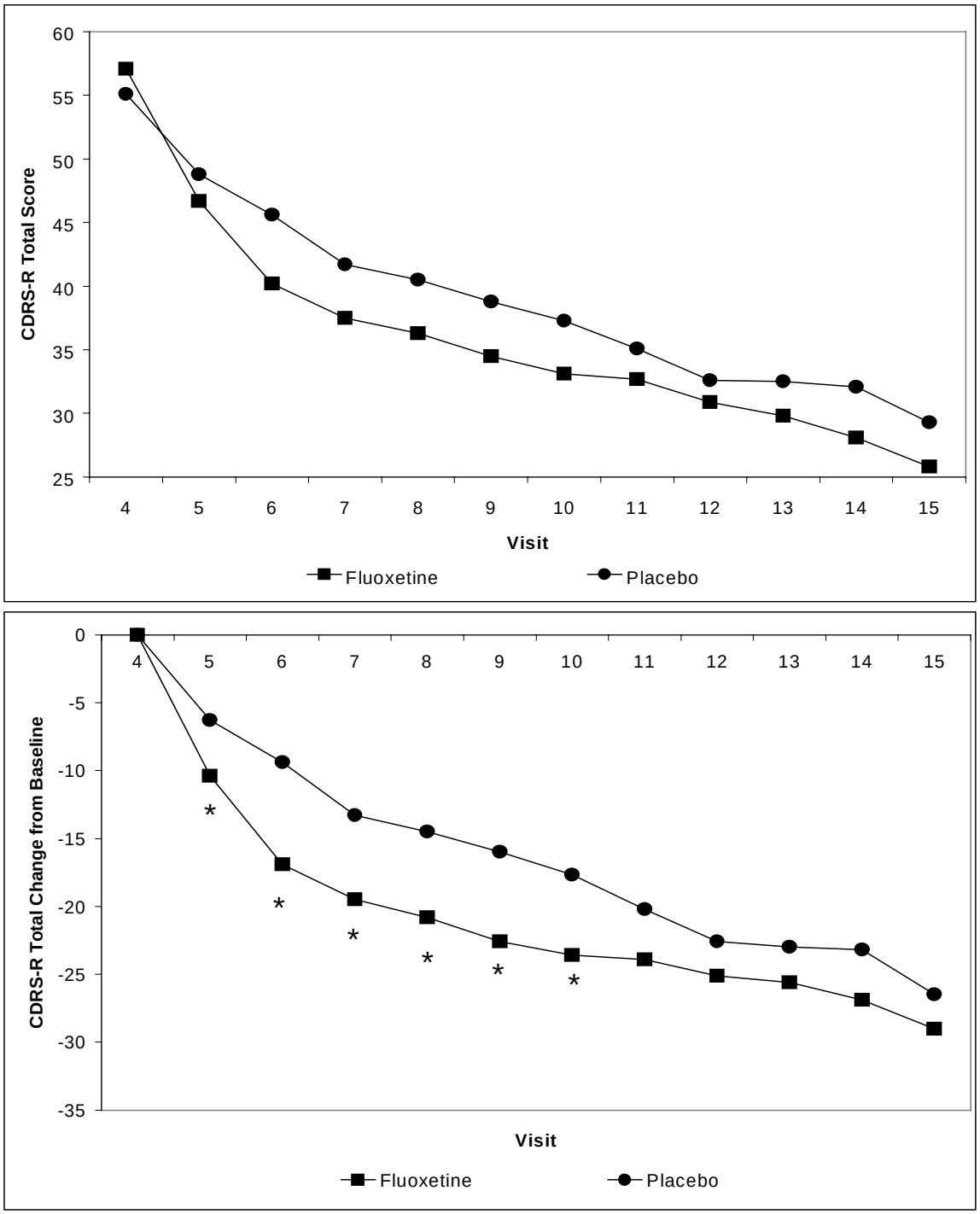
Table 14.14. **CDRS-R Scores**
Change from Baseline to Endpoint
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE

Variable	Therapy	n	Baseline Mean	Baseline SD	Endpoint Mean	Endpoint SD	Change Mean	Change SD	p-Value *1
TOTAL	Flx	109	57.1	9.9	33.8	14.1	-23.4	14.6	.021
	Placebo	105	55.1	11.8	36.6	14.0	-18.6	15.6	
MOOD SUBTOTAL	Flx	109	15.9	4.0	9.1	5.0	-6.9	5.6	.055
	Placebo	105	15.4	4.8	10.1	4.8	-5.3	6.2	
SOMATIC SUBTOTAL	Flx	109	17.2	4.5	10.4	4.4	-6.8	5.4	.181
	Placebo	105	17.0	4.3	11.2	5.1	-5.8	4.9	
SUBJECTIVE SUBTOTAL	Flx	109	11.1	3.0	6.9	2.9	-4.2	3.4	.078
	Placebo	105	10.8	3.3	7.5	2.6	-3.3	3.5	
BEHAVIOR SUBTOTAL	Flx	109	12.9	2.9	7.3	4.0	-5.6	3.9	.011
	Placebo	105	11.9	3.2	7.8	3.7	-4.1	4.3	

*1 Type III Sums of Squares from an analysis of variance (ANOVA): PROC GLM model=treatment.
RMP.B1YP.JCLLIB2(LAS3JEAB)
RMP.B1YO.HCJEREP(LAS3JEAB)

14.2.3.2.3. By-Visit Analyses

Figure 14.4 displays the mean endpoint score and change from baseline for the CDRS-R total score for both treatment groups by visit (observed cases). Table 14.15 presents the CDRS-R total change from baseline to each visit for observed cases. Fluoxetine-treated patients consistently showed a greater reduction in CDRS-R total scores from baseline compared with placebo-treated patients. These differences were statistically significant from Visits 5 through 10, but not from Visits 11 through 15.



Data for this figure were taken from RMP.B1YO.HCJEREP (PRCNJEAQ).
* Statistically significant difference between treatment groups.

Figure 14.4. **CDRS-R total score versus visit (observed cases) by treatment group for the subchronic treatment phase (Study Periods III-V) of B1Y-MC-HCJE.**

Table 14.15. **CDRS-R Total Score**
Change from Baseline to Each Visit (Observed Cases)
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE

Visit	Therapy	n	Baseline Mean	Baseline SD	Endpoint Mean	Endpoint SD	Change Mean	Change SD	Overall p-Value *1
5	Flx	109	57.1	9.9	46.7	12.5	-10.4	10.3	.002
	Placebo	105	55.1	11.8	48.8	12.0	-6.3	8.9	
6	Flx	109	57.1	9.9	40.2	12.2	-16.9	11.6	<.001
	Placebo	101	55.0	11.8	45.6	11.7	-9.4	9.9	
7	Flx	108	57.0	9.9	37.5	11.6	-19.5	11.8	<.001
	Placebo	95	55.0	11.8	41.7	10.8	-13.3	10.1	
8	Flx	103	57.1	10.1	36.3	13.7	-20.8	14.6	.001
	Placebo	92	55.1	11.8	40.5	11.3	-14.5	11.7	
9	Flx	99	57.2	10.2	34.5	12.5	-22.6	14.4	<.001
	Placebo	82	54.8	11.8	38.8	12.7	-16.0	11.7	
10	Flx	93	56.7	10.2	33.1	12.9	-23.6	14.2	.005
	Placebo	73	55.0	11.9	37.3	12.4	-17.7	12.4	
11	Flx	86	56.5	10.3	32.7	11.4	-23.9	13.6	.095
	Placebo	66	55.3	11.9	35.1	10.6	-20.2	12.7	
12	Flx	70	56.0	10.3	30.9	9.1	-25.1	12.1	.244
	Placebo	61	55.1	12.2	32.6	8.7	-22.6	12.6	

* 1 Type III Sums of Squares from an analysis of variance (ANOVA): PROC GLM model=treatment.
RMP.B1YP.JCLLIB2(LAS3JEAQ)
RMP.B1YO.HCJEREP(PRCNJEAQ)

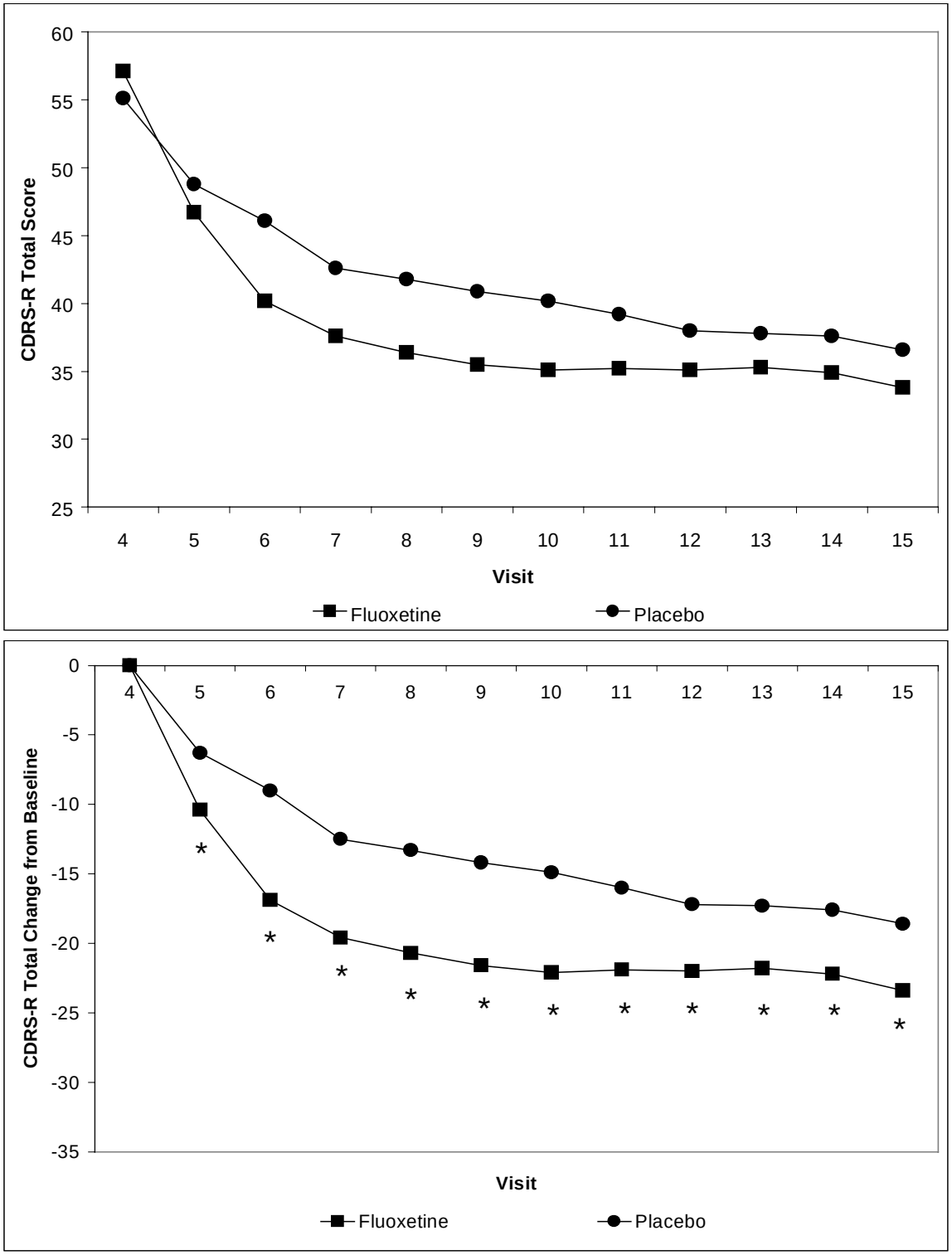
Table 14.15. CDRS-R Total Score
Change from Baseline to Each Visit (Observed Cases)
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE (concluded)

Visit	Therapy	n	Baseline Mean	Baseline SD	Endpoint Mean	Endpoint SD	Change Mean	Change SD	Overall p-Value *1
13	Flx	62	55.4	10.2	29.8	9.6	-25.6	12.4	.288
	Placebo	55	55.5	12.3	32.5	9.5	-23.0	13.5	
14	Flx	57	55.0	10.0	28.1	8.4	-26.9	12.2	.150
	Placebo	51	55.3	12.7	32.1	11.3	-23.2	14.3	
15	Flx	51	54.8	10.2	25.8	8.6	-29.0	12.9	.357
	Placebo	49	55.8	12.7	29.3	9.8	-26.5	13.8	

* 1 Type III Sums of Squares from an analysis of variance (ANOVA): PROC GLM model=treatment.
RMP.B1YP.JCLLIB2(LAS3JEAQ)
RMP.B1YO.HCJEREP(PRCNJEAQ)

Figure 14.5 displays the mean endpoint score and change from baseline for the CDRS-R total score for both treatment groups by visit using LOCF analysis. Table 14.16 presents the LOCF analysis of CDRS-R total change from baseline to each visit. For the LOCF analysis, all patients' last available measure was carried forward for analysis at each visit.

In contrast to the observed case analysis, the LOCF analysis indicates that fluoxetine-treated patients had a statistically significantly greater improvement than placebo-treated patients did at all visits. Fluoxetine-treated patients demonstrated consistently lower endpoint scores compared with placebo-treated patients, and the CDRS-R total change from baseline to endpoint was statistically significant in favor of fluoxetine treatment compared with placebo treatment at all visits.



Data for this figure taken from RMP.B1YO.HCJEREP (PRCNJEAR).
* Statistically significant difference between treatment groups.

Figure 14.5. **CDRS-R total score versus visit (LOCF) by treatment group for the subchronic treatment phase (Study Periods III-V) of B1Y-MC-HCJE.**

Table 14.16. **CDRS-R Total Score**
Change from Baseline to Each Visit (LOCF)
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE

Visit	Therapy	n	Baseline Mean	Baseline SD	Endpoint Mean	Endpoint SD	Change Mean	Change SD	Overall p-Value *1
5	Flx	109	57.1	9.9	46.7	12.5	-10.4	10.3	.002
	Placebo	105	55.1	11.8	48.8	12.0	-6.3	8.9	
6	Flx	109	57.1	9.9	40.2	12.2	-16.9	11.6	<.001
	Placebo	105	55.1	11.8	46.1	11.8	-9.0	10.1	
7	Flx	109	57.1	9.9	37.6	11.5	-19.6	11.8	<.001
	Placebo	105	55.1	11.8	42.6	11.4	-12.5	10.5	
8	Flx	109	57.1	9.9	36.4	13.4	-20.7	14.4	<.001
	Placebo	105	55.1	11.8	41.8	11.8	-13.3	12.2	
9	Flx	109	57.1	9.9	35.5	12.7	-21.6	14.5	<.001
	Placebo	105	55.1	11.8	40.9	13.2	-14.2	12.3	
10	Flx	109	57.1	9.9	35.1	13.5	-22.1	14.4	<.001
	Placebo	105	55.1	11.8	40.2	13.5	-14.9	13.3	
11	Flx	109	57.1	9.9	35.2	13.0	-21.9	14.0	.002
	Placebo	105	55.1	11.8	39.2	13.2	-16.0	13.8	
12	Flx	109	57.1	9.9	35.1	12.6	-22.0	13.5	.011
	Placebo	105	55.1	11.8	38.0	12.8	-17.2	14.1	

* 1 Type III Sums of Squares from an analysis of variance (ANOVA): PROC GLM model=treatment.
RMP.B1YP.JCLLIB2(LAS3JEAR)
RMP.B1YO.HCJEREP(PRCNJEAR)

Table 14.16. CDRS-R Total Score
Change from Baseline to Each Visit (LOCF)
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE (concluded)

Visit	Therapy	n	Baseline Mean	Baseline SD	Endpoint Mean	Endpoint SD	Change Mean	Change SD	Overall p-Value *1
13	Flx	109	57.1	9.9	35.3	13.4	-21.8	13.8	.021
	Placebo	105	55.1	11.8	37.8	13.1	-17.3	14.5	
14	Flx	109	57.1	9.9	34.9	13.4	-22.2	14.1	.020
	Placebo	105	55.1	11.8	37.6	13.9	-17.6	14.9	
15	Flx	109	57.1	9.9	33.8	14.1	-23.4	14.6	.021
	Placebo	105	55.1	11.8	36.6	14.0	-18.6	15.6	

* 1 Type III Sums of Squares from an analysis of variance (ANOVA): PROC GLM model=treatment.
RMP.B1YP.JCLLIB2(LAS3JEAR)
RMP.B1YO.HCJEREP(PRCNJEAR)

14.2.3.2.4. Repeated Measured Analysis

A repeated measures ANOVA was performed on the CDRS-R total score from baseline to the endpoint of the 19-week subchronic treatment phase, which includes the 9-week acute treatment phase. The baseline and each postbaseline visit were included in the model as the dependent variable. The initial model for this analysis included treatment, visit (within-subject factor), treatment-by-visit interaction, investigator, and investigator-by-treatment interaction with an unstructured within-subject variance-covariance matrix. The investigator-by-treatment interaction was not statistically significant (p=.856) and was dropped from the model. The results from the reduced model are displayed in Table 14.17. There was a significant treatment-by-visit interaction (p=.004) indicating that the treatment course over time differed for the two treatment groups. Table 14.18 presents the least-square means and Figure 14.6 displays a plot of the least-square means from this model.

CDRS-R total scores decreased for fluoxetine-treated patients at a much faster rate during the early visits than placebo-treated patients. The overall treatment effect was also statistically significant (p=.022). The contrast comparing change from baseline to Visit 10 between the treatment groups was significant (p=.003); however, the change to Visit 15 was not (p=.130). These results are consistent with the by-visit analyses.

Table 14.17. CDRS-R Total Score
Repeated Measures Model Parameters
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE

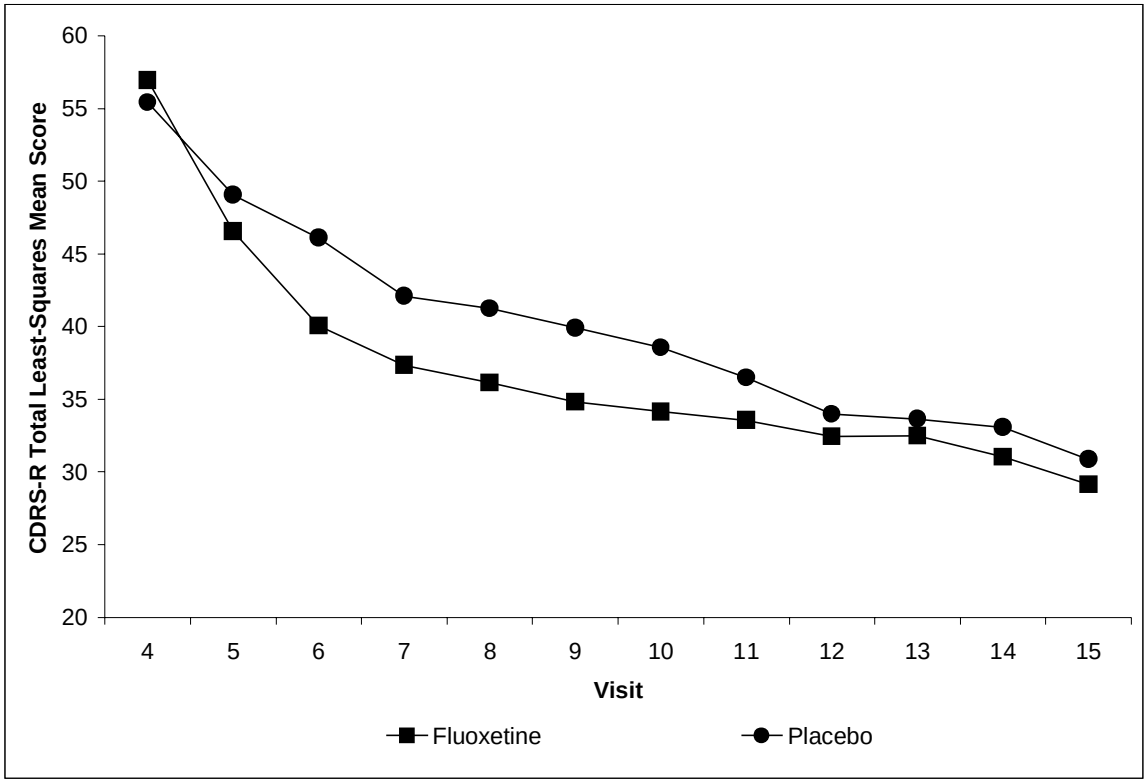
Parameter	ndf	ddf	F-test Value	p-Value
Treatment	1	169	5.33	.022
Visit	11	152	73.79	<.001
Treatment-by-Visit	11	152	2.63	.004
Investigator[a]	13	190	2.80	.001
Contrast for change from Visit 4 to Visit 10 between treatment groups	1	190	8.87	.003
Contrast for change from Visit 4 to Visit 15 between treatment groups	1	157	2.31	.130

Data for this table were taken from RMP.B1YSHCJE.SASPMG (CDRSREP2).
[a]Treatment by investigator interaction was not significant and was dropped from the model (p=.856).
Abbreviations: ddf = denominator degrees of freedom; ndf = numerator degrees of freedom.

Table 14.18. CDRS-R Total Score
Repeated Measures Least-Squares Means
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE

Visit	Fluoxetine LS Mean	Placebo LS Mean
4	56.94	55.43
5	46.53	49.05
6	40.06	46.10
7	37.34	42.10
8	36.13	41.24
9	34.83	39.90
10	34.14	38.56
11	33.56	36.49
12	32.45	33.98
13	32.49	33.64
14	31.03	33.07
15	29.15	30.88
Overall	37.05	40.04

Data for this table were taken from RMP.B1YSHCJE.SASPMG (CDRSREP2).
Abbreviations: LS = least-squares.



Data for this figure were taken from: RMP.B1YSHCJE.SASPGM (CDRSREP2).

Figure 14.6. Plot of least-square means from the reduced model of CDRS-R total score for the subchronic treatment phase (Study Periods III-V) of B1Y-MC-HCJE.

14.2.3.3. Secondary Efficacy Measures

Secondary analyses were conducted on CGI-Improvement endpoint score, response based on CGI-Improvement, and recovery based on CDRS-R total and CGI-Improvement scores. These analyses are presented in Tables 14.19, 14.20, and 14.21, respectively.

Fluoxetine-treated patients demonstrated greater improvement on all three of these analyses compared with placebo-treated patients; however, the differences were not statistically significant.

Table 14.19. CGI-Improvement Score
Endpoint Analysis
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE

Variable	Flx (N=109)	Placebo (N=110)	Total (N=219)	p-Value
CGI-Improvement Score				
No. Patients	109	106	215	.323**
Mean	2.42	2.59	2.51	
Median	2.00	2.00	2.00	
Standard Dev.	1.36	1.19	1.27	
Minimum	1.00	1.00	1.00	
Maximum	7.00	6.00	7.00	

RMP.B1YP.JCLLIB2(DES1JEAG)
RMP.B1YO.HCJEREP(DES1JEAG)
** Means are analyzed using a Type III Sum of Squares analysis of variance (ANOVA): PROC GLM model=treatment.
XDES0001

Table 14.20. CGI-Improvement Score
Number of Patients Meeting Criteria for Response
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE

Protocol: B1Y-MC-HCJE
Outcome Variable: RESPONSE - SCORE = 1 OR 2
Stratification Variable: INVESTIGATOR (number of strata = 14)

		NO		YES	
Therapy	N	n	%	n	%
A. Flx	109	40	36.7	69	63.3
B. Placebo	106	51	48.1	55	51.9

COMPARISON OF TREATMENT GROUPS

STATISTICS	VALUE	P-VALUE
Fisher's exact test (2-tailed)		0.099
Pearson's chi-square test df=1	2.9	0.090
# Cochran-Mantel-Haenszel general association test df=1	3.7	0.053

#: Stratification variable included.

Investigators 6 and 17 are pooled into Investigator 999
RMP.B1YP.JCLLIB2(EFS1JEAB)
RMP.B1YO.HCJEREP(EFS1JEAB)
XEFS0001

**Table 14.21. CDRS-R Total and CGI-Improvement Scores
Number of Patients Meeting Criteria for Recovery
All Randomized Patients
Subchronic Treatment Phase (Study Periods IV-V)
B1Y-MC-HCJE**

```
Protocol: B1Y-MC-HCJE
Outcome Variable: RECOVERY - CDRS-R <=28 AND CGI-IMPROVEMENT = 1 OR 2
Stratification Variable: INVESTIGATOR (number of strata = 14)

                                                NO                YES
   Therapy                  N              n        %         n        %
-- ------------------    -------        ------ ----------  ------ ----------
A. Flx                     109             54      49.5       55      50.5
B. Placebo                 101             55      54.5       46      45.5

COMPARISON OF TREATMENT GROUPS

STATISTICS                            VALUE      P-VALUE
------------------------------    ----------- -----------
Fisher's exact test                                0.493
   (2-tailed)
Pearson's chi-square test               0.5        0.476
   df=1
$# Cochran-Mantel-Haenszel              1.2        0.275
   general association test
   df=1

#: Stratification variable included.
$: Based on TABLE Scores.


Investigators 6 and 17 are pooled into Investigator 999
RMP.B1YP.JCLLIB2(EFS1JEAD)
RMP.B1YO.HCJEREP(EFS1JEAD)
XEFS0001
```

14.2.3.4. Analyses of Subgroups

14.2.3.4.1. CDRS-R Total Response

The number of patients meeting response criteria (based on CDRS-R total score) during the subchronic treatment phase was also examined by subgroups based on age category, gender, and family history of depression (see Table 14.22).

During the subchronic treatment phase, the Breslow-Day test for homogeneity of odds ratios across subgroups was not statistically significant for any of the three strata. Between-treatment group comparisons were significant for adolescents and patients with a positive family history of depression. Fluoxetine-treated adolescents exhibited a significantly higher response rate compared with placebo-treated adolescents (p=.014). A higher response rate was observed in fluoxetine-treated patients with a positive family history of depression compared with placebo-treated patients with a positive family history of depression (p=.043).

Table 14.22. CDRS-R Total Score
Number of Patients Meeting Criteria for Response
Efficacy Subgroup Analysis, All Randomized Patients
Subchronic Treatment Phase (Study Periods IV-V)
B1Y-MC-HCJE

		Fluoxetine			Placebo				Between Group
Subgroup of Interest	Strata	N	n	%	N	n	%	Homogeneity of Odds Ratio p-Value[a]	Comparison Within Strata p-Value[b]
Age	8 to <13	61	43	71	55	35	64	.148	.553
	13 to <18	48	39	81	46	26	57		.014
Gender	Female	54	40	74	48	30	63	.630	.285
	Male	55	42	76	53	31	59		.064
Family History of Depression	Yes	61	49	80	57	36	63	.473	.043
	No	41	29	71	34	21	62		.466

Data for this table were taken from RMP.B1YO.HCJEREP (EFS1JEMJ).
[a]The homogeneity of odds ratio p-Value is taken from the Breslow-Day test.
[b]The between group comparison p-Value is taken from the Fisher's Exact test.

14.2.3.4.2. CDRS-R Total Score

Table 14.23 summarizes the ANOVA of the change from baseline to endpoint for the CDRS-R total score for the three different strata during the subchronic treatment phase. None of the subgroup categories showed statistically significant treatment-by-subgroup interactions or overall subgroup effect.

Fluoxetine-treated patients consistently showed a numerically greater response as compared with placebo-treated patients across all subgroups. These responses were statistically significant for adolescents (p=.035) and patients with a positive family history of depression (p=.016).

Table 14.23. CDRS-R Total Score
Change from Baseline to Endpoint
Efficacy Subgroup Analysis, All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE

Subgroup of Interest	Therapy by Subgroup Interaction[1]	Subgroup Main Effect	Subgroup	N	Therapy	Baseline N	Baseline Mean	Baseline SD	Change Mean	Change SD	Therapy p-Value[a]
Age (years)	.479	.287	8 to <13	120	Flx	61	55.2	9.0	-21.7	15.5	.221
					Placebo	59	53.0	11.9	-18.3	15.5	
			13 to <18	94	Flx	48	59.6	10.5	-25.4	13.2	.035
					Placebo	46	57.9	11.1	-19.0	15.9	
Gender	.806	.845	Female	104	Flx	54	58.8	10.3	-23.3	15.1	.157
					Placebo	50	57.1	11.9	-19.1	15.3	
			Male	110	Flx	55	55.5	9.3	-23.4	14.3	.071
					Placebo	55	53.3	11.4	-18.1	16.0	
Family History of Depression	.374	.922	Yes	120	Flx	61	56.6	9.4	-24.4	13.6	.016
					Placebo	59	55.5	12.1	-18.2	14.4	
			No	77	Flx	41	59.2	10.4	-22.7	16.4	.558
					Placebo	36	56.9	11.4	-20.4	17.4	

Data take from RMP.B1YSHCJE.SASPGM (EFFMOD).
[a]Type III Sum of Squares used.
PROC GLM model = therapy for the therapy p-value within stratum.
PROC GLM model = therapy, strata, and therapy by strata for interaction and subgroup p-values.
Abbreviations: Flx = fluoxetine; SD = Standard deviation.

14.2.3.4.3. CGI-Improvement Score

Table 14.24 summarizes the ANOVA of endpoint scores for the CGI-Improvement for three different strata during the subchronic treatment phase. None of the subgroup categories showed statistically significant treatment-by-subgroup interactions or overall main effect of the subgroup.

Fluoxetine-treated patients showed numerically lower endpoint scores as compared with placebo-treated patients in adolescent, male, female, and positive family history of depression subgroups. None of these differences were statistically significant.

Table 14.24. CGI-Improvement Score
Endpoint Analysis
Efficacy Subgroup Analysis, All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE

Subgroup of Interest	Therapy by Subgroup Interaction[1]	Subgroup Main Effect	Subgroup	Therapy	Endpoint N	Endpoint Mean	Endpoint SD	Therapy p-Value[a]
Age (years)	.268	.995	8 to <13	Flx	61	2.51	1.53	.999
				Placebo	59	2.51	1.18	
			13 to <18	Flx	48	2.31	1.09	.101
				Placebo	47	2.70	1.20	
Gender	.760	.713	Female	Flx	54	2.48	1.24	.621
				Placebo	50	2.60	1.20	
			Male	Flx	55	2.36	1.47	.375
				Placebo	56	2.59	1.19	
Family History of Depression								
	.206	.185	Yes	Flx	61	2.25	1.30	.120
				Placebo	59	2.61	1.25	
			No	Flx	41	2.73	1.45	.710
				Placebo	37	2.62	1.11	

Data for this table were taken from RMP.B1YSHCJE.SASPGM (CGIMOD).
[a]Type III Sum of Squares used.
PROC GLM model = therapy for the therapy p-value within subgroups.
PROC GLM model = therapy, strata, and therapy by subgroup for interaction and subgroup p-values.
Abbreviations: Flx = fluoxetine; SD = Standard deviation.

14.2.3.5. Additional Efficacy Analyses

Table 14.25 summarizes mean change from baseline results for CGI-Severity, BDI total, CDI total, MADRS total, HAMA total, and GAF (Current Functioning) scores for the subchronic treatment phase. There are two patients (Patients 0206 and 0425) included in the subchronic treatment phase CDI analysis that were not included in the acute phase analysis. Both patients had baseline measurements only during the acute phase. Post-baseline measurements were collected for these patients during Study Period V and mean change analyses could be conducted.

CGI-Severity scores were statistically significantly different between the two treatment groups, with fluoxetine-treated patients experiencing greater reductions in the severity of their illness than placebo-treated patients (fluoxetine -1.7, placebo -1.3; p=.025).

Changes in MADRS total and HAMA total scores exhibited the same numerical trend as CGI-Severity scores; however there were no statistically significant differences between the two treatment groups for these measures.

Mean change from baseline for BDI total scores were equal for both treatment groups, and placebo-treated patients demonstrated greater mean change from baseline for CDI total and GAF (Current Functioning) scores compared with fluoxetine-treated patients. There were no statistically significant differences between treatment groups with respect to these measures.

By-patient listings for CGI-Severity, BDI total, CDI total, MADRS total, HAMA total, and GAF (Current Functioning) scores are located in Appendix 16.2.7.

Table 14.25. Secondary Efficacy Variables
Change from Baseline to Endpoint
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE

Variable	Therapy	n	Baseline Mean	Baseline SD	Endpoint Mean	Endpoint SD	Change Mean	Change SD	p-Value *1
CGI Severity	Flx	109	4.5	0.6	2.8	1.3	-1.7	1.3	.025
	Placebo	106	4.4	0.6	3.0	1.2	-1.3	1.2	
BDI Total	Flx	46	15.5	11.1	9.0	11.3	-6.5	8.6	1.00
	Placebo	38	16.6	11.6	10.1	9.0	-6.5	8.1	
CDI Total	Flx	56	9.2	8.3	7.8	11.2	-1.4	10.3	.068
	Placebo	55	9.1	10.0	4.6	5.5	-4.5	7.3	
MADRS Total	Flx	109	21.6	7.5	10.1	8.8	-11.5	9.2	.212
	Placebo	105	21.5	8.3	11.6	8.5	-9.9	9.2	
HAMA Total	Flx	106	10.2	5.2	5.1	4.8	-5.2	5.2	.669
	Placebo	94	11.0	5.8	6.2	4.8	-4.8	5.7	
GAF: Current Functioning	Flx	104	53.3	6.7	65.1	13.5	11.8	12.9	.803
	Placebo	86	54.6	7.1	66.9	10.6	12.3	12.2	

* 1 Type III Sums of Squares from an analysis of variance (ANOVA): PROC GLM model=treatment.
RMP.B1YP.JCLLIB2(LAS3JEAD)
RMP.B1YO.HCJEREP(PRCNJEAD)

The change in CDRS-R individual item scores from baseline to endpoint for the subchronic treatment phase, CGI-Efficacy Index scores, and endpoint analysis of K-SADS-PL (Affective Disorders module) scores are presented in Tables 14.26, 14.27, and 14.28, respectively.

Fluoxetine-treated patients showed statistically significantly greater improvement in 4 of the 17 CDRS-R individual items compared with placebo-treated patients.

Physicians used the CGI-Efficacy Index (shown in Figure 14.1) to rate overall therapeutic effect in conjunction with side effects for each patient. Over half the patients in both the fluoxetine treatment group (63%) and the placebo treatment group (55%) had a score of 1, 2, 5, or 6, which indicated that therapeutic effects outweighed any side effects present. Five percent of fluoxetine-treated patients and 0% of placebo-treated patients experienced minimal to no therapeutic benefit and had intolerable side effects, reflected as a score of 11, 12, 15, or 16. Endpoint analyses of the current depression and mania questions of the K-SADS-PL (Affective Disorders module) were intended to rate each patient as to current states of depression and mania at the endpoint of the specific study period. It should be noted that there was some confusion in the interpretation of current depression by the investigators for this study. The presence of depression referred to MDD specifically; however, several investigators interpreted this as a category for all depressive disorders. No statistically significant differences were observed between treatment groups.

Table 14.26. CDRS-R Individual Item Scores
Change from Baseline to Endpoint
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE

Research Project Code: B1Y

Variables Analyzed	Therapy	n	Baseline Mean	Baseline SD	Change to Endpoint Mean	Change to Endpoint SD	p-Values Therapy
CDRS01	Flx	109	4.0	1.8	-1.2	1.8	.630
	Placebo	105	3.8	1.8	-1.1	1.9	
CDRS02	Flx	109	4.8	1.2	-2.4	1.8	.030
	Placebo	105	4.5	1.4	-1.8	1.8	
CDRS03	Flx	109	4.1	1.4	-1.9	1.8	.002
	Placebo	105	3.6	1.5	-1.2	1.7	
CDRS04	Flx	109	3.3	1.5	-1.5	2.0	.275
	Placebo	105	3.4	1.5	-1.2	1.6	
CDRS05	Flx	109	2.5	1.3	-0.9	1.4	.835
	Placebo	105	2.6	1.4	-0.9	1.5	
CDRS06	Flx	109	4.4	1.7	-1.8	2.2	.931
	Placebo	105	4.3	1.8	-1.8	2.0	
CDRS07	Flx	109	2.9	1.6	-1.2	1.7	.109
	Placebo	105	2.9	1.6	-0.8	1.7	
CDRS08	Flx	109	4.9	1.5	-2.1	2.0	.020
	Placebo	105	4.7	1.5	-1.5	2.1	
CDRS09	Flx	109	2.4	1.4	-1.0	1.4	.629
	Placebo	105	2.5	1.5	-1.0	1.4	

RMP.B1YP.JCLLIB2(LAS6JEAG)
RMP.B1YO.HCJEREP(LAS6JEAG)
Note: n = Total number of patients in each treatment group having the variable in both baseline and postbaseline visits.
XLAS0006

Table 14.26. CDRS-R Individual Item Scores
Change from Baseline to Endpoint
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE (continued)

Research Project Code: B1Y

Note: Models:

FULL1 - Type III Sums of Squares from an analysis of variance (ANOVA): PROC GLM model=treatment.
Least-squares mean option in PROC GLM from the ANOVA using the mean square for error.

XLAS0006

Table 14.26. CDRS-R Individual Item Scores
Change from Baseline to Endpoint
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE (continued)

Legend of Variable Abbreviations:

Abbrev.	Description
CDRS01	Schoolwork
CDRS02	Fun
CDRS03	Social Withdrawal
CDRS04	Sleep
CDRS05	Appetite
CDRS06	Fatigue
CDRS07	Phyiscal Complaints
CDRS08	Irritability
CDRS09	Guilt

Table 14.26. CDRS-R Individual Item Scores
Change from Baseline to Endpoint
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE (continued)

Research Project Code: B1Y

Variables Analyzed	Therapy	n	Baseline Mean	Baseline SD	Change to Endpoint Mean	Change to Endpoint SD	p-Values Therapy
CDRS10	Flx	109	4.9	1.4	-2.0	1.8	.010
	Placebo	105	4.7	1.4	-1.4	1.7	
CDRS11	Flx	109	4.3	1.2	-2.0	1.7	.233
	Placebo	105	4.1	1.4	-1.7	1.7	
CDRS12	Flx	109	2.0	1.3	-0.6	1.3	.543
	Placebo	105	2.0	1.3	-0.5	1.3	
CDRS13	Flx	109	1.8	1.1	-0.6	1.2	.149
	Placebo	105	1.6	0.9	-0.4	1.0	
CDRS14	Flx	109	3.3	1.8	-1.3	2.1	.453
	Placebo	105	3.4	2.0	-1.1	2.3	
CDRS15	Flx	109	3.6	1.5	-1.4	1.6	.060
	Placebo	105	3.3	1.4	-1.0	1.6	
CDRS16	Flx	109	1.9	0.9	-0.6	0.9	.139
	Placebo	105	1.8	0.8	-0.4	0.8	
CDRS17	Flx	109	2.2	1.3	-0.8	1.2	.359
	Placebo	105	2.1	1.1	-0.6	1.2	

RMP.B1YP.JCLLIB2(LAS6JEAG)
RMP.B1YO.HCJEREP(LAS6JEAG)
Note: n = Total number of patients in each treatment group having the variable in both baseline and postbaseline visits.

Note: Models:

FULL1 - Type III Sums of Squares from an analysis of variance (ANOVA): PROC GLM model=treatment.
Least-squares mean option in PROC GLM from the ANOVA using the mean square for error.
XLAS0006

Table 14.26. CDRS-R Individual Item Scores
Change from Baseline to Endpoint
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE (concluded)

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Legend of Variable Abbreviations:
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Abbrev.     Description
-------     -----------

CDRS10      Self-Esteem
CDRS11      Depressed
CDRS12      Morbid Ideation
CDRS13      Suicidal
CDRS14      Weeping
CDRS15      Depressed Affect
CDRS16      Speech
CDRS17      Hypoactivity
```

Table 14.27. CGI-Efficacy Index Score
Endpoint Analysis
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE

Variable	Flx (N=109)	Placebo (N=110)	Total (N=219)
CGI-Efficacy Score			
No. Patients	109	106	215
01	35 (32.1)	26 (24.5)	61 (28.4)
02	3 (2.8)	2 (1.9)	5 (2.3)
05	25 (22.9)	21 (19.8)	46 (21.4)
06	6 (5.5)	9 (8.5)	15 (7.0)
07	1 (0.9)	1 (0.9)	2 (0.9)
08	0	1 (0.9)	1 (0.5)
09	11 (10.1)	10 (9.4)	21 (9.8)
10	3 (2.8)	13 (12.3)	16 (7.4)
13	16 (14.7)	18 (17.0)	34 (15.8)
14	4 (3.7)	5 (4.7)	9 (4.2)
15	3 (2.8)	0	3 (1.4)
16	2 (1.8)	0	2 (0.9)

RMP.B1YP.JCLLIB2(DES1JEAI)
RMP.B1YO.HCJEREP(DES1JEAI)
XDES0001

Table 14.28. K-SADS-PL
Endpoint Analysis
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE

Variable	Flx (N=109)	Placebo (N=110)	Total (N=219)	p-Value
Current Depression				
No. Patients	103	85	188	.290*
Yes	35 (34.0)	36 (42.4)	71 (37.8)	
No	68 (66.0)	49 (57.6)	117 (62.2)	
Current Mania				
No. Patients	103	85	188	.628*
Yes	3 (2.9)	1 (1.2)	4 (2.1)	
No	100 (97.1)	84 (98.8)	184 (97.9)	

RMP.B1YP.JCLLIB2(DES1JEAN)
RMP.B1YO.HCJEREP(DES1JEAN)
* Frequencies are analyzed using a Fishers-Exact test.
XDES0001

14.2.3.6. By-Investigator Analyses

There were a total of 19 investigators recruited for this study. Four investigators never randomized patients. Investigator 6 had no patients randomized to fluoxetine treatment and only 1 patient randomized to placebo treatment. As specified in the protocol, investigators with no patients randomized into one or more treatment groups were to be pooled for statistical analysis purposes. Since no other investigator experienced this situation, Investigator 6 was pooled with the next lowest enroller, Investigator 17. As a result of this pooling, all by-investigator analyses include 14 investigators.

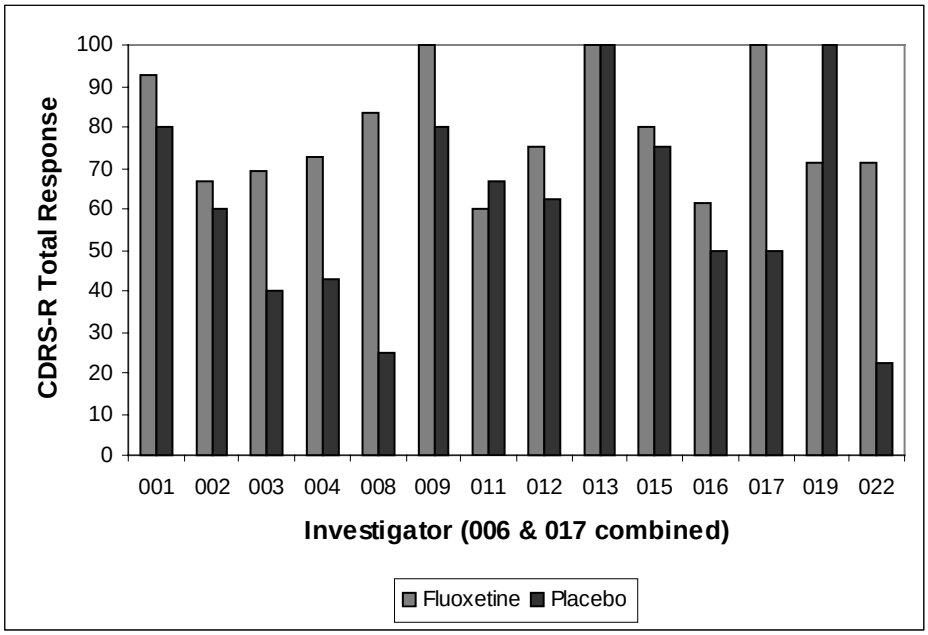
14.2.3.6.1. CDRS-R Total Response

The number of patients meeting CDRS-R total response criteria by investigator during the subchronic treatment phase is presented in Table 14.29. These data are presented graphically in Figure 14.7. No statistically significant differences were observed between treatment groups for any investigator.

Table 14.29. CDRS-R Total Score
Number of Patients Meeting Criteria for Response
All Randomized Patients by Investigator
Subchronic Treatment Phase (Study Periods IV-V)
B1Y-MC-HCJE

			No		Yes		
Investigator	Therapy	N	n	%	n	%	p-Value[a]
Inv 1	Flx	14	1	7.1	13	92.9	.550
	Placebo	10	2	20.0	8	80.0	
Inv 2	Flx	3	1	33.3	2	66.7	1.000
	Placebo	5	2	40.0	3	60.0	
Inv 3	Flx	13	4	30.8	9	69.2	.151
	Placebo	15	9	60.0	6	40.0	
Inv 4	Flx	11	3	27.3	8	72.7	.332
	Placebo	7	4	57.1	3	42.9	
Inv 8	Flx	6	1	16.7	5	83.3	.190
	Placebo	4	3	75.0	1	25.0	
Inv 9	Flx	5	0	0	5	100.0	1.000
	Placebo	5	1	20.0	4	80.0	
Inv 11	Flx	10	4	40.0	6	60.0	1.000
	Placebo	12	4	33.3	8	66.7	
Inv 12	Flx	12	3	25.0	9	75.0	.642
	Placebo	8	3	37.5	5	62.5	
Inv 13	Flx	1	0	0	1	100.0	ND
	Placebo	6	0	0	6	100.0	
Inv 15	Flx	5	1	20.0	4	80.0	1.000
	Placebo	4	1	25.0	3	75.0	
Inv 16	Flx	13	5	38.5	8	61.5	1.000
	Placebo	6	3	50.0	3	50.0	
Inv 17	Flx	2	0	0	2	100.0	1.000
	Placebo	2	1	50.0	1	50.0	
Inv 19	Flx	7	2	28.6	5	71.4	.200
	Placebo	8	0	0	8	100.0	
Inv 22	Flx	7	2	28.6	5	71.4	.126
	Placebo	9	7	77.8	2	22.2	

Data for this table were taken from RMT.B1YSHCJE.SASPGM (CDRSRSP1.SAS).
[a]Fisher's Exact test (2-tail) used.
Abbreviation: Flx = fluoxetine.



Data for this figure were derived from RMT.B1YSHCJE.SASPGM (CDRSRSP1.SAS).

Figure 14.7. CDRS-R total score for number of patients meeting criteria for response during the subchronic treatment phase (Study Periods IV-V) of B1Y-MC-HCJE for all randomized patients by investigator.

14.2.3.6.2. Change in CDRS-R Total Score from Baseline to Endpoint

By-investigator analyses of mean change from baseline to endpoint in CDRS-R total score for the subchronic treatment phase are presented in Table 14.30.

Fluoxetine-treated patients showed greater reductions in CDRS-R total scores as compared with placebo-treated patients for 13 of 14 investigators. The mean change was greater for placebo-treated patients as compared with fluoxetine-treated patients for Investigator 11. No statistically significant differences were observed between treatment groups for any investigator.

Table 14.30. CDRS-R Total Score
Change from Baseline to Endpoint
All Randomized Patients by Investigator
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE

Investigator	Therapy	n	Baseline Mean	Baseline SD	Endpoint Mean	Endpoint SD	Change Mean	Change SD	Overall p-Value *1
Inv 1	Flx	14	58.4	7.7	29.7	12.4	-28.7	12.1	.070
	Placebo	11	55.9	7.6	36.9	14.6	-19.0	13.5	
Inv 2	Flx	3	53.0	3.0	33.0	13.1	-20.0	10.8	.955
	Placebo	5	58.6	14.6	39.4	23.8	-19.2	21.6	
Inv 3	Flx	13	52.9	10.4	36.0	14.6	-16.9	13.8	.434
	Placebo	15	50.5	8.2	37.4	10.0	-13.1	11.9	
Inv 4	Flx	11	63.5	9.5	39.8	18.4	-23.7	16.8	.536
	Placebo	7	62.9	17.1	44.4	17.7	-18.4	18.2	
Inv 6	Placebo	1	43.0		60.0		17.0		
Inv 8	Flx	6	59.2	9.5	34.5	21.2	-24.7	19.3	.859
	Placebo	4	64.8	7.9	42.3	9.9	-22.5	16.4	
Inv 9	Flx	5	53.6	12.5	28.6	7.3	-25.0	7.9	.173
	Placebo	5	47.0	14.1	32.8	10.5	-14.2	14.1	
Inv 11	Flx	10	52.8	9.2	38.0	13.0	-14.8	13.7	.703
	Placebo	12	52.4	7.4	35.2	15.1	-17.3	15.6	

*1 Type III Sums of Squares from an analysis of variance (ANOVA): PROC GLM model=treatment.
RMP.B1YP.JCLLIB2(LAS3JEAK)
RMP.B1YO.HCJEREP(LAS3JEAK)

Table 14.30. CDRS-R Total Score
Change from Baseline to Endpoint
All Randomized Patients by Investigator
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE (concluded)

Investigator	Therapy	n	Baseline Mean	Baseline SD	Endpoint Mean	Endpoint SD	Change Mean	Change SD	Overall p-Value *1
Inv 12	Flx	12	62.3	8.1	33.5	14.2	-28.8	13.9	.699
	Placebo	8	66.5	5.5	40.4	19.5	-26.1	16.8	
Inv 13	Flx	1	75.0		18.0		-57.0		.182
	Placebo	7	62.6	10.9	28.6	13.4	-34.0	14.3	
Inv 15	Flx	5	55.4	11.4	31.6	20.4	-23.8	9.8	.442
	Placebo	4	51.8	9.8	32.5	9.7	-19.3	5.9	
Inv 16	Flx	13	55.3	9.1	34.5	12.9	-20.8	15.6	.373
	Placebo	6	50.7	10.7	36.7	16.0	-14.0	13.9	
Inv 17	Flx	2	55.0	4.2	22.0	0.0	-33.0	4.2	.306
	Placebo	2	46.0	5.7	34.5	16.3	-11.5	21.9	
Inv 19	Flx	7	63.6	10.9	34.9	12.4	-28.7	15.3	.650
	Placebo	8	61.9	10.9	30.3	8.9	-31.6	8.4	
Inv 22	Flx	7	48.1	6.6	30.6	10.6	-17.6	14.0	.194
	Placebo	10	45.1	11.5	36.5	11.6	-8.6	13.0	

*1 Type III Sums of Squares from an analysis of variance (ANOVA): PROC GLM model=treatment.
RMP.B1YP.JCLLIB2(LAS3JEAK)
RMP.B1YO.HCJEREP(LAS3JEAK)

14.2.3.6.3. CGI-Improvement Score

By-investigator analyses of mean CGI-Improvement endpoint scores for the subchronic treatment phase are presented in Table 14.31.

Fluoxetine-treated patients showed greater reductions in CGI-Improvement scores as compared with placebo-treated patients for 7 investigators. The mean endpoint score was similar for fluoxetine-treated and placebo-treated patients for 6 investigators, and placebo-treated patients demonstrated a greater reduction in CGI-Improvement score as compared with fluoxetine-treated patients for 1 investigator. No statistically significant differences were observed between treatment groups for any investigator.

Table 14.31. CGI-Improvement Score
Endpoint Analysis
All Randomized Patients by Investigator
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE

Inv	Therapy	n	Baseline Mean	Baseline SD	Endpoint Mean	Endpoint SD	Change Mean	Change SD	Overall p-Value *1
Inv 1	Flx	14	.	.	1.9	1.0	.	.	.195
	Placebo	11	.	.	2.5	1.2	.	.	
Inv 2	Flx	3	.	.	3.7	3.1	.	.	.607
	Placebo	6	.	.	2.8	1.7	.	.	
Inv 3	Flx	13	.	.	2.5	1.3	.	.	.308
	Placebo	15	.	.	2.9	0.7	.	.	
Inv 4	Flx	11	.	.	2.6	1.4	.	.	.911
	Placebo	7	.	.	2.7	1.5	.	.	
Inv 6	Placebo	1	.	.	6.0		.	.	
Inv 8	Flx	6	.	.	1.7	1.2	.	.	.444
	Placebo	4	.	.	2.3	1.0	.	.	
Inv 9	Flx	5	.	.	1.8	0.8	.	.	.580
	Placebo	5	.	.	2.2	1.3	.	.	
Inv 11	Flx	10	.	.	3.0	1.1	.	.	.616
	Placebo	12	.	.	2.8	1.2	.	.	
Inv 12	Flx	12	.	.	2.1	0.9	.	.	.722
	Placebo	8	.	.	2.3	1.2	.	.	

*1 Type III Sums of Squares from an analysis of variance (ANOVA): PROC GLM model=treatment.
RMP.B1YP.JCLLIB2(LAS3JEMB)
RMP.B1YO.HCJEREP(LAS3JEMB)

Table 14.31. CGI-Improvement Score
Endpoint Analysis
All Randomized Patients by Investigator
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE (concluded)

Inv	Therapy	n	Baseline Mean	Baseline SD	Endpoint Mean	Endpoint SD	Change Mean	Change SD	Overall p-Value *1
Inv 13	Flx	1	.	.	1.0		.	.	.411
	Placebo	7	.	.	1.7	0.8	.	.	
Inv 15	Flx	5	.	.	1.6	0.9	.	.	.575
	Placebo	4	.	.	2.0	1.2	.	.	
Inv 16	Flx	13	.	.	3.4	1.7	.	.	.951
	Placebo	6	.	.	3.3	1.5	.	.	
Inv 17	Flx	2	.	.	1.0	0.0	.	.	.423
	Placebo	2	.	.	2.0	1.4	.	.	
Inv 19	Flx	7	.	.	2.6	1.4	.	.	.734
	Placebo	8	.	.	2.4	0.7	.	.	
Inv 22	Flx	7	.	.	2.6	1.1	.	.	.672
	Placebo	10	.	.	2.8	1.0	.	.	

*1 Type III Sums of Squares from an analysis of variance (ANOVA): PROC GLM model=treatment.
RMP.B1YP.JCLLIB2(LAS3JEMB)
RMP.B1YO.HCJEREP(LAS3JEMB)

14.2.3.6.4. Change in MADRS Score from Baseline to Endpoint

By-investigator analyses of mean change from baseline to endpoint in MADRS total score for the subchronic treatment phase are presented in Table 14.32.

Fluoxetine-treated patients showed greater reductions in MADRS total scores as compared with placebo-treated patients for 10 investigators, and comparable results between the two treatment groups were seen for 1 investigator. Trends in favor of placebo-treated patients as compared with fluoxetine-treated patients were observed for 3 investigators. No statistically significant differences were observed between treatment groups for any investigator.

Table 14.32. MADRS Score
Change from Baseline to Endpoint
All Randomized Patients by Investigator
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE

Investigator	Therapy	n	Baseline Mean	Baseline SD	Endpoint Mean	Endpoint SD	Change Mean	Change SD	Overall p-Value *1
Inv 1	Flx	14	27.2	4.8	9.2	9.5	-18.0	8.8	.246
	Placebo	11	27.7	5.1	14.1	10.2	-13.6	9.5	
Inv 2	Flx	3	23.0	3.6	9.0	7.5	-14.0	5.3	.842
	Placebo	5	26.6	9.1	14.0	14.7	-12.6	10.6	
Inv 3	Flx	13	21.8	7.5	13.5	10.6	-8.3	10.7	.627
	Placebo	15	18.4	5.8	11.7	6.0	-6.7	6.8	
Inv 4	Flx	11	21.9	9.1	12.5	8.9	-9.5	9.3	.710
	Placebo	7	24.9	9.2	13.6	9.5	-11.3	11.0	
Inv 6	Placebo	1	18.0		18.0		0.0		
Inv 8	Flx	6	14.8	9.2	5.8	7.0	-9.0	5.4	.219
	Placebo	4	27.5	7.2	11.8	6.3	-15.8	10.8	
Inv 9	Flx	5	19.4	5.4	9.4	9.4	-10.0	5.8	.615
	Placebo	5	17.8	11.4	9.6	8.4	-8.2	5.1	
Inv 11	Flx	10	23.4	5.0	16.7	8.8	-6.7	9.1	.240
	Placebo	12	24.3	5.7	12.4	9.0	-11.9	10.8	
Inv 12	Flx	12	23.8	7.9	9.0	8.6	-14.8	10.2	.434
	Placebo	8	27.0	6.8	15.8	12.6	-11.3	8.6	

RMP.B1YP.JCLLIB2(LAS3JEAM)
RMP.B1YO.HCJEREP(LAS3JEAM)

Table 14.32. MADRS Score
Change from Baseline to Endpoint
All Randomized Patients by Investigator
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE (concluded)

Investigator	Therapy	n	Baseline Mean	Baseline SD	Endpoint Mean	Endpoint SD	Change Mean	Change SD	Overall p-Value *1
Inv 13	Flx	1	33.0		2.0		-31.0		.120
	Placebo	7	24.9	6.7	8.0	8.4	-16.9	7.3	
Inv 15	Flx	5	20.2	6.5	6.0	10.4	-14.2	7.2	.379
	Placebo	4	17.5	3.7	7.0	3.6	-10.5	3.4	
Inv 16	Flx	13	19.8	5.7	10.2	7.5	-9.5	8.7	.394
	Placebo	6	18.3	2.1	12.3	7.6	-6.0	6.9	
Inv 17	Flx	2	23.5	0.7	3.0	1.4	-20.5	2.1	.410
	Placebo	2	17.0	7.1	9.0	9.9	-8.0	17.0	
Inv 19	Flx	7	19.1	10.9	9.0	7.6	-10.1	8.3	.917
	Placebo	8	18.4	8.1	7.8	6.0	-10.6	9.2	
Inv 22	Flx	7	14.3	4.0	5.7	5.4	-8.6	5.1	.051
	Placebo	10	10.8	7.6	9.3	7.1	-1.5	7.7	

RMP.B1YP.JCLLIB2(LAS3JEAM)
RMP.B1YO.HCJEREP(LAS3JEAM)

14.2.3.6.5. Change in CGI-Severity Score from Baseline to Endpoint

By-investigator analyses of mean change from baseline to endpoint in CGI-Severity score for the subchronic treatment phase are presented in Table 14.33.

Fluoxetine-treated patients showed greater reductions in CGI-Severity scores as compared with placebo-treated patients for 10 investigators, and comparable reductions were observed for both treatment groups for 4 investigators. No statistically significant differences were observed between treatment groups for any investigator.

Table 14.33. CGI-Severity Score
Change from Baseline to Endpoint
All Randomized Patients by Investigator
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE

Investigator	Therapy	n	Baseline Mean	Baseline SD	Endpoint Mean	Endpoint SD	Change Mean	Change SD	Overall p-Value *1
Inv 1	Flx	14	4.9	0.6	2.4	1.4	-2.6	1.3	.115
	Placebo	11	4.7	0.5	3.0	1.3	-1.7	1.2	
Inv 2	Flx	3	4.7	0.6	3.3	2.5	-1.3	3.1	.756
	Placebo	6	4.3	0.5	3.5	1.8	-0.8	1.7	
Inv 3	Flx	13	4.2	0.4	2.8	1.1	-1.4	1.1	.346
	Placebo	15	4.3	0.5	3.3	0.8	-1.0	1.0	
Inv 4	Flx	11	4.6	0.5	3.1	1.4	-1.5	1.4	.969
	Placebo	7	4.7	0.8	3.1	1.6	-1.6	1.4	
Inv 6	Placebo	1	4.0		5.0		1.0		
Inv 8	Flx	6	4.8	0.8	2.5	1.9	-2.3	1.8	.419
	Placebo	4	5.0	0.0	3.5	1.0	-1.5	1.0	
Inv 9	Flx	5	4.6	0.5	2.6	0.9	-2.0	0.7	.141
	Placebo	5	4.2	1.1	3.0	1.0	-1.2	0.8	
Inv 11	Flx	10	4.0	0.0	3.3	0.8	-0.7	0.8	.538
	Placebo	12	4.0	0.0	3.1	0.8	-0.9	0.8	
Inv 12	Flx	12	4.6	0.7	2.8	1.1	-1.8	1.0	.397
	Placebo	8	4.5	0.5	3.1	1.0	-1.4	0.9	

RMP.B1YP.JCLLIB2(LAS3JEAO)
RMP.B1YO.HCJEREP(LAS3JEAO)

Table 14.33. CGI-Severity Score
Change from Baseline to Endpoint
All Randomized Patients by Investigator
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE (concluded)

Investigator	Therapy	n	Baseline Mean	Baseline SD	Endpoint Mean	Endpoint SD	Change Mean	Change SD	Overall p-Value *1
Inv 13	Flx	1	5.0		1.0		-4.0		.292
	Placebo	7	4.6	0.5	2.1	1.5	-2.4	1.3	
Inv 15	Flx	5	4.6	0.5	2.0	1.7	-2.6	1.5	.429
	Placebo	4	4.0	0.0	2.3	1.5	-1.8	1.5	
Inv 16	Flx	13	4.7	0.5	3.3	0.9	-1.4	1.0	.292
	Placebo	6	4.3	0.5	3.5	1.0	-0.8	1.2	
Inv 17	Flx	2	4.0	0.0	2.0	0.0	-2.0	0.0	.771
	Placebo	2	4.0	0.0	2.5	2.1	-1.5	2.1	
Inv 19	Flx	7	4.6	0.5	2.6	1.1	-2.0	1.3	1.00
	Placebo	8	4.3	0.5	2.3	0.9	-2.0	0.8	
Inv 22	Flx	7	4.1	0.4	2.9	1.2	-1.3	1.4	.890
	Placebo	10	4.2	0.6	3.0	1.2	-1.2	1.1	

RMP.B1YP.JCLLIB2(LAS3JEAO)
RMP.B1YO.HCJEREP(LAS3JEAO)

14.2.4. Secondary Statistical Models

All primary and secondary analyses are presented in a summary table (see Table 14.34) that includes ranked analyses of the endpoints. Alternative statistical models that include covariates were also analyzed. Tables 14.35 through 14.37 present these alternative models. Table 14.35 presents the results of ANOVA with investigator, age category (children/adolescents), gender, and treatment-by-investigator in the model for all continuous outcome measurements. In general, the investigator-by-treatment interaction was not significant; therefore, in Table 14.36, the results of the analyses excluding the investigator-by-treatment term are presented. In addition, the results of a logistic regression are presented for the primary outcome of response (see Table 14.37).

The conclusions from the primary analysis (with treatment in the model) did not differ from conclusions made when analyzing the data while adjusting for the covariates; that is, when treatment was statistically significant using the primary model, it was also statistically significant using the alternative model. In addition, there were two instances when statistical significance was not obtained for the primary model but was obtained for the secondary model. For the subchronic treatment phase, there was not a statistically significant difference between treatment groups for either CDRS-R Mood subtotal (p=.055) or CDI (p=.068); however, there were statistically significant differences when including covariates of investigator, age group, and gender (CDRS-R Mood subtotal p=.025, CDI p=.012). Generally, both the covariates of gender and age group were not statistically significant. Table 14.37 presents another alternative model with treatment and investigator in the model. Again, conclusions did not differ substantially compared with the primary analysis.

Table 14.34. Efficacy Scores
Primary Statistical Model
B1Y-MC-HCJE

	Unranked Treatment p-Value (Primary)	Ranked Treatment p-Value
Acute Treatment		
CDRS-R Response	.093	NA
CDRS-R Total[a]	<.001	<.001
CDRS-R Mood[a]	.002	.002
CDRS-R Somatic[a]	.004	.017
CDRS-R Subjective[a]	.026	.013
CDRS-R Behavior[a]	<.001	<.001
CGI-Improvement[b]	.025	.008
CGI-Severity[a]	<.001	<.001
MADRS[a]	.023	.031
CDI[a]	.822	.443
BDI[a]	.700	.996
GAF[a]	.176	.143
HAMA[a]	.115	.201
Subchronic Treatment		
CDRS-R Response	.026	NA
CDRS-R Total[a]	.021	.020
CDRS-R Mood[a]	.055	.032
CDRS-R Somatic[a]	.181	.267
CDRS-R Subjective[a]	.078	.036
CDRS-R Behavior[a]	.011	.006
CGI-Improvement[b]	.323	.126
CGI-Severity[a]	.025	.028
MADRS[a]	.212	.159
CDI[a]	.068	.422
BDI[a]	1.000	.964
GAF[a]	.803	.913
HAMA[a]	.669	.470

Data for this table were taken from RMP.B1YSHCJE.SASPGM (EFFCHG, CGIIMPR), RMP.B1YO.HCHEREP (EFS1JEMA, EFS1JEMB).
[a]Dependent variable is change from baseline to endpoint score.
[b]Dependent variable is endpoint score.
Abbreviations: NA = not available.

Table 14.35. Efficacy Scores
Secondary Statistical Model 1
B1Y-MC-HCJE

	p-Values				
	Treatment	Inv	Age Group	Gender	Trt by Inv
Acute Treatment					
CDRS-R Response[a]	.209	.011	.082	.068	.931
CDRS-R Total[b]	<.001	<.001	.519	.044	.699
CDRS-R Mood[b]	<.001	.022	.823	.059	.942
CDRS-R Somatic[b]	<.001	<.001	.957	.050	.441
CDRS-R Subjective[b]	.058	.150	.081	.118	.199
CDRS-R Behavior[b]	<.001	.003	.718	.507	.706
CGI-Improvement[c]	.019	<.001	.158	.111	.517
CGI-Severity[b]	<.001	<.001	.262	.162	.512
MADRS[b]	.013	<.001	.733	.130	.240
CDI[b]	.390	.304	NA	.020	.711
BDI[b]	.577	.146	NA	.294	.340
GAF[b]	.101	<.001	.015	.009	.042
HAMA[b]	.081	<.001	.878	.354	.219
Subchronic Treatment					
CDRS-R Response[a]	.054	.020	.981	.430	.408
CDRS-R Total[b]	.002	.002	.907	.859	.725
CDRS-R Mood[b]	.009	.056	.871	.831	.878
CDRS-R Somatic[b]	.026	.001	.931	.685	.253
CDRS-R Subjective[b]	.073	.328	.117	.766	.599
CDRS-R Behavior[b]	.002	.006	.409	.230	.456
CGI-Improvement[c]	.123	.008	.192	.386	.881
CGI-Severity[b]	.006	.002	.134	.653	.961
MADRS[b]	.044	.004	.735	.854	.427
CDI[b]	.036	.321	NA	.277	.854
BDI[b]	.252	.125	NA	.338	.641
GAF[b]	.778	<.001	.058	.298	.240
HAMA[b]	.248	.004	.486	.447	.043

Data for this table were taken from RMP.B1YSHCJE.SASPGM (EFFMOD2, CGIMOD, CDRSLOG).

[a]Logistic regression model. Additional investigators needed to be pooled for this model: 6, 17, and 13 were pooled. Test for interaction was done comparing model 1 with model 2 (given in next table). Test for investigator was done comparing model 2 and model including treatment, age group, and gender only.

[b]Dependent variable is change from baseline to endpoint score.

[c]Dependent variable is endpoint score.

Abbreviations: NA = not applicable.

Table 14.36. Efficacy Scores
Secondary Statistical Model 2
B1Y-MC-HCJE

	p-Values			
	Treatment	Inv	Age Group	Gender
Acute Treatment				
CDRS-R Response[a]	.082	.011	.054	.040
CDRS-R Total[b]	<.001	<.001	.569	.080
CDRS-R Mood[b]	.001	.023	.871	.119
CDRS-R Somatic[b]	.003	<.001	.918	.063
CDRS-R Subjective[b]	.044	.294	.112	.151
CDRS-R Behavior[b]	<.001	.002	.818	.691
CGI-Improvement[c]	.018	<.001	.179	.220
CGI-Severity[b]	<.001	<.001	.244	.346
MADRS[b]	.025	<.001	.882	.268
CDI[b]	.323	.234	NA	.076
BDI[b]	.807	.319	NA	.469
GAF[b]	.300	<.001	.041	.073
HAMA[b]	.105	<.001	.825	.474
Subchronic Treatment				
CDRS-R Response[a]	.010	.020	.758	.614
CDRS-R Total[b]	.010	<.001	.896	.712
CDRS-R Mood[b]	.025	.012	.881	.952
CDRS-R Somatic[b]	.121	<.001	.835	.776
CDRS-R Subjective[b]	.075	.334	.150	.671
CDRS-R Behavior[b]	.007	.002	.405	.159
CGI-Improvement[c]	.175	.002	.198	.282
CGI-Severity[b]	.012	<.001	.110	.464
MADRS[b]	.150	.003	.608	.604
CDI[b]	.012	.384	NA	.488
BDI[b]	.777	.171	NA	.593
GAF[b]	.865	<.001	.111	.561
HAMA[b]	.429	<.001	.651	.519

Data for this table were taken from RMP.B1YSHCJE.SASPGM (EFFMOD2, CGIMOD, CDRSLOG).

[a]Logistic regression model. Additional investigators needed to be pooled for this model: 6, 17, and 13 were pooled.

[b]Dependent variable is change from baseline to endpoint score.

[c]Dependent variable is endpoint score.

Abbreviations: NA = not applicable.

Table 14.37. Efficacy Scores
Secondary Statistical Model 3
B1Y-MC-HCJE

	Unranked Data p-Values	
	Treatment	Inv
Acute Treatment		
CDRS-R Response[a]	.073	.016
CDRS-R Total[b]	<.001	<.001
CDRS-R Mood[b]	.001	.009
CDRS-R Somatic[b]	.002	<.001
CDRS-R Subjective[b]	.045	.291
CDRS-R Behavior[b]	<.001	<.001
CGI-Improvement[c]	.018	<.001
CGI-Severity[b]	<.001	<.001
MADRS[b]	.023	<.001
CDI[b]	.408	.159
BDI[b]	.835	.315
GAF[b]	.313	<.001
HAMA[b]	.090	<.001
Subchronic Treatment		
CDRS-R Response[a]	.011	.022
CDRS-R Total[b]	.010	<.001
CDRS-R Mood[b]	.024	.004
CDRS-R Somatic[b]	.118	<.001
CDRS-R Subjective[b]	.085	.322
CDRS-R Behavior[b]	.007	.001
CGI-Improvement[c]	.198	.004
CGI-Severity[b]	.014	<.001
MADRS[b]	.148	.002
CDI[b]	.014	.316
BDI[b]	.754	.157
GAF[b]	.814	<.001
HAMA[b]	.416	<.001

Data for this table were taken from RMP.B1YSHCJE.SASPGM(EFFMOD2, CGIMOD, CDRSLOG).

[a]Logistic regression model. Additional investigators needed to be pooled for this model: 6, 17, and 13 were pooled.

[b]Dependent variable is change from baseline to endpoint score.

[c]Dependent variable is endpoint score.

14.3. Safety Data Summary

This section contains additional analyses of adverse events and laboratory analytes.

14.3.1. Displays of Adverse Events

14.3.1.1. Acute Treatment Phase (Study Periods III-IV)

14.3.1.1.1. Treatment-Emergent Non-Solicited Adverse Events by Body System

Treatment-emergent non-solicited adverse events by body system are summarized for all randomized patients for the acute treatment phase in Table 14.38.

Forty-eight (44%) fluoxetine-treated patients reported at least one treatment-emergent non-solicited adverse event related to the respiratory system as compared with 33 (30%) placebo-treated patients (p=.036). No statistically significant differences in the incidence of any specific adverse event were observed between the two treatment groups.

Table 14.38. Treatment-Emergent Non-Solicited Adverse Events Incidence by Body System All Randomized Patients Acute Treatment Phase (Study Periods III-IV) B1Y-MC-HCJE

Body System: Overall

Event Classification	Flx 20 (N=109) n (%)	Placebo (N=110) n (%)	Total (N=219) n (%)	p-Value*
PATIENTS WITH >= 1 TESS	94 (86.2)	80 (72.7)	174 (79.5)	.019
PATIENTS WITH NO TESS	15 (13.8)	30 (27.3)	45 (20.5)	.019

RMP.B1YP.JCLLIB2(AES2JEAA)
RMP.B1YO.HCJEREP(AES2JEAA)
* Frequencies are analyzed using a Fisher's Exact test.
XAES0002

Table 14.38. Treatment-Emergent Non-Solicited Adverse Events Incidence by Body System All Randomized Patients Acute Treatment Phase (Study Periods III-IV) B1Y-MC-HCJE (continued)

Body System: BODY AS A WHOLE

Event Classification	Flx 20 (N=109) n (%)	Placebo (N=110) n (%)	Total (N=219) n (%)	p-Value*
PATIENTS WITH >= 1 TESS	62 (56.9)	52 (47.3)	114 (52.1)	.177
PATIENTS WITH NO TESS	47 (43.1)	58 (52.7)	105 (47.9)	.177
HEADACHE	33 (30.3)	18 (16.4)	51 (23.3)	.017
ABDOMINAL PAIN	17 (15.6)	16 (14.5)	33 (15.1)	.852
ACCIDENTAL INJURY	13 (11.9)	8 (7.3)	21 (9.6)	.261
ASTHENIA	8 (7.3)	6 (5.5)	14 (6.4)	.594
PAIN	8 (7.3)	9 (8.2)	17 (7.8)	1.00
FEVER	7 (6.4)	5 (4.5)	12 (5.5)	.569
FLU SYNDROME	4 (3.7)	3 (2.7)	7 (3.2)	.721
BACK PAIN	3 (2.8)	5 (4.5)	8 (3.7)	.721
CHEST PAIN	3 (2.8)	2 (1.8)	5 (2.3)	.683
NECK PAIN	3 (2.8)	0	3 (1.4)	.122
ALLERGIC REACTION	2 (1.8)	2 (1.8)	4 (1.8)	1.00
CHILLS	2 (1.8)	0	2 (0.9)	.247
INFECTION	2 (1.8)	2 (1.8)	4 (1.8)	1.00
PHOTOSENSITIVITY REACTION	2 (1.8)	0	2 (0.9)	.247
OVERDOSE	1 (0.9)	0	1 (0.5)	.498
SURGICAL PROCEDURE	1 (0.9)	1 (0.9)	2 (0.9)	1.00
ABDOMINAL SYNDROME ACUTE	0	1 (0.9)	1 (0.5)	1.00
FACE EDEMA	0	1 (0.9)	1 (0.5)	1.00
INTENTIONAL INJURY	0	1 (0.9)	1 (0.5)	1.00
UNEXPECTED BENEFIT	0	1 (0.9)	1 (0.5)	1.00

RMP.B1YP.JCLLIB2(AES2JEAA)
RMP.B1YO.HCJEREP(AES2JEAA)
* Frequencies are analyzed using a Fisher’s Exact test.
XAES0002

Table 14.38. Treatment-Emergent Non-Solicited Adverse Events Incidence by Body System All Randomized Patients Acute Treatment Phase (Study Periods III-IV) B1Y-MC-HCJE (continued)

Body System: CARDIOVASCULAR SYSTEM

Event Classification	Flx 20 (N=109) n (%)	Placebo (N=110) n (%)	Total (N=219) n (%)	p-Value*
PATIENTS WITH >= 1 TESS	5 (4.6)	3 (2.7)	8 (3.7)	.499
PATIENTS WITH NO TESS	104 (95.4)	107 (97.3)	211 (96.3)	.499
HYPOTENSION	1 (0.9)	0	1 (0.5)	.498
MIGRAINE	1 (0.9)	1 (0.9)	2 (0.9)	1.00
PALPITATION	1 (0.9)	1 (0.9)	2 (0.9)	1.00
SYNCOPE	1 (0.9)	0	1 (0.5)	.498
TACHYCARDIA	1 (0.9)	0	1 (0.5)	.498
VASODILATATION	1 (0.9)	0	1 (0.5)	.498
BRADYCARDIA	0	1 (0.9)	1 (0.5)	1.00

RMP.B1YP.JCLLIB2(AES2JEAA)
RMP.B1YO.HCJEREP(AES2JEAA)
* Frequencies are analyzed using a Fisher’s Exact test.
XAES0002

Table 14.38. Treatment-Emergent Non-Solicited Adverse Events Incidence by Body System All Randomized Patients Acute Treatment Phase (Study Periods III-IV) B1Y-MC-HCJE (continued)

Body System: DIGESTIVE SYSTEM

Event Classification	Flx 20 (N=109) n (%)	Placebo (N=110) n (%)	Total (N=219) n (%)	p-Value*
PATIENTS WITH >= 1 TESS	35 (32.1)	37 (33.6)	72 (32.9)	.886
PATIENTS WITH NO TESS	74 (67.9)	73 (66.4)	147 (67.1)	.886
DIARRHEA	11 (10.1)	11 (10.0)	22 (10.0)	1.00
ANOREXIA	9 (8.3)	6 (5.5)	15 (6.8)	.437
NAUSEA	9 (8.3)	8 (7.3)	17 (7.8)	.806
VOMITING	8 (7.3)	8 (7.3)	16 (7.3)	1.00
DRY MOUTH	4 (3.7)	5 (4.5)	9 (4.1)	1.00
CONSTIPATION	3 (2.8)	2 (1.8)	5 (2.3)	.683
DYSPEPSIA	3 (2.8)	4 (3.6)	7 (3.2)	1.00
GASTROENTERITIS	2 (1.8)	0	2 (0.9)	.247
THIRST	2 (1.8)	2 (1.8)	4 (1.8)	1.00
DYSPHAGIA	1 (0.9)	1 (0.9)	2 (0.9)	1.00
FECAL INCONTINENCE	1 (0.9)	0	1 (0.5)	.498
FLATULENCE	1 (0.9)	0	1 (0.5)	.498
HEPATITIS NONSPECIFIC	1 (0.9)	0	1 (0.5)	.498
HEPATOMEGALY	1 (0.9)	0	1 (0.5)	.498
TOOTH DISORDER	1 (0.9)	0	1 (0.5)	.498
APHTHOUS STOMATITIS	0	1 (0.9)	1 (0.5)	1.00
GASTROINTESTINAL DISORDER	0	1 (0.9)	1 (0.5)	1.00
INCREASED APPETITE	0	3 (2.7)	3 (1.4)	.247
MOUTH ULCERATION	0	1 (0.9)	1 (0.5)	1.00

RMP.B1YP.JCLLIB2(AES2JEAA)
RMP.B1YO.HCJEREP(AES2JEAA)
* Frequencies are analyzed using a Fisher’s Exact test.
XAES0002

Table 14.38. Treatment-Emergent Non-Solicited Adverse Events Incidence by Body System All Randomized Patients Acute Treatment Phase (Study Periods III-IV) B1Y-MC-HCJE (continued)

Body System: HEMIC AND LYMPHATIC SYSTEM

Event Classification	Flx 20 (N=109) n (%)	Placebo (N=110) n (%)	Total (N=219) n (%)	p-Value*
PATIENTS WITH >= 1 TESS	3 (2.8)	2 (1.8)	5 (2.3)	.683
PATIENTS WITH NO TESS	106 (97.2)	108 (98.2)	214 (97.7)	.683
ECCHYMOSIS	3 (2.8)	2 (1.8)	5 (2.3)	.683

RMP.B1YP.JCLLIB2(AES2JEAA)
RMP.B1YO.HCJEREP(AES2JEAA)
* Frequencies are analyzed using a Fisher’s Exact test.
XAES0002

Table 14.38. Treatment-Emergent Non-Solicited Adverse Events Incidence by Body System All Randomized Patients Acute Treatment Phase (Study Periods III-IV) B1Y-MC-HCJE (continued)

Body System: METABOLIC AND NUTRITIONAL DISORDERS

Event Classification	Flx 20 (N=109) n (%)	Placebo (N=110) n (%)	Total (N=219) n (%)	p-Value*
PATIENTS WITH >= 1 TESS	2 (1.8)	4 (3.6)	6 (2.7)	.683
PATIENTS WITH NO TESS	107 (98.2)	106 (96.4)	213 (97.3)	.683
WEIGHT LOSS	2 (1.8)	1 (0.9)	3 (1.4)	.622
DEHYDRATION	0	2 (1.8)	2 (0.9)	.498
WEIGHT GAIN	0	1 (0.9)	1 (0.5)	1.00

RMP.B1YP.JCLLIB2(AES2JEAA)
RMP.B1YO.HCJEREP(AES2JEAA)
* Frequencies are analyzed using a Fisher’s Exact test.
XAES0002

Table 14.38. Treatment-Emergent Non-Solicited Adverse Events Incidence by Body System All Randomized Patients Acute Treatment Phase (Study Periods III-IV) B1Y-MC-HCJE (continued)

Body System: MUSCULOSKELETAL SYSTEM

Event Classification	Flx 20 (N=109) n (%)	Placebo (N=110) n (%)	Total (N=219) n (%)	p-Value*
PATIENTS WITH >= 1 TESS	3 (2.8)	7 (6.4)	10 (4.6)	.332
PATIENTS WITH NO TESS	106 (97.2)	103 (93.6)	209 (95.4)	.332
JOINT DISORDER	1 (0.9)	0	1 (0.5)	.498
LEG CRAMPS	1 (0.9)	1 (0.9)	2 (0.9)	1.00
MYALGIA	1 (0.9)	5 (4.5)	6 (2.7)	.212
ARTHRALGIA	0	1 (0.9)	1 (0.5)	1.00

RMP.B1YP.JCLLIB2(AES2JEAA)
RMP.B1YO.HCJEREP(AES2JEAA)
* Frequencies are analyzed using a Fisher’s Exact test.
XAES0002

Table 14.38. Treatment-Emergent Non-Solicited Adverse Events Incidence by Body System All Randomized Patients Acute Treatment Phase (Study Periods III-IV) B1Y-MC-HCJE (continued)

Body System: NERVOUS SYSTEM

Event Classification	Flx 20 (N=109) n (%)	Placebo (N=110) n (%)	Total (N=219) n (%)	p-Value*
PATIENTS WITH >= 1 TESS	35 (32.1)	24 (21.8)	59 (26.9)	.095
PATIENTS WITH NO TESS	74 (67.9)	86 (78.2)	160 (73.1)	.095
DIZZINESS	10 (9.2)	4 (3.6)	14 (6.4)	.106
NERVOUSNESS	9 (8.3)	6 (5.5)	15 (6.8)	.437
ABNORMAL DREAMS	6 (5.5)	3 (2.7)	9 (4.1)	.332
INSOMNIA	4 (3.7)	5 (4.5)	9 (4.1)	1.00
AGITATION	3 (2.8)	0	3 (1.4)	.122
SOMNOLENCE	3 (2.8)	3 (2.7)	6 (2.7)	1.00
TREMOR	3 (2.8)	0	3 (1.4)	.122
AKATHISIA	2 (1.8)	0	2 (0.9)	.247
ANXIETY	2 (1.8)	0	2 (0.9)	.247
DEPRESSION	2 (1.8)	1 (0.9)	3 (1.4)	.622
HOSTILITY	2 (1.8)	5 (4.5)	7 (3.2)	.446
HYPERKINESIA	2 (1.8)	0	2 (0.9)	.247
PERSONALITY DISORDER	2 (1.8)	1 (0.9)	3 (1.4)	.622
SLEEP DISORDER	2 (1.8)	0	2 (0.9)	.247
SPEECH DISORDER	2 (1.8)	2 (1.8)	4 (1.8)	1.00
ACUTE BRAIN SYNDROME	1 (0.9)	0	1 (0.5)	.498
APATHY	1 (0.9)	0	1 (0.5)	.498
BUCCOGLOSSAL SYNDROME	1 (0.9)	0	1 (0.5)	.498
DELUSIONS	1 (0.9)	0	1 (0.5)	.498
EMOTIONAL LABILITY	1 (0.9)	0	1 (0.5)	.498
EUPHORIA	1 (0.9)	0	1 (0.5)	.498
HALLUCINATIONS	1 (0.9)	0	1 (0.5)	.498
HYPERTONIA	1 (0.9)	1 (0.9)	2 (0.9)	1.00
MANIC REACTION	1 (0.9)	0	1 (0.5)	.498
NEUROSIS	1 (0.9)	0	1 (0.5)	.498
AMNESIA	0	1 (0.9)	1 (0.5)	1.00
HYPESTHESIA	0	1 (0.9)	1 (0.5)	1.00
THINKING ABNORMAL	0	1 (0.9)	1 (0.5)	1.00

RMP.B1YP.JCLLIB2(AES2JEAA)
RMP.B1YO.HCJEREP(AES2JEAA)
* Frequencies are analyzed using a Fisher’s Exact test.
XAES0002

Table 14.38. Treatment-Emergent Non-Solicited Adverse Events Incidence by Body System All Randomized Patients Acute Treatment Phase (Study Periods III-IV) B1Y-MC-HCJE (continued)

Body System: RESPIRATORY SYSTEM

Event Classification	Flx 20 (N=109) n (%)	Placebo (N=110) n (%)	Total (N=219) n (%)	p-Value*
PATIENTS WITH >= 1 TESS	48 (44.0)	33 (30.0)	81 (37.0)	.036
PATIENTS WITH NO TESS	61 (56.0)	77 (70.0)	138 (63.0)	.036
RHINITIS	24 (22.0)	21 (19.1)	45 (20.5)	.619
PHARYNGITIS	16 (14.7)	9 (8.2)	25 (11.4)	.143
COUGH INCREASED	9 (8.3)	7 (6.4)	16 (7.3)	.615
EPISTAXIS	5 (4.6)	1 (0.9)	6 (2.7)	.119
SINUSITIS	3 (2.8)	2 (1.8)	5 (2.3)	.683
ASTHMA	2 (1.8)	0	2 (0.9)	.247
BRONCHITIS	1 (0.9)	0	1 (0.5)	.498
DYSPNEA	1 (0.9)	0	1 (0.5)	.498
LUNG DISORDER	1 (0.9)	0	1 (0.5)	.498
PNEUMONIA	1 (0.9)	0	1 (0.5)	.498
YAWN	1 (0.9)	0	1 (0.5)	.498
HYPOVENTILATION	0	1 (0.9)	1 (0.5)	1.00
LARYNGITIS	0	1 (0.9)	1 (0.5)	1.00

RMP.B1YP.JCLLIB2(AES2JEAA)
RMP.B1YO.HCJEREP(AES2JEAA)
* Frequencies are analyzed using a Fisher’s Exact test.
XAES0002

Table 14.38. Treatment-Emergent Non-Solicited Adverse Events Incidence by Body System All Randomized Patients Acute Treatment Phase (Study Periods III-IV) B1Y-MC-HCJE (continued)

Body System: SKIN AND APPENDAGES

Event Classification	Flx 20 (N=109) n (%)	Placebo (N=110) n (%)	Total (N=219) n (%)	p-Value*
PATIENTS WITH >= 1 TESS	16 (14.7)	11 (10.0)	27 (12.3)	.312
PATIENTS WITH NO TESS	93 (85.3)	99 (90.0)	192 (87.7)	.312
RASH	10 (9.2)	4 (3.6)	14 (6.4)	.106
PRURITUS	4 (3.7)	5 (4.5)	9 (4.1)	1.00
DRY SKIN	2 (1.8)	1 (0.9)	3 (1.4)	.622
CONTACT DERMATITIS	1 (0.9)	0	1 (0.5)	.498
FUNGAL DERMATITIS	1 (0.9)	1 (0.9)	2 (0.9)	1.00
HERPES SIMPLEX	1 (0.9)	0	1 (0.5)	.498
MACULOPAPULAR RASH	1 (0.9)	1 (0.9)	2 (0.9)	1.00
SWEATING	1 (0.9)	0	1 (0.5)	.498
ACNE	0	1 (0.9)	1 (0.5)	1.00
ALOPECIA	0	1 (0.9)	1 (0.5)	1.00
SKIN DISCOLORATION	0	1 (0.9)	1 (0.5)	1.00
SKIN ULCER	0	1 (0.9)	1 (0.5)	1.00
SUBCUTANEOUS NODULE	0	1 (0.9)	1 (0.5)	1.00

RMP.B1YP.JCLLIB2(AES2JEAA)
RMP.B1YO.HCJEREP(AES2JEAA)
* Frequencies are analyzed using a Fisher’s Exact test.
XAES0002

Table 14.38. Treatment-Emergent Non-Solicited Adverse Events Incidence by Body System All Randomized Patients Acute Treatment Phase (Study Periods III-IV) B1Y-MC-HCJE (continued)

Body System: SPECIAL SENSES

Event Classification	Flx 20 (N=109) n (%)	Placebo (N=110) n (%)	Total (N=219) n (%)	p-Value*
PATIENTS WITH >= 1 TESS	11 (10.1)	4 (3.6)	15 (6.8)	.066
PATIENTS WITH NO TESS	98 (89.9)	106 (96.4)	204 (93.2)	.066
EAR PAIN	4 (3.7)	3 (2.7)	7 (3.2)	.721
EYE DISORDER	2 (1.8)	0	2 (0.9)	.247
OTITIS EXTERNA	2 (1.8)	1 (0.9)	3 (1.4)	.622
EAR DISORDER	1 (0.9)	1 (0.9)	2 (0.9)	1.00
EYE PAIN	1 (0.9)	0	1 (0.5)	.498
TINNITUS	1 (0.9)	0	1 (0.5)	.498

RMP.B1YP.JCLLIB2(AES2JEAA)
RMP.B1YO.HCJEREP(AES2JEAA)
* Frequencies are analyzed using a Fisher’s Exact test.
XAES0002

Table 14.38. Treatment-Emergent Non-Solicited Adverse Events Incidence by Body System All Randomized Patients Acute Treatment Phase (Study Periods III-IV) B1Y-MC-HCJE (concluded)

Body System: UROGENITAL SYSTEM

Event Classification	Flx 20 (N=109) n (%)	Placebo (N=110) n (%)	Total (N=219) n (%)	p-Value*
PATIENTS WITH >= 1 TESS	7 (6.4)	8 (7.3)	15 (6.8)	1.00
PATIENTS WITH NO TESS	102 (93.6)	102 (92.7)	204 (93.2)	1.00
DYSMENORRHEA	4 (3.7)	3 (2.7)	7 (3.2)	.721
ENDOMETRIAL HYPERPLASIA	1 (0.9)	0	1 (0.5)	.498
URINARY FREQUENCY	1 (0.9)	2 (1.8)	3 (1.4)	1.00
URINARY TRACT INFECTION	1 (0.9)	1 (0.9)	2 (0.9)	1.00
CYSTITIS	0	1 (0.9)	1 (0.5)	1.00
DYSURIA	0	1 (0.9)	1 (0.5)	1.00
LEUKORRHEA	0	1 (0.9)	1 (0.5)	1.00
METRORRHAGIA	0	1 (0.9)	1 (0.5)	1.00

RMP.B1YP.JCLLIB2(AES2JEAA)
RMP.B1YO.HCJEREP(AES2JEAA)
* Frequencies are analyzed using a Fisher's Exact test.
XAES0002

14.3.1.1.2. Treatment-Emergent Non-Solicited Adverse Events by Maximum Severity

The incidence of treatment-emergent non-solicited adverse events by maximum severity for the acute treatment phase is presented in Table 14.39. This analysis measures the severity of adverse events and comparison to baseline events, and thus points out clinically relevant changes in adverse events. Overall, the majority of reported treatment-emergent non-solicited adverse events were mild or moderate in severity. There were no statistically significant differences between treatment groups in the incidence of treatment-emergent non-solicited adverse events classified as severe.

Table 14.39. Treatment-Emergent Non-Solicited Adverse Events Incidence by Maximum Severity All Randomized Patients Acute Treatment Phase (Study Periods III-IV) B1Y-MC-HCJE

Maximum Severity	Flx 20 (N=109) n (%)	Placebo (N=110) n (%)	Total (N=219) n (%)	p-Value*
PATIENTS WITH >= 1 TESS				
Mild	26 (23.9)	24 (21.8)	50 (22.8)	
Moderate	49 (45.0)	41 (37.3)	90 (41.1)	
Severe	19 (17.4)	15 (13.6)	34 (15.5)	.461
Total	94 (86.2)	80 (72.7)	174 (79.5)	.019
HEADACHE				
Mild	16 (14.7)	7 (6.4)	23 (10.5)	
Moderate	13 (11.9)	10 (9.1)	23 (10.5)	
Severe	4 (3.7)	1 (0.9)	5 (2.3)	.212
Total	33 (30.3)	18 (16.4)	51 (23.3)	.017
RHINITIS				
Mild	15 (13.8)	12 (10.9)	27 (12.3)	
Moderate	8 (7.3)	9 (8.2)	17 (7.8)	
Severe	1 (0.9)	0	1 (0.5)	.498
Total	24 (22.0)	21 (19.1)	45 (20.5)	.619
ABDOMINAL PAIN				
Mild	12 (11.0)	6 (5.5)	18 (8.2)	
Moderate	4 (3.7)	9 (8.2)	13 (5.9)	
Severe	1 (0.9)	1 (0.9)	2 (0.9)	1.00
Total	17 (15.6)	16 (14.5)	33 (15.1)	.852
PHARYNGITIS				
Mild	7 (6.4)	8 (7.3)	15 (6.8)	
Moderate	8 (7.3)	1 (0.9)	9 (4.1)	
Severe	1 (0.9)	0	1 (0.5)	.498
Total	16 (14.7)	9 (8.2)	25 (11.4)	.143

RMP.B1YP.JCLLIB2(AES8JEAA)
RMP.B1YO.HCJEREP(AES8JEAA)
* Frequencies are analyzed using a Fisher's Exact test.
XAES0008

Table 14.39. Treatment-Emergent Non-Solicited Adverse Events Incidence by Maximum Severity All Randomized Patients Acute Treatment Phase (Study Periods III-IV) B1Y-MC-HCJE (continued)

Maximum Severity	Flx 20 (N=109) n	(%)	Placebo (N=110) n	(%)	Total (N=219) n	(%)	p-Value*
ACCIDENTAL INJURY							
Mild	7	(6.4)	5	(4.5)	12	(5.5)	
Moderate	6	(5.5)	2	(1.8)	8	(3.7)	
Severe	0		1	(0.9)	1	(0.5)	1.00
Total	13	(11.9)	8	(7.3)	21	(9.6)	.261
DIARRHEA							
Mild	6	(5.5)	7	(6.4)	13	(5.9)	
Moderate	3	(2.8)	4	(3.6)	7	(3.2)	
Severe	2	(1.8)	0		2	(0.9)	.247
Total	11	(10.1)	11	(10.0)	22	(10.0)	1.00
DIZZINESS							
Mild	9	(8.3)	3	(2.7)	12	(5.5)	
Moderate	1	(0.9)	0		1	(0.5)	
Severe	0		1	(0.9)	1	(0.5)	1.00
Total	10	(9.2)	4	(3.6)	14	(6.4)	.106
RASH							
Mild	7	(6.4)	3	(2.7)	10	(4.6)	
Moderate	3	(2.8)	1	(0.9)	4	(1.8)	
Severe	0		0		0		
Total	10	(9.2)	4	(3.6)	14	(6.4)	.106
ANOREXIA							
Mild	7	(6.4)	4	(3.6)	11	(5.0)	
Moderate	2	(1.8)	2	(1.8)	4	(1.8)	
Severe	0		0		0		
Total	9	(8.3)	6	(5.5)	15	(6.8)	.437

RMP.B1YP.JCLLIB2(AES8JEAA)
RMP.B1YO.HCJEREP(AES8JEAA)
* Frequencies are analyzed using a Fisher's Exact test.
XAES0008

Table 14.39. Treatment-Emergent Non-Solicited Adverse Events Incidence by Maximum Severity All Randomized Patients Acute Treatment Phase (Study Periods III-IV) B1Y-MC-HCJE (continued)

Maximum Severity	Flx 20 (N=109) n	(%)	Placebo (N=110) n	(%)	Total (N=219) n	(%)	p-Value*
COUGH INCREASED							
Mild	3	(2.8)	6	(5.5)	9	(4.1)	
Moderate	5	(4.6)	1	(0.9)	6	(2.7)	
Severe	1	(0.9)	0		1	(0.5)	.498
Total	9	(8.3)	7	(6.4)	16	(7.3)	.615
NAUSEA							
Mild	4	(3.7)	6	(5.5)	10	(4.6)	
Moderate	3	(2.8)	2	(1.8)	5	(2.3)	
Severe	2	(1.8)	0		2	(0.9)	.247
Total	9	(8.3)	8	(7.3)	17	(7.8)	.806
NERVOUSNESS							
Mild	3	(2.8)	1	(0.9)	4	(1.8)	
Moderate	3	(2.8)	3	(2.7)	6	(2.7)	
Severe	3	(2.8)	2	(1.8)	5	(2.3)	.683
Total	9	(8.3)	6	(5.5)	15	(6.8)	.437
ASTHENIA							
Mild	0		2	(1.8)	2	(0.9)	
Moderate	7	(6.4)	2	(1.8)	9	(4.1)	
Severe	1	(0.9)	2	(1.8)	3	(1.4)	1.00
Total	8	(7.3)	6	(5.5)	14	(6.4)	.594
PAIN							
Mild	7	(6.4)	7	(6.4)	14	(6.4)	
Moderate	1	(0.9)	2	(1.8)	3	(1.4)	
Severe	0		0		0		
Total	8	(7.3)	9	(8.2)	17	(7.8)	1.00

RMP.B1YP.JCLLIB2(AES8JEAA)
RMP.B1YO.HCJEREP(AES8JEAA)
* Frequencies are analyzed using a Fisher’s Exact test.
XAES0008

Table 14.39. Treatment-Emergent Non-Solicited Adverse Events Incidence by Maximum Severity All Randomized Patients Acute Treatment Phase (Study Periods III-IV) B1Y-MC-HCJE (continued)

Maximum Severity	Flx 20 (N=109) n	(%)	Placebo (N=110) n	(%)	Total (N=219) n	(%)	p-Value*
VOMITING							
Mild	4	(3.7)	4	(3.6)	8	(3.7)	
Moderate	3	(2.8)	3	(2.7)	6	(2.7)	
Severe	1	(0.9)	1	(0.9)	2	(0.9)	1.00
Total	8	(7.3)	8	(7.3)	16	(7.3)	1.00
FEVER							
Mild	5	(4.6)	1	(0.9)	6	(2.7)	
Moderate	2	(1.8)	3	(2.7)	5	(2.3)	
Severe	0		1	(0.9)	1	(0.5)	1.00
Total	7	(6.4)	5	(4.5)	12	(5.5)	.569
ABNORMAL DREAMS							
Mild	2	(1.8)	1	(0.9)	3	(1.4)	
Moderate	2	(1.8)	1	(0.9)	3	(1.4)	
Severe	2	(1.8)	1	(0.9)	3	(1.4)	.622
Total	6	(5.5)	3	(2.7)	9	(4.1)	.332
EPISTAXIS							
Mild	2	(1.8)	0		2	(0.9)	
Moderate	3	(2.8)	1	(0.9)	4	(1.8)	
Severe	0		0		0		
Total	5	(4.6)	1	(0.9)	6	(2.7)	.119
DRY MOUTH							
Mild	3	(2.8)	5	(4.5)	8	(3.7)	
Moderate	1	(0.9)	0		1	(0.5)	
Severe	0		0		0		
Total	4	(3.7)	5	(4.5)	9	(4.1)	1.00

RMP.B1YP.JCLLIB2(AES8JEAA)
RMP.B1YO.HCJEREP(AES8JEAA)
* Frequencies are analyzed using a Fisher’s Exact test.
XAES0008

Table 14.39. Treatment-Emergent Non-Solicited Adverse Events Incidence by Maximum Severity All Randomized Patients Acute Treatment Phase (Study Periods III-IV) B1Y-MC-HCJE (continued)

Maximum Severity	Flx 20 (N=109) n	(%)	Placebo (N=110) n	(%)	Total (N=219) n	(%)	p-Value*
DYSMENORRHEA							
Mild	2	(1.8)	3	(2.7)	5	(2.3)	
Moderate	2	(1.8)	0		2	(0.9)	
Severe	0		0		0		
Total	4	(3.7)	3	(2.7)	7	(3.2)	.721
EAR PAIN							
Mild	3	(2.8)	2	(1.8)	5	(2.3)	
Moderate	1	(0.9)	0		1	(0.5)	
Severe	0		1	(0.9)	1	(0.5)	1.00
Total	4	(3.7)	3	(2.7)	7	(3.2)	.721
FLU SYNDROME							
Mild	3	(2.8)	1	(0.9)	4	(1.8)	
Moderate	1	(0.9)	2	(1.8)	3	(1.4)	
Severe	0		0		0		
Total	4	(3.7)	3	(2.7)	7	(3.2)	.721
INSOMNIA							
Mild	1	(0.9)	0		1	(0.5)	
Moderate	1	(0.9)	3	(2.7)	4	(1.8)	
Severe	2	(1.8)	2	(1.8)	4	(1.8)	1.00
Total	4	(3.7)	5	(4.5)	9	(4.1)	1.00
PRURITUS							
Mild	1	(0.9)	4	(3.6)	5	(2.3)	
Moderate	2	(1.8)	1	(0.9)	3	(1.4)	
Severe	1	(0.9)	0		1	(0.5)	.498
Total	4	(3.7)	5	(4.5)	9	(4.1)	1.00

RMP.B1YP.JCLLIB2(AES8JEAA)
RMP.B1YO.HCJEREP(AES8JEAA)
* Frequencies are analyzed using a Fisher’s Exact test.
XAES0008

Table 14.39. Treatment-Emergent Non-Solicited Adverse Events Incidence by Maximum Severity All Randomized Patients Acute Treatment Phase (Study Periods III-IV) B1Y-MC-HCJE (continued)

Maximum Severity	Flx 20 (N=109) n	(%)	Placebo (N=110) n	(%)	Total (N=219) n	(%)	p-Value*
AGITATION							
Mild	1	(0.9)	0		1	(0.5)	
Moderate	0		0		0		
Severe	2	(1.8)	0		2	(0.9)	.247
Total	3	(2.8)	0		3	(1.4)	.122
BACK PAIN							
Mild	3	(2.8)	4	(3.6)	7	(3.2)	
Moderate	0		0		0		
Severe	0		1	(0.9)	1	(0.5)	1.00
Total	3	(2.8)	5	(4.5)	8	(3.7)	.721
CHEST PAIN							
Mild	2	(1.8)	1	(0.9)	3	(1.4)	
Moderate	1	(0.9)	1	(0.9)	2	(0.9)	
Severe	0		0		0		
Total	3	(2.8)	2	(1.8)	5	(2.3)	.683
CONSTIPATION							
Mild	1	(0.9)	1	(0.9)	2	(0.9)	
Moderate	1	(0.9)	1	(0.9)	2	(0.9)	
Severe	1	(0.9)	0		1	(0.5)	.498
Total	3	(2.8)	2	(1.8)	5	(2.3)	.683
DYSPEPSIA							
Mild	2	(1.8)	3	(2.7)	5	(2.3)	
Moderate	1	(0.9)	1	(0.9)	2	(0.9)	
Severe	0		0		0		
Total	3	(2.8)	4	(3.6)	7	(3.2)	1.00

RMP.B1YP.JCLLIB2(AES8JEAA)
RMP.B1YO.HCJEREP(AES8JEAA)
* Frequencies are analyzed using a Fisher’s Exact test.
XAES0008

Table 14.39. Treatment-Emergent Non-Solicited Adverse Events Incidence by Maximum Severity All Randomized Patients Acute Treatment Phase (Study Periods III-IV) B1Y-MC-HCJE (continued)

Maximum Severity	Flx 20 (N=109) n	(%)	Placebo (N=110) n	(%)	Total (N=219) n	(%)	p-Value*
ECCHYMOSIS							
Mild	0		1	(0.9)	1	(0.5)	
Moderate	3	(2.8)	1	(0.9)	4	(1.8)	
Severe	0		0		0		
Total	3	(2.8)	2	(1.8)	5	(2.3)	.683
NECK PAIN							
Mild	2	(1.8)	0		2	(0.9)	
Moderate	1	(0.9)	0		1	(0.5)	
Severe	0		0		0		
Total	3	(2.8)	0		3	(1.4)	.122
SINUSITIS							
Mild	0		0		0		
Moderate	3	(2.8)	2	(1.8)	5	(2.3)	
Severe	0		0		0		
Total	3	(2.8)	2	(1.8)	5	(2.3)	.683
SOMNOLENCE							
Mild	2	(1.8)	2	(1.8)	4	(1.8)	
Moderate	1	(0.9)	1	(0.9)	2	(0.9)	
Severe	0		0		0		
Total	3	(2.8)	3	(2.7)	6	(2.7)	1.00
TREMOR							
Mild	2	(1.8)	0		2	(0.9)	
Moderate	1	(0.9)	0		1	(0.5)	
Severe	0		0		0		
Total	3	(2.8)	0		3	(1.4)	.122

RMP.B1YP.JCLLIB2(AES8JEAA)
RMP.B1YO.HCJEREP(AES8JEAA)
* Frequencies are analyzed using a Fisher’s Exact test.
XAES0008

Table 14.39. Treatment-Emergent Non-Solicited Adverse Events Incidence by Maximum Severity All Randomized Patients Acute Treatment Phase (Study Periods III-IV) B1Y-MC-HCJE (continued)

Maximum Severity	Flx 20 (N=109) n (%)	Placebo (N=110) n (%)	Total (N=219) n (%)	p-Value*
AKATHISIA				
Mild	2 (1.8)	0	2 (0.9)	
Moderate	0	0	0	
Severe	0	0	0	
Total	2 (1.8)	0	2 (0.9)	.247
ALLERGIC REACTION				
Mild	1 (0.9)	0	1 (0.5)	
Moderate	0	2 (1.8)	2 (0.9)	
Severe	1 (0.9)	0	1 (0.5)	.498
Total	2 (1.8)	2 (1.8)	4 (1.8)	1.00
ANXIETY				
Mild	0	0	0	
Moderate	1 (0.9)	0	1 (0.5)	
Severe	1 (0.9)	0	1 (0.5)	.498
Total	2 (1.8)	0	2 (0.9)	.247
ASTHMA				
Mild	0	0	0	
Moderate	1 (0.9)	0	1 (0.5)	
Severe	1 (0.9)	0	1 (0.5)	.498
Total	2 (1.8)	0	2 (0.9)	.247
CHILLS				
Mild	2 (1.8)	0	2 (0.9)	
Moderate	0	0	0	
Severe	0	0	0	
Total	2 (1.8)	0	2 (0.9)	.247

RMP.B1YP.JCLLIB2(AES8JEAA)
RMP.B1YO.HCJEREP(AES8JEAA)
* Frequencies are analyzed using a Fisher’s Exact test.
XAES0008

Table 14.39. Treatment-Emergent Non-Solicited Adverse Events Incidence by Maximum Severity All Randomized Patients Acute Treatment Phase (Study Periods III-IV) B1Y-MC-HCJE (continued)

Maximum Severity	Flx 20 (N=109) n	(%)	Placebo (N=110) n	(%)	Total (N=219) n	(%)	p-Value*
DEPRESSION							
Mild	0		0		0		
Moderate	1	(0.9)	1	(0.9)	2	(0.9)	
Severe	1	(0.9)	0		1	(0.5)	.498
Total	2	(1.8)	1	(0.9)	3	(1.4)	.622
DRY SKIN							
Mild	2	(1.8)	1	(0.9)	3	(1.4)	
Moderate	0		0		0		
Severe	0		0		0		
Total	2	(1.8)	1	(0.9)	3	(1.4)	.622
EYE DISORDER							
Mild	2	(1.8)	0		2	(0.9)	
Moderate	0		0		0		
Severe	0		0		0		
Total	2	(1.8)	0		2	(0.9)	.247
GASTROENTERITIS							
Mild	2	(1.8)	0		2	(0.9)	
Moderate	0		0		0		
Severe	0		0		0		
Total	2	(1.8)	0		2	(0.9)	.247
HOSTILITY							
Mild	0		1	(0.9)	1	(0.5)	
Moderate	0		3	(2.7)	3	(1.4)	
Severe	2	(1.8)	1	(0.9)	3	(1.4)	.622
Total	2	(1.8)	5	(4.5)	7	(3.2)	.446

RMP.B1YP.JCLLIB2(AES8JEAA)
RMP.B1YO.HCJEREP(AES8JEAA)
* Frequencies are analyzed using a Fisher's Exact test.
XAES0008

Table 14.39. Treatment-Emergent Non-Solicited Adverse Events Incidence by Maximum Severity All Randomized Patients Acute Treatment Phase (Study Periods III-IV) B1Y-MC-HCJE (continued)

Maximum Severity	Flx 20 (N=109) n	(%)	Placebo (N=110) n	(%)	Total (N=219) n	(%)	p-Value*
HYPERKINESIA							
Mild	0		0		0		
Moderate	0		0		0		
Severe	2	(1.8)	0		2	(0.9)	.247
Total	2	(1.8)	0		2	(0.9)	.247
INFECTION							
Mild	2	(1.8)	1	(0.9)	3	(1.4)	
Moderate	0		0		0		
Severe	0		1	(0.9)	1	(0.5)	1.00
Total	2	(1.8)	2	(1.8)	4	(1.8)	1.00
OTITIS EXTERNA							
Mild	1	(0.9)	0		1	(0.5)	
Moderate	1	(0.9)	1	(0.9)	2	(0.9)	
Severe	0		0		0		
Total	2	(1.8)	1	(0.9)	3	(1.4)	.622
PERSONALITY DISORDER							
Mild	1	(0.9)	0		1	(0.5)	
Moderate	0		1	(0.9)	1	(0.5)	
Severe	1	(0.9)	0		1	(0.5)	.498
Total	2	(1.8)	1	(0.9)	3	(1.4)	.622
PHOTOSENSITIVITY REACTION							
Mild	1	(0.9)	0		1	(0.5)	
Moderate	1	(0.9)	0		1	(0.5)	
Severe	0		0		0		
Total	2	(1.8)	0		2	(0.9)	.247

RMP.B1YP.JCLLIB2(AES8JEAA)
RMP.B1YO.HCJEREP(AES8JEAA)
* Frequencies are analyzed using a Fisher’s Exact test.
XAES0008

Table 14.39. Treatment-Emergent Non-Solicited Adverse Events Incidence by Maximum Severity All Randomized Patients Acute Treatment Phase (Study Periods III-IV) B1Y-MC-HCJE (continued)

Maximum Severity	Flx 20 (N=109) n	(%)	Placebo (N=110) n	(%)	Total (N=219) n	(%)	p-Value*
SLEEP DISORDER							
Mild	2	(1.8)	0		2	(0.9)	
Moderate	0		0		0		
Severe	0		0		0		
Total	2	(1.8)	0		2	(0.9)	.247
SPEECH DISORDER							
Mild	1	(0.9)	2	(1.8)	3	(1.4)	
Moderate	0		0		0		
Severe	1	(0.9)	0		1	(0.5)	.498
Total	2	(1.8)	2	(1.8)	4	(1.8)	1.00
THIRST							
Mild	2	(1.8)	2	(1.8)	4	(1.8)	
Moderate	0		0		0		
Severe	0		0		0		
Total	2	(1.8)	2	(1.8)	4	(1.8)	1.00
WEIGHT LOSS							
Mild	2	(1.8)	0		2	(0.9)	
Moderate	0		1	(0.9)	1	(0.5)	
Severe	0		0		0		
Total	2	(1.8)	1	(0.9)	3	(1.4)	.622
ACUTE BRAIN SYNDROME							
Mild	0		0		0		
Moderate	1	(0.9)	0		1	(0.5)	
Severe	0		0		0		
Total	1	(0.9)	0		1	(0.5)	.498

RMP.B1YP.JCLLIB2(AES8JEAA)
RMP.B1YO.HCJEREP(AES8JEAA)
* Frequencies are analyzed using a Fisher’s Exact test.
XAES0008

Table 14.39. Treatment-Emergent Non-Solicited Adverse Events Incidence by Maximum Severity All Randomized Patients Acute Treatment Phase (Study Periods III-IV) B1Y-MC-HCJE (continued)

Maximum Severity	Flx 20 (N=109) n	(%)	Placebo (N=110) n	(%)	Total (N=219) n	(%)	p-Value*
APATHY							
Mild	0		0		0		
Moderate	1	(0.9)	0		1	(0.5)	
Severe	0		0		0		
Total	1	(0.9)	0		1	(0.5)	.498
BRONCHITIS							
Mild	0		0		0		
Moderate	1	(0.9)	0		1	(0.5)	
Severe	0		0		0		
Total	1	(0.9)	0		1	(0.5)	.498
BUCCOGLOSSAL SYNDROME							
Mild	0		0		0		
Moderate	0		0		0		
Severe	1	(0.9)	0		1	(0.5)	.498
Total	1	(0.9)	0		1	(0.5)	.498
CONTACT DERMATITIS							
Mild	0		0		0		
Moderate	1	(0.9)	0		1	(0.5)	
Severe	0		0		0		
Total	1	(0.9)	0		1	(0.5)	.498
DELUSIONS							
Mild	0		0		0		
Moderate	0		0		0		
Severe	1	(0.9)	0		1	(0.5)	.498
Total	1	(0.9)	0		1	(0.5)	.498

RMP.B1YP.JCLLIB2(AES8JEAA)
RMP.B1YO.HCJEREP(AES8JEAA)
* Frequencies are analyzed using a Fisher’s Exact test.
XAES0008

Table 14.39. Treatment-Emergent Non-Solicited Adverse Events Incidence by Maximum Severity All Randomized Patients Acute Treatment Phase (Study Periods III-IV) B1Y-MC-HCJE (continued)

Maximum Severity	Flx 20 (N=109) n	(%)	Placebo (N=110) n	(%)	Total (N=219) n	(%)	p-Value*
DYSPHAGIA							
Mild	0		1	(0.9)	1	(0.5)	
Moderate	1	(0.9)	0		1	(0.5)	
Severe	0		0		0		
Total	1	(0.9)	1	(0.9)	2	(0.9)	1.00
DYSPNEA							
Mild	1	(0.9)	0		1	(0.5)	
Moderate	0		0		0		
Severe	0		0		0		
Total	1	(0.9)	0		1	(0.5)	.498
EAR DISORDER							
Mild	0		0		0		
Moderate	1	(0.9)	1	(0.9)	2	(0.9)	
Severe	0		0		0		
Total	1	(0.9)	1	(0.9)	2	(0.9)	1.00
EMOTIONAL LABILITY							
Mild	0		0		0		
Moderate	1	(0.9)	0		1	(0.5)	
Severe	0		0		0		
Total	1	(0.9)	0		1	(0.5)	.498
ENDOMETRIAL HYPERPLASIA							
Mild	0		0		0		
Moderate	1	(0.9)	0		1	(0.5)	
Severe	0		0		0		
Total	1	(0.9)	0		1	(0.5)	.498

RMP.B1YP.JCLLIB2(AES8JEAA)
RMP.B1YO.HCJEREP(AES8JEAA)
* Frequencies are analyzed using a Fisher's Exact test.
XAES0008

Table 14.39. Treatment-Emergent Non-Solicited Adverse Events Incidence by Maximum Severity All Randomized Patients Acute Treatment Phase (Study Periods III-IV) B1Y-MC-HCJE (continued)

Maximum Severity	Flx 20 (N=109) n (%)	Placebo (N=110) n (%)	Total (N=219) n (%)	p-Value*
EUPHORIA				
Mild	1 (0.9)	0	1 (0.5)	
Moderate	0	0	0	
Severe	0	0	0	
Total	1 (0.9)	0	1 (0.5)	.498
EYE PAIN				
Mild	1 (0.9)	0	1 (0.5)	
Moderate	0	0	0	
Severe	0	0	0	
Total	1 (0.9)	0	1 (0.5)	.498
FECAL INCONTINENCE				
Mild	0	0	0	
Moderate	1 (0.9)	0	1 (0.5)	
Severe	0	0	0	
Total	1 (0.9)	0	1 (0.5)	.498
FLATULENCE				
Mild	0	0	0	
Moderate	0	0	0	
Severe	1 (0.9)	0	1 (0.5)	.498
Total	1 (0.9)	0	1 (0.5)	.498
FUNGAL DERMATITIS				
Mild	0	1 (0.9)	1 (0.5)	
Moderate	1 (0.9)	0	1 (0.5)	
Severe	0	0	0	
Total	1 (0.9)	1 (0.9)	2 (0.9)	1.00

RMP.B1YP.JCLLIB2(AES8JEAA)
RMP.B1YO.HCJEREP(AES8JEAA)
* Frequencies are analyzed using a Fisher’s Exact test.
XAES0008

Table 14.39. Treatment-Emergent Non-Solicited Adverse Events Incidence by Maximum Severity All Randomized Patients Acute Treatment Phase (Study Periods III-IV) B1Y-MC-HCJE (continued)

Maximum Severity	Flx 20 (N=109) n (%)	Placebo (N=110) n (%)	Total (N=219) n (%)	p-Value*
HALLUCINATIONS				
Mild	1 (0.9)	0	1 (0.5)	
Moderate	0	0	0	
Severe	0	0	0	
Total	1 (0.9)	0	1 (0.5)	.498
HEPATITIS NONSPECIFIC				
Mild	0	0	0	
Moderate	1 (0.9)	0	1 (0.5)	
Severe	0	0	0	
Total	1 (0.9)	0	1 (0.5)	.498
HEPATOMEGALY				
Mild	1 (0.9)	0	1 (0.5)	
Moderate	0	0	0	
Severe	0	0	0	
Total	1 (0.9)	0	1 (0.5)	.498
HERPES SIMPLEX				
Mild	0	0	0	
Moderate	1 (0.9)	0	1 (0.5)	
Severe	0	0	0	
Total	1 (0.9)	0	1 (0.5)	.498
HYPERTONIA				
Mild	0	1 (0.9)	1 (0.5)	
Moderate	1 (0.9)	0	1 (0.5)	
Severe	0	0	0	
Total	1 (0.9)	1 (0.9)	2 (0.9)	1.00

RMP.B1YP.JCLLIB2(AES8JEAA)
RMP.B1YO.HCJEREP(AES8JEAA)
* Frequencies are analyzed using a Fisher’s Exact test.
XAES0008

Table 14.39. Treatment-Emergent Non-Solicited Adverse Events Incidence by Maximum Severity All Randomized Patients Acute Treatment Phase (Study Periods III-IV) B1Y-MC-HCJE (continued)

Maximum Severity	Flx 20 (N=109) n (%)	Placebo (N=110) n (%)	Total (N=219) n (%)	p-Value*
HYPOTENSION				
Mild	1 (0.9)	0	1 (0.5)	
Moderate	0	0	0	
Severe	0	0	0	
Total	1 (0.9)	0	1 (0.5)	.498
JOINT DISORDER				
Mild	0	0	0	
Moderate	1 (0.9)	0	1 (0.5)	
Severe	0	0	0	
Total	1 (0.9)	0	1 (0.5)	.498
LEG CRAMPS				
Mild	0	0	0	
Moderate	1 (0.9)	0	1 (0.5)	
Severe	0	1 (0.9)	1 (0.5)	1.00
Total	1 (0.9)	1 (0.9)	2 (0.9)	1.00
LUNG DISORDER				
Mild	1 (0.9)	0	1 (0.5)	
Moderate	0	0	0	
Severe	0	0	0	
Total	1 (0.9)	0	1 (0.5)	.498
MACULOPAPULAR RASH				
Mild	0	0	0	
Moderate	1 (0.9)	1 (0.9)	2 (0.9)	
Severe	0	0	0	
Total	1 (0.9)	1 (0.9)	2 (0.9)	1.00

RMP.B1YP.JCLLIB2(AES8JEAA)
RMP.B1YO.HCJEREP(AES8JEAA)
* Frequencies are analyzed using a Fisher’s Exact test.
XAES0008

Table 14.39. Treatment-Emergent Non-Solicited Adverse Events Incidence by Maximum Severity All Randomized Patients Acute Treatment Phase (Study Periods III-IV) B1Y-MC-HCJE (continued)

Maximum Severity	Flx 20 (N=109) n	(%)	Placebo (N=110) n	(%)	Total (N=219) n	(%)	p-Value*
MANIC REACTION							
Mild	0		0		0		
Moderate	0		0		0		
Severe	1	(0.9)	0		1	(0.5)	.498
Total	1	(0.9)	0		1	(0.5)	.498
MIGRAINE							
Mild	0		0		0		
Moderate	0		0		0		
Severe	1	(0.9)	1	(0.9)	2	(0.9)	1.00
Total	1	(0.9)	1	(0.9)	2	(0.9)	1.00
MYALGIA							
Mild	0		3	(2.7)	3	(1.4)	
Moderate	1	(0.9)	2	(1.8)	3	(1.4)	
Severe	0		0		0		
Total	1	(0.9)	5	(4.5)	6	(2.7)	.212
NEUROSIS							
Mild	1	(0.9)	0		1	(0.5)	
Moderate	0		0		0		
Severe	0		0		0		
Total	1	(0.9)	0		1	(0.5)	.498
OVERDOSE							
Mild	1	(0.9)	0		1	(0.5)	
Moderate	0		0		0		
Severe	0		0		0		
Total	1	(0.9)	0		1	(0.5)	.498

RMP.B1YP.JCLLIB2(AES8JEAA)
RMP.B1YO.HCJEREP(AES8JEAA)
* Frequencies are analyzed using a Fisher’s Exact test.
XAES0008

Table 14.39. Treatment-Emergent Non-Solicited Adverse Events Incidence by Maximum Severity All Randomized Patients Acute Treatment Phase (Study Periods III-IV) B1Y-MC-HCJE (continued)

Maximum Severity	Flx 20 (N=109) n	(%)	Placebo (N=110) n	(%)	Total (N=219) n	(%)	p-Value*
PALPITATION							
Mild	1	(0.9)	0		1	(0.5)	
Moderate	0		1	(0.9)	1	(0.5)	
Severe	0		0		0		
Total	1	(0.9)	1	(0.9)	2	(0.9)	1.00
PNEUMONIA							
Mild	1	(0.9)	0		1	(0.5)	
Moderate	0		0		0		
Severe	0		0		0		
Total	1	(0.9)	0		1	(0.5)	.498
SURGICAL PROCEDURE							
Mild	1	(0.9)	0		1	(0.5)	
Moderate	0		1	(0.9)	1	(0.5)	
Severe	0		0		0		
Total	1	(0.9)	1	(0.9)	2	(0.9)	1.00
SWEATING							
Mild	1	(0.9)	0		1	(0.5)	
Moderate	0		0		0		
Severe	0		0		0		
Total	1	(0.9)	0		1	(0.5)	.498
SYNCOPE							
Mild	0		0		0		
Moderate	1	(0.9)	0		1	(0.5)	
Severe	0		0		0		
Total	1	(0.9)	0		1	(0.5)	.498

RMP.B1YP.JCLLIB2(AES8JEAA)
RMP.B1YO.HCJEREP(AES8JEAA)
* Frequencies are analyzed using a Fisher’s Exact test.
XAES0008

Table 14.39. Treatment-Emergent Non-Solicited Adverse Events Incidence by Maximum Severity All Randomized Patients Acute Treatment Phase (Study Periods III-IV) B1Y-MC-HCJE (continued)

Maximum Severity	Flx 20 (N=109) n (%)	Placebo (N=110) n (%)	Total (N=219) n (%)	p-Value*
TACHYCARDIA				
Mild	1 (0.9)	0	1 (0.5)	
Moderate	0	0	0	
Severe	0	0	0	
Total	1 (0.9)	0	1 (0.5)	.498
TINNITUS				
Mild	1 (0.9)	0	1 (0.5)	
Moderate	0	0	0	
Severe	0	0	0	
Total	1 (0.9)	0	1 (0.5)	.498
TOOTH DISORDER				
Mild	0	0	0	
Moderate	1 (0.9)	0	1 (0.5)	
Severe	0	0	0	
Total	1 (0.9)	0	1 (0.5)	.498
URINARY FREQUENCY				
Mild	1 (0.9)	2 (1.8)	3 (1.4)	
Moderate	0	0	0	
Severe	0	0	0	
Total	1 (0.9)	2 (1.8)	3 (1.4)	1.00
URINARY TRACT INFECTION				
Mild	0	0	0	
Moderate	1 (0.9)	1 (0.9)	2 (0.9)	
Severe	0	0	0	
Total	1 (0.9)	1 (0.9)	2 (0.9)	1.00

RMP.B1YP.JCLLIB2(AES8JEAA)
RMP.B1YO.HCJEREP(AES8JEAA)
* Frequencies are analyzed using a Fisher’s Exact test.
XAES0008

Table 14.39. Treatment-Emergent Non-Solicited Adverse Events Incidence by Maximum Severity All Randomized Patients Acute Treatment Phase (Study Periods III-IV) B1Y-MC-HCJE (continued)

Maximum Severity	Flx 20 (N=109) n (%)	Placebo (N=110) n (%)	Total (N=219) n (%)	p-Value*
VASODILATATION				
Mild	1 (0.9)	0	1 (0.5)	
Moderate	0	0	0	
Severe	0	0	0	
Total	1 (0.9)	0	1 (0.5)	.498
YAWN				
Mild	1 (0.9)	0	1 (0.5)	
Moderate	0	0	0	
Severe	0	0	0	
Total	1 (0.9)	0	1 (0.5)	.498
ABDOMINAL SYNDROME ACUTE				
Mild	0	0	0	
Moderate	0	0	0	
Severe	0	1 (0.9)	1 (0.5)	1.00
Total	0	1 (0.9)	1 (0.5)	1.00
ACNE				
Mild	0	1 (0.9)	1 (0.5)	
Moderate	0	0	0	
Severe	0	0	0	
Total	0	1 (0.9)	1 (0.5)	1.00
ALOPECIA				
Mild	0	1 (0.9)	1 (0.5)	
Moderate	0	0	0	
Severe	0	0	0	
Total	0	1 (0.9)	1 (0.5)	1.00

RMP.B1YP.JCLLIB2(AES8JEAA)
RMP.B1YO.HCJEREP(AES8JEAA)
* Frequencies are analyzed using a Fisher’s Exact test.
XAES0008

Table 14.39. Treatment-Emergent Non-Solicited Adverse Events Incidence by Maximum Severity All Randomized Patients Acute Treatment Phase (Study Periods III-IV) B1Y-MC-HCJE (continued)

Maximum Severity	Flx 20 (N=109) n	(%)	Placebo (N=110) n	(%)	Total (N=219) n	(%)	p-Value*
AMNESIA							
Mild	0		1	(0.9)	1	(0.5)	
Moderate	0		0		0		
Severe	0		0		0		
Total	0		1	(0.9)	1	(0.5)	1.00
APHTHOUS STOMATITIS							
Mild	0		1	(0.9)	1	(0.5)	
Moderate	0		0		0		
Severe	0		0		0		
Total	0		1	(0.9)	1	(0.5)	1.00
ARTHRALGIA							
Mild	0		1	(0.9)	1	(0.5)	
Moderate	0		0		0		
Severe	0		0		0		
Total	0		1	(0.9)	1	(0.5)	1.00
BRADYCARDIA							
Mild	0		1	(0.9)	1	(0.5)	
Moderate	0		0		0		
Severe	0		0		0		
Total	0		1	(0.9)	1	(0.5)	1.00
CYSTITIS							
Mild	0		0		0		
Moderate	0		1	(0.9)	1	(0.5)	
Severe	0		0		0		
Total	0		1	(0.9)	1	(0.5)	1.00

RMP.B1YP.JCLLIB2(AES8JEAA)
RMP.B1YO.HCJEREP(AES8JEAA)
* Frequencies are analyzed using a Fisher's Exact test.
XAES0008

Table 14.39. Treatment-Emergent Non-Solicited Adverse Events Incidence by Maximum Severity All Randomized Patients Acute Treatment Phase (Study Periods III-IV) B1Y-MC-HCJE (continued)

Maximum Severity	Flx 20 (N=109) n	(%)	Placebo (N=110) n	(%)	Total (N=219) n	(%)	p-Value*
DEHYDRATION							
Mild	0		2	(1.8)	2	(0.9)	
Moderate	0		0		0		
Severe	0		0		0		
Total	0		2	(1.8)	2	(0.9)	.498
DYSURIA							
Mild	0		0		0		
Moderate	0		1	(0.9)	1	(0.5)	
Severe	0		0		0		
Total	0		1	(0.9)	1	(0.5)	1.00
FACE EDEMA							
Mild	0		1	(0.9)	1	(0.5)	
Moderate	0		0		0		
Severe	0		0		0		
Total	0		1	(0.9)	1	(0.5)	1.00
GASTROINTESTINAL DISORDER							
Mild	0		0		0		
Moderate	0		1	(0.9)	1	(0.5)	
Severe	0		0		0		
Total	0		1	(0.9)	1	(0.5)	1.00
HYPESTHESIA							
Mild	0		1	(0.9)	1	(0.5)	
Moderate	0		0		0		
Severe	0		0		0		
Total	0		1	(0.9)	1	(0.5)	1.00

RMP.B1YP.JCLLIB2(AES8JEAA)
RMP.B1YO.HCJEREP(AES8JEAA)
* Frequencies are analyzed using a Fisher’s Exact test.
XAES0008

Table 14.39. Treatment-Emergent Non-Solicited Adverse Events Incidence by Maximum Severity All Randomized Patients Acute Treatment Phase (Study Periods III-IV) B1Y-MC-HCJE (continued)

Maximum Severity	Flx 20 (N=109) n	(%)	Placebo (N=110) n	(%)	Total (N=219) n	(%)	p-Value*
HYPOVENTILATION							
Mild	0		1	(0.9)	1	(0.5)	
Moderate	0		0		0		
Severe	0		0		0		
Total	0		1	(0.9)	1	(0.5)	1.00
INCREASED APPETITE							
Mild	0		3	(2.7)	3	(1.4)	
Moderate	0		0		0		
Severe	0		0		0		
Total	0		3	(2.7)	3	(1.4)	.247
INTENTIONAL INJURY							
Mild	0		0		0		
Moderate	0		0		0		
Severe	0		1	(0.9)	1	(0.5)	1.00
Total	0		1	(0.9)	1	(0.5)	1.00
LARYNGITIS							
Mild	0		0		0		
Moderate	0		1	(0.9)	1	(0.5)	
Severe	0		0		0		
Total	0		1	(0.9)	1	(0.5)	1.00
LEUKORRHEA							
Mild	0		0		0		
Moderate	0		1	(0.9)	1	(0.5)	
Severe	0		0		0		
Total	0		1	(0.9)	1	(0.5)	1.00

RMP.B1YP.JCLLIB2(AES8JEAA)
RMP.B1YO.HCJEREP(AES8JEAA)
* Frequencies are analyzed using a Fisher’s Exact test.
XAES0008

Table 14.39. Treatment-Emergent Non-Solicited Adverse Events Incidence by Maximum Severity All Randomized Patients Acute Treatment Phase (Study Periods III-IV) B1Y-MC-HCJE (continued)

Maximum Severity	Flx 20 (N=109) n	(%)	Placebo (N=110) n	(%)	Total (N=219) n	(%)	p-Value*
METRORRHAGIA							
Mild	0		1	(0.9)	1	(0.5)	
Moderate	0		0		0		
Severe	0		0		0		
Total	0		1	(0.9)	1	(0.5)	1.00
MOUTH ULCERATION							
Mild	0		1	(0.9)	1	(0.5)	
Moderate	0		0		0		
Severe	0		0		0		
Total	0		1	(0.9)	1	(0.5)	1.00
SKIN DISCOLORATION							
Mild	0		1	(0.9)	1	(0.5)	
Moderate	0		0		0		
Severe	0		0		0		
Total	0		1	(0.9)	1	(0.5)	1.00
SKIN ULCER							
Mild	0		1	(0.9)	1	(0.5)	
Moderate	0		0		0		
Severe	0		0		0		
Total	0		1	(0.9)	1	(0.5)	1.00
SUBCUTANEOUS NODULE							
Mild	0		1	(0.9)	1	(0.5)	
Moderate	0		0		0		
Severe	0		0		0		
Total	0		1	(0.9)	1	(0.5)	1.00

RMP.B1YP.JCLLIB2(AES8JEAA)
RMP.B1YO.HCJEREP(AES8JEAA)
* Frequencies are analyzed using a Fisher’s Exact test.
XAES0008

Table 14.39. Treatment-Emergent Non-Solicited Adverse Events Incidence by Maximum Severity All Randomized Patients Acute Treatment Phase (Study Periods III-IV) B1Y-MC-HCJE (concluded)

Maximum Severity	Flx 20 (N=109) n	(%)	Placebo (N=110) n	(%)	Total (N=219) n	(%)	p-Value*
THINKING ABNORMAL							
Mild	0		1	(0.9)	1	(0.5)	
Moderate	0		0		0		
Severe	0		0		0		
Total	0		1	(0.9)	1	(0.5)	1.00
UNEXPECTED BENEFIT							
Mild	0		1	(0.9)	1	(0.5)	
Moderate	0		0		0		
Severe	0		0		0		
Total	0		1	(0.9)	1	(0.5)	1.00
WEIGHT GAIN							
Mild	0		1	(0.9)	1	(0.5)	
Moderate	0		0		0		
Severe	0		0		0		
Total	0		1	(0.9)	1	(0.5)	1.00

RMP.B1YP.JCLLIB2(AES8JEAA)
RMP.B1YO.HCJEREP(AES8JEAA)
* Frequencies are analyzed using a Fisher's Exact test.
XAES0008

14.3.1.1.3. Treatment-Emergent Solicited Adverse Events from the Side-Effects Checklist by Maximum Intensity

Treatment-emergent solicited adverse events were also analyzed by maximum intensity for the acute treatment phase (see Table 14.40). The Side-Effects Checklist measured intensity, rather than severity, as is typically done in Lilly-sponsored trials. An intensity score of "1," which meant the event occurred "just a little" (according to the Side-Effects Checklist) was mapped to the term "mild" for severity analysis in Lilly's system. Similarly, a score of "2" (pretty much) was mapped to moderate, and a score of "3" (very much) was mapped to severe.

Table 14.40 presents a summary of the incidence of treatment-emergent solicited adverse events by maximum intensity. Statistically significant differences were observed in the reported intensity of three treatment-emergent solicited adverse events. Nineteen (17%) fluoxetine-treated patients reported a severe intensity of feeling sleepy compared with 7 (6%) placebo-treated patients (p=.013). A severe intensity of trouble getting along with parents was reported by 19 (17%) fluoxetine-treated patients compared with 9 (8%) placebo-treated patients (p=.045). Eighteen (17%) patients in the fluoxetine treatment

group reported a severe intensity of trouble paying attention compared with 7 (6%) patients in the placebo treatment group (p=.020).

Although statistically significant differences in the reported intensity (that is, frequency of some events captured on the Side-Effects checklist) were observed during acute treatment, these changes tended to be small and did not result in patient discontinuation from the study.

Table 14.40. Treatment-Emergent Solicited Adverse Events Side-Effects Checklist Incidence by Maximum Intensity All Randomized Patients Acute Treatment Phase (Study Periods III-IV) B1Y-MC-HCJE

Maximum Severity	Flx 20 (N=109) n (%)	Placebo (N=110) n (%)	Total (N=219) n (%)	p-Value*
PATIENTS WITH >= 1 TESS				
Mild	15 (13.8)	13 (11.8)	28 (12.8)	
Moderate	26 (23.9)	35 (31.8)	61 (27.9)	
Severe	64 (58.7)	52 (47.3)	116 (53.0)	.105
Total	105 (96.3)	100 (90.9)	205 (93.6)	.165
01. EATING				
Mild	15 (13.8)	14 (12.7)	29 (13.2)	
Moderate	14 (12.8)	13 (11.8)	27 (12.3)	
Severe	2 (1.8)	8 (7.3)	10 (4.6)	.101
Total	31 (28.4)	35 (31.8)	66 (30.1)	.659
02. DRINKING				
Mild	5 (4.6)	9 (8.2)	14 (6.4)	
Moderate	4 (3.7)	7 (6.4)	11 (5.0)	
Severe	5 (4.6)	4 (3.6)	9 (4.1)	.748
Total	14 (12.8)	20 (18.2)	34 (15.5)	.351
03. DRY MOUTH AND LIPS				
Mild	18 (16.5)	17 (15.5)	35 (16.0)	
Moderate	10 (9.2)	10 (9.1)	20 (9.1)	
Severe	4 (3.7)	11 (10.0)	15 (6.8)	.106
Total	32 (29.4)	38 (34.5)	70 (32.0)	.469
04. WETNESS IN MOUTH				
Mild	4 (3.7)	10 (9.1)	14 (6.4)	
Moderate	6 (5.5)	4 (3.6)	10 (4.6)	
Severe	0	5 (4.5)	5 (2.3)	.060
Total	10 (9.2)	19 (17.3)	29 (13.2)	.110

1Treatment-Emergent = was present at baseline (Visit 4) and worsened as defined by increase in score on the side-effects checklist at any Postbaseline visit (Visits 5-10) or new occurrence after baseline
RMP.B1YP.JCLLIB2(AES8JEAC)
RMP.B1YO.HCJEREP(AES8JEAC)
* Frequencies are analyzed using a Fisher's Exact test.
XAES0008

Table 14.40. Treatment-Emergent Solicited Adverse Events Side-Effects Checklist Incidence by Maximum Intensity All Randomized Patients Acute Treatment Phase (Study Periods III-IV) B1Y-MC-HCJE (continued)

Maximum Severity	Flx 20 (N=109) n (%)	Placebo (N=110) n (%)	Total (N=219) n (%)	p-Value*
05. CONSTIPATION				
Mild	5 (4.6)	5 (4.5)	10 (4.6)	
Moderate	1 (0.9)	3 (2.7)	4 (1.8)	
Severe	3 (2.8)	2 (1.8)	5 (2.3)	.683
Total	9 (8.3)	10 (9.1)	19 (8.7)	1.00
06. DIARRHEA				
Mild	15 (13.8)	13 (11.8)	28 (12.8)	
Moderate	3 (2.8)	4 (3.6)	7 (3.2)	
Severe	4 (3.7)	2 (1.8)	6 (2.7)	.446
Total	22 (20.2)	19 (17.3)	41 (18.7)	.607
07. STOMACHACHES				
Mild	24 (22.0)	25 (22.7)	49 (22.4)	
Moderate	10 (9.2)	12 (10.9)	22 (10.0)	
Severe	3 (2.8)	6 (5.5)	9 (4.1)	.499
Total	37 (33.9)	43 (39.1)	80 (36.5)	.484
08. MUSCLE CRAMPS				
Mild	16 (14.7)	25 (22.7)	41 (18.7)	
Moderate	6 (5.5)	5 (4.5)	11 (5.0)	
Severe	5 (4.6)	4 (3.6)	9 (4.1)	.748
Total	27 (24.8)	34 (30.9)	61 (27.9)	.366
09. BEING SICK TO YOUR STOMACH				
Mild	26 (23.9)	21 (19.1)	47 (21.5)	
Moderate	9 (8.3)	11 (10.0)	20 (9.1)	
Severe	4 (3.7)	1 (0.9)	5 (2.3)	.212
Total	39 (35.8)	33 (30.0)	72 (32.9)	.390

1Treatment-Emergent = was present at baseline (Visit 4) and worsened as defined by increase in score on the side-effects checklist at any Postbaseline visit (Visits 5-10) or new occurrence after baseline
RMP.B1YP.JCLLIB2(AES8JEAC)
RMP.B1YO.HCJEREP(AES8JEAC)
* Frequencies are analyzed using a Fisher's Exact test.
XAES0008

Table 14.40. Treatment-Emergent Solicited Adverse Events Side-Effects Checklist Incidence by Maximum Intensity All Randomized Patients Acute Treatment Phase (Study Periods III-IV) B1Y-MC-HCJE (continued)

Maximum Severity	Flx 20 (N=109) n (%)	Placebo (N=110) n (%)	Total (N=219) n (%)	p-Value*
10. WETTING THE BED				
Mild	2 (1.8)	4 (3.6)	6 (2.7)	
Moderate	1 (0.9)	0	1 (0.5)	
Severe	0	1 (0.9)	1 (0.5)	1.00
Total	3 (2.8)	5 (4.5)	8 (3.7)	.721
11. URINATING				
Mild	6 (5.5)	5 (4.5)	11 (5.0)	
Moderate	3 (2.8)	5 (4.5)	8 (3.7)	
Severe	1 (0.9)	2 (1.8)	3 (1.4)	1.00
Total	10 (9.2)	12 (10.9)	22 (10.0)	.823
12. ITCHY OR SCRATCHY SKIN				
Mild	14 (12.8)	15 (13.6)	29 (13.2)	
Moderate	7 (6.4)	12 (10.9)	19 (8.7)	
Severe	6 (5.5)	5 (4.5)	11 (5.0)	.768
Total	27 (24.8)	32 (29.1)	59 (26.9)	.543
13. RASHES				
Mild	12 (11.0)	12 (10.9)	24 (11.0)	
Moderate	3 (2.8)	4 (3.6)	7 (3.2)	
Severe	2 (1.8)	2 (1.8)	4 (1.8)	1.00
Total	17 (15.6)	18 (16.4)	35 (16.0)	1.00
14. COLD OR SNIFFLES				
Mild	19 (17.4)	23 (20.9)	42 (19.2)	
Moderate	11 (10.1)	15 (13.6)	26 (11.9)	
Severe	11 (10.1)	12 (10.9)	23 (10.5)	1.00
Total	41 (37.6)	50 (45.5)	91 (41.6)	.273

1Treatment-Emergent = was present at baseline (Visit 4) and worsened as defined by increase in score on the side-effects checklist at any Postbaseline visit (Visits 5-10) or new occurrence after baseline
RMP.B1YP.JCLLIB2(AES8JEAC)
RMP.B1YO.HCJEREP(AES8JEAC)
* Frequencies are analyzed using a Fisher's Exact test.
XAES0008

Table 14.40. Treatment-Emergent Solicited Adverse Events Side-Effects Checklist Incidence by Maximum Intensity All Randomized Patients Acute Treatment Phase (Study Periods III-IV) B1Y-MC-HCJE (continued)

Maximum Severity	Flx 20 (N=109) n (%)	Placebo (N=110) n (%)	Total (N=219) n (%)	p-Value*
15. HEADACHE				
Mild	24 (22.0)	23 (20.9)	47 (21.5)	
Moderate	21 (19.3)	11 (10.0)	32 (14.6)	
Severe	4 (3.7)	7 (6.4)	11 (5.0)	.538
Total	49 (45.0)	41 (37.3)	90 (41.1)	.273
16. DIZZINESS				
Mild	24 (22.0)	19 (17.3)	43 (19.6)	
Moderate	7 (6.4)	2 (1.8)	9 (4.1)	
Severe	3 (2.8)	2 (1.8)	5 (2.3)	.683
Total	34 (31.2)	23 (20.9)	57 (26.0)	.092
17. PLAYING SPORTS				
Mild	7 (6.4)	12 (10.9)	19 (8.7)	
Moderate	4 (3.7)	7 (6.4)	11 (5.0)	
Severe	6 (5.5)	1 (0.9)	7 (3.2)	.065
Total	17 (15.6)	20 (18.2)	37 (16.9)	.719
18. SHAKINESS				
Mild	13 (11.9)	18 (16.4)	31 (14.2)	
Moderate	2 (1.8)	3 (2.7)	5 (2.3)	
Severe	6 (5.5)	2 (1.8)	8 (3.7)	.171
Total	21 (19.3)	23 (20.9)	44 (20.1)	.866
19. PRONOUNCING WORDS				
Mild	10 (9.2)	18 (16.4)	28 (12.8)	
Moderate	1 (0.9)	7 (6.4)	8 (3.7)	
Severe	2 (1.8)	3 (2.7)	5 (2.3)	1.00
Total	13 (11.9)	28 (25.5)	41 (18.7)	.015

1Treatment-Emergent = was present at baseline (Visit 4) and worsened as defined by increase in score on the side-effects checklist at any Postbaseline visit (Visits 5-10) or new occurrence after baseline
RMP.B1YP.JCLLIB2(AES8JEAC)
RMP.B1YO.HCJEREP(AES8JEAC)
* Frequencies are analyzed using a Fisher's Exact test.
XAES0008

Table 14.40. Treatment-Emergent Solicited Adverse Events Side-Effects Checklist Incidence by Maximum Intensity All Randomized Patients Acute Treatment Phase (Study Periods III-IV) B1Y-MC-HCJE (continued)

Maximum Severity	Flx 20 (N=109) n (%)	Placebo (N=110) n (%)	Total (N=219) n (%)	p-Value*
20. DOING THINGS WITH YOUR HANDS				
Mild	7 (6.4)	10 (9.1)	17 (7.8)	
Moderate	4 (3.7)	6 (5.5)	10 (4.6)	
Severe	2 (1.8)	3 (2.7)	5 (2.3)	1.00
Total	13 (11.9)	19 (17.3)	32 (14.6)	.339
21. SITTING STILL				
Mild	10 (9.2)	22 (20.0)	32 (14.6)	
Moderate	11 (10.1)	15 (13.6)	26 (11.9)	
Severe	9 (8.3)	5 (4.5)	14 (6.4)	.285
Total	30 (27.5)	42 (38.2)	72 (32.9)	.114
22. TIREDNESS				
Mild	20 (18.3)	16 (14.5)	36 (16.4)	
Moderate	12 (11.0)	17 (15.5)	29 (13.2)	
Severe	18 (16.5)	13 (11.8)	31 (14.2)	.339
Total	50 (45.9)	46 (41.8)	96 (43.8)	.587
23. FEELING SLEEPY				
Mild	16 (14.7)	23 (20.9)	39 (17.8)	
Moderate	17 (15.6)	17 (15.5)	34 (15.5)	
Severe	19 (17.4)	7 (6.4)	26 (11.9)	.013
Total	52 (47.7)	47 (42.7)	99 (45.2)	.499
24. SLEEPING				
Mild	15 (13.8)	17 (15.5)	32 (14.6)	
Moderate	11 (10.1)	14 (12.7)	25 (11.4)	
Severe	13 (11.9)	14 (12.7)	27 (12.3)	1.00
Total	39 (35.8)	45 (40.9)	84 (38.4)	.488

1Treatment-Emergent = was present at baseline (Visit 4) and worsened as defined by increase in score on the side-effects checklist at any Postbaseline visit (Visits 5-10) or new occurrence after baseline
RMP.B1YP.JCLLIB2(AES8JEAC)
RMP.B1YO.HCJEREP(AES8JEAC)
* Frequencies are analyzed using a Fisher's Exact test.
XAES0008

Table 14.40. Treatment-Emergent Solicited Adverse Events Side-Effects Checklist Incidence by Maximum Intensity All Randomized Patients Acute Treatment Phase (Study Periods III-IV) B1Y-MC-HCJE (continued)

Maximum Severity	Flx 20 (N=109) n (%)	Placebo (N=110) n (%)	Total (N=219) n (%)	p-Value*
25. BAD DREAMS				
Mild	17 (15.6)	20 (18.2)	37 (16.9)	
Moderate	5 (4.6)	5 (4.5)	10 (4.6)	
Severe	5 (4.6)	2 (1.8)	7 (3.2)	.280
Total	27 (24.8)	27 (24.5)	54 (24.7)	1.00
26. GETTING ALONG WITH PARENTS				
Mild	9 (8.3)	25 (22.7)	34 (15.5)	
Moderate	15 (13.8)	11 (10.0)	26 (11.9)	
Severe	19 (17.4)	9 (8.2)	28 (12.8)	.045
Total	43 (39.4)	45 (40.9)	88 (40.2)	.891
27. GETTING ALONG WITH KIDS				
Mild	15 (13.8)	14 (12.7)	29 (13.2)	
Moderate	10 (9.2)	9 (8.2)	19 (8.7)	
Severe	8 (7.3)	8 (7.3)	16 (7.3)	1.00
Total	33 (30.3)	31 (28.2)	64 (29.2)	.768
28. CRYING				
Mild	21 (19.3)	19 (17.3)	40 (18.3)	
Moderate	11 (10.1)	16 (14.5)	27 (12.3)	
Severe	7 (6.4)	4 (3.6)	11 (5.0)	.374
Total	39 (35.8)	39 (35.5)	78 (35.6)	1.00
29. GETTING MAD				
Mild	15 (13.8)	24 (21.8)	39 (17.8)	
Moderate	14 (12.8)	15 (13.6)	29 (13.2)	
Severe	11 (10.1)	8 (7.3)	19 (8.7)	.483
Total	40 (36.7)	47 (42.7)	87 (39.7)	.408

1Treatment-Emergent = was present at baseline (Visit 4) and worsened as defined by increase in score on the side-effects checklist at any Postbaseline visit (Visits 5-10) or new occurrence after baseline
RMP.B1YP.JCLLIB2(AES8JEAC)
RMP.B1YO.HCJEREP(AES8JEAC)
* Frequencies are analyzed using a Fisher's Exact test.
XAES0008

Table 14.40. Treatment-Emergent Solicited Adverse Events Side-Effects Checklist Incidence by Maximum Intensity All Randomized Patients Acute Treatment Phase (Study Periods III-IV) B1Y-MC-HCJE (concluded)

Maximum Severity	Flx 20 (N=109) n (%)	Placebo (N=110) n (%)	Total (N=219) n (%)	p-Value*
30. NOT BEING HAPPY				
Mild	14 (12.8)	14 (12.7)	28 (12.8)	
Moderate	16 (14.7)	11 (10.0)	27 (12.3)	
Severe	10 (9.2)	9 (8.2)	19 (8.7)	.815
Total	40 (36.7)	34 (30.9)	74 (33.8)	.394
31. BEING SAD				
Mild	14 (12.8)	15 (13.6)	29 (13.2)	
Moderate	16 (14.7)	11 (10.0)	27 (12.3)	
Severe	11 (10.1)	6 (5.5)	17 (7.8)	.218
Total	41 (37.6)	32 (29.1)	73 (33.3)	.199
32. PAYING ATTENTION				
Mild	8 (7.3)	14 (12.7)	22 (10.0)	
Moderate	17 (15.6)	10 (9.1)	27 (12.3)	
Severe	18 (16.5)	7 (6.4)	25 (11.4)	.020
Total	43 (39.4)	31 (28.2)	74 (33.8)	.088

1Treatment-Emergent = was present at baseline (Visit 4) and worsened as defined by increase in score on the side-effects checklist at any Postbaseline visit (Visits 5-10) or new occurrence after baseline
RMP.B1YP.JCLLIB2(AES8JEAC)
RMP.B1YO.HCJEREP(AES8JEAC)
* Frequencies are analyzed using a Fisher's Exact test.
XAES0008

14.3.1.2. Subchronic Treatment Phase (Study Periods III-V)

14.3.1.2.1. Treatment-Emergent Non-Solicited Adverse Events by Body System

Treatment-emergent non-solicited adverse events by body system are summarized for all randomized patients for the subchronic treatment phase in Table 14.41.

Statistically significant differences between the two treatment groups were observed with respect to the incidence of adverse events related to the nervous, respiratory, and special senses body systems. Forty-six (42%) fluoxetine-treated patients reported at least one adverse event related to the nervous system compared with 28 (26%) placebo-treated patients (p=.010). Sixty-one (56%) fluoxetine-treated patients reported at least one adverse event related to the respiratory system compared with 42 (38%) placebo-treated patients (p=.010), and 16 (15%) fluoxetine-treated patients reported at least one adverse event related to special senses compared with 4 (4%) placebo-treated patients (p=.005).

There were no statistically significant differences between the two treatment groups with respect to any specific adverse event for any of these body systems.

Table 14.41. Treatment-Emergent Non-Solicited Adverse Events Incidence by Body System All Randomized Patients Subchronic Treatment Phase (Study Periods III-V) B1Y-MC-HCJE

Body System: Overall

Event Classification	Flx (N=109) n (%)	Placebo (N=110) n (%)	Total (N=219) n (%)	p-Value*
PATIENTS WITH >= 1 TESS	101 (92.7)	87 (79.1)	188 (85.8)	.006
PATIENTS WITH NO TESS	8 (7.3)	23 (20.9)	31 (14.2)	.006

RMP.B1YP.JCLLIB2(AES2JEAB)
RMP.B1YO.HCJEREP(AES2JEAB)
* Frequencies are analyzed using a Fisher's Exact test.
XAES0002

Table 14.41. Treatment-Emergent Non-Solicited Adverse Events Incidence by Body System All Randomized Patients Subchronic Treatment Phase (Study Periods III-V) B1Y-MC-HCJE (continued)

Body System: BODY AS A WHOLE

Event Classification	Flx (N=109) n (%)	Placebo (N=110) n (%)	Total (N=219) n (%)	p-Value*
PATIENTS WITH >= 1 TESS	76 (69.7)	64 (58.2)	140 (63.9)	.091
PATIENTS WITH NO TESS	33 (30.3)	46 (41.8)	79 (36.1)	.091
HEADACHE	37 (33.9)	21 (19.1)	58 (26.5)	.014
ABDOMINAL PAIN	22 (20.2)	22 (20.0)	44 (20.1)	1.00
ACCIDENTAL INJURY	19 (17.4)	10 (9.1)	29 (13.2)	.076
ASTHENIA	10 (9.2)	7 (6.4)	17 (7.8)	.462
FEVER	10 (9.2)	8 (7.3)	18 (8.2)	.632
PAIN	10 (9.2)	12 (10.9)	22 (10.0)	.823
BACK PAIN	6 (5.5)	5 (4.5)	11 (5.0)	.768
INFECTION	5 (4.6)	5 (4.5)	10 (4.6)	1.00
ALLERGIC REACTION	4 (3.7)	2 (1.8)	6 (2.7)	.446
FLU SYNDROME	4 (3.7)	3 (2.7)	7 (3.2)	.721
PHOTOSENSITIVITY REACTION	4 (3.7)	1 (0.9)	5 (2.3)	.212
CHEST PAIN	3 (2.8)	2 (1.8)	5 (2.3)	.683
NECK PAIN	3 (2.8)	1 (0.9)	4 (1.8)	.369
CHILLS	2 (1.8)	1 (0.9)	3 (1.4)	.622
NECK RIGIDITY	2 (1.8)	1 (0.9)	3 (1.4)	.622
SURGICAL PROCEDURE	2 (1.8)	2 (1.8)	4 (1.8)	1.00
INTENTIONAL INJURY	1 (0.9)	1 (0.9)	2 (0.9)	1.00
OVERDOSE	1 (0.9)	1 (0.9)	2 (0.9)	1.00
ABDOMINAL SYNDROME ACUTE	0	1 (0.9)	1 (0.5)	1.00
FACE EDEMA	0	1 (0.9)	1 (0.5)	1.00
UNEXPECTED BENEFIT	0	1 (0.9)	1 (0.5)	1.00

RMP.B1YP.JCLLIB2(AES2JEAB)
RMP.B1YO.HCJEREP(AES2JEAB)
* Frequencies are analyzed using a Fisher’s Exact test.
XAES0002

Table 14.41. Treatment-Emergent Non-Solicited Adverse Events Incidence by Body System All Randomized Patients Subchronic Treatment Phase (Study Periods III-V) B1Y-MC-HCJE (continued)

Body System: CARDIOVASCULAR SYSTEM

Event Classification	Flx (N=109) n (%)	Placebo (N=110) n (%)	Total (N=219) n (%)	p-Value*
PATIENTS WITH >= 1 TESS	7 (6.4)	3 (2.7)	10 (4.6)	.215
PATIENTS WITH NO TESS	102 (93.6)	107 (97.3)	209 (95.4)	.215
BRADYCARDIA	1 (0.9)	1 (0.9)	2 (0.9)	1.00
CARDIOVASCULAR DISORDER	1 (0.9)	0	1 (0.5)	.498
HYPOTENSION	1 (0.9)	0	1 (0.5)	.498
MIGRAINE	1 (0.9)	1 (0.9)	2 (0.9)	1.00
PALPITATION	1 (0.9)	1 (0.9)	2 (0.9)	1.00
SINUS BRADYCARDIA	1 (0.9)	0	1 (0.5)	.498
SYNCOPE	1 (0.9)	0	1 (0.5)	.498
TACHYCARDIA	1 (0.9)	0	1 (0.5)	.498
VASODILATATION	1 (0.9)	0	1 (0.5)	.498

RMP.B1YP.JCLLIB2(AES2JEAB)
RMP.B1YO.HCJEREP(AES2JEAB)
* Frequencies are analyzed using a Fisher’s Exact test.
XAES0002

Table 14.41. Treatment-Emergent Non-Solicited Adverse Events Incidence by Body System All Randomized Patients Subchronic Treatment Phase (Study Periods III-V) B1Y-MC-HCJE (continued)

Body System: DIGESTIVE SYSTEM

Event Classification	Flx (N=109) n (%)	Placebo (N=110) n (%)	Total (N=219) n (%)	p-Value*
PATIENTS WITH >= 1 TESS	42 (38.5)	48 (43.6)	90 (41.1)	.493
PATIENTS WITH NO TESS	67 (61.5)	62 (56.4)	129 (58.9)	.493
DIARRHEA	14 (12.8)	13 (11.8)	27 (12.3)	.840
VOMITING	11 (10.1)	12 (10.9)	23 (10.5)	1.00
ANOREXIA	10 (9.2)	9 (8.2)	19 (8.7)	.815
NAUSEA	9 (8.3)	11 (10.0)	20 (9.1)	.815
DRY MOUTH	6 (5.5)	6 (5.5)	12 (5.5)	1.00
DYSPEPSIA	4 (3.7)	5 (4.5)	9 (4.1)	1.00
CONSTIPATION	3 (2.8)	6 (5.5)	9 (4.1)	.499
GASTROENTERITIS	2 (1.8)	0	2 (0.9)	.247
INCREASED APPETITE	2 (1.8)	3 (2.7)	5 (2.3)	1.00
THIRST	2 (1.8)	2 (1.8)	4 (1.8)	1.00
TOOTH DISORDER	2 (1.8)	0	2 (0.9)	.247
DYSPHAGIA	1 (0.9)	1 (0.9)	2 (0.9)	1.00
FECAL INCONTINENCE	1 (0.9)	0	1 (0.5)	.498
FLATULENCE	1 (0.9)	0	1 (0.5)	.498
GASTROINTESTINAL DISORDER	1 (0.9)	1 (0.9)	2 (0.9)	1.00
HEPATITIS NONSPECIFIC	1 (0.9)	0	1 (0.5)	.498
HEPATOMEGALY	1 (0.9)	1 (0.9)	2 (0.9)	1.00
INCREASED SALIVATION	1 (0.9)	1 (0.9)	2 (0.9)	1.00
RECTAL HEMORRHAGE	1 (0.9)	0	1 (0.5)	.498
ULCERATIVE STOMATITIS	1 (0.9)	0	1 (0.5)	.498
APHTHOUS STOMATITIS	0	1 (0.9)	1 (0.5)	1.00
MOUTH ULCERATION	0	1 (0.9)	1 (0.5)	1.00

RMP.B1YP.JCLLIB2(AES2JEAB)
RMP.B1YO.HCJEREP(AES2JEAB)
* Frequencies are analyzed using a Fisher’s Exact test.
XAES0002

Table 14.41. Treatment-Emergent Non-Solicited Adverse Events Incidence by Body System All Randomized Patients Subchronic Treatment Phase (Study Periods III-V) B1Y-MC-HCJE (continued)

Body System: ENDOCRINE SYSTEM

Event Classification	Flx (N=109) n (%)	Placebo (N=110) n (%)	Total (N=219) n (%)	p-Value*
PATIENTS WITH >= 1 TESS	2 (1.8)	0	2 (0.9)	.247
PATIENTS WITH NO TESS	107 (98.2)	110 (100)	217 (99.1)	.247
ENDOCRINE DISORDER	1 (0.9)	0	1 (0.5)	.498
THYROID DISORDER	1 (0.9)	0	1 (0.5)	.498

RMP.B1YP.JCLLIB2(AES2JEAB)
RMP.B1YO.HCJEREP(AES2JEAB)
* Frequencies are analyzed using a Fisher’s Exact test.
XAES0002

Table 14.41. Treatment-Emergent Non-Solicited Adverse Events Incidence by Body System All Randomized Patients Subchronic Treatment Phase (Study Periods III-V) B1Y-MC-HCJE (continued)

Body System: HEMIC AND LYMPHATIC SYSTEM

Event Classification	Flx (N=109) n (%)	Placebo (N=110) n (%)	Total (N=219) n (%)	p-Value*
PATIENTS WITH >= 1 TESS	7 (6.4)	4 (3.6)	11 (5.0)	.374
PATIENTS WITH NO TESS	102 (93.6)	106 (96.4)	208 (95.0)	.374
ECCHYMOSIS	4 (3.7)	2 (1.8)	6 (2.7)	.446
ANEMIA	1 (0.9)	0	1 (0.5)	.498
LEUKOPENIA	1 (0.9)	0	1 (0.5)	.498
LYMPHADENOPATHY	1 (0.9)	1 (0.9)	2 (0.9)	1.00
LYMPHOCYTOSIS	0	1 (0.9)	1 (0.5)	1.00
SPLENOMEGALY	0	1 (0.9)	1 (0.5)	1.00

RMP.B1YP.JCLLIB2(AES2JEAB)
RMP.B1YO.HCJEREP(AES2JEAB)
* Frequencies are analyzed using a Fisher’s Exact test.
XAES0002

Table 14.41. Treatment-Emergent Non-Solicited Adverse Events Incidence by Body System All Randomized Patients Subchronic Treatment Phase (Study Periods III-V) B1Y-MC-HCJE (continued)

Body System: METABOLIC AND NUTRITIONAL DISORDERS

Event Classification	Flx (N=109) n (%)	Placebo (N=110) n (%)	Total (N=219) n (%)	p-Value*
PATIENTS WITH >= 1 TESS	2 (1.8)	4 (3.6)	6 (2.7)	.683
PATIENTS WITH NO TESS	107 (98.2)	106 (96.4)	213 (97.3)	.683
WEIGHT LOSS	2 (1.8)	1 (0.9)	3 (1.4)	.622
HYPERCHOLESTEREMIA	1 (0.9)	0	1 (0.5)	.498
DEHYDRATION	0	2 (1.8)	2 (0.9)	.498
WEIGHT GAIN	0	1 (0.9)	1 (0.5)	1.00

RMP.B1YP.JCLLIB2(AES2JEAB)
RMP.B1YO.HCJEREP(AES2JEAB)
* Frequencies are analyzed using a Fisher’s Exact test.
XAES0002

Table 14.41. Treatment-Emergent Non-Solicited Adverse Events Incidence by Body System All Randomized Patients Subchronic Treatment Phase (Study Periods III-V) B1Y-MC-HCJE (continued)

Body System: MUSCULOSKELETAL SYSTEM

Event Classification	Flx (N=109) n (%)	Placebo (N=110) n (%)	Total (N=219) n (%)	p-Value*
PATIENTS WITH >= 1 TESS	5 (4.6)	10 (9.1)	15 (6.8)	.285
PATIENTS WITH NO TESS	104 (95.4)	100 (90.9)	204 (93.2)	.285
MYALGIA	3 (2.8)	6 (5.5)	9 (4.1)	.499
JOINT DISORDER	1 (0.9)	0	1 (0.5)	.498
LEG CRAMPS	1 (0.9)	3 (2.7)	4 (1.8)	.622
ARTHRALGIA	0	1 (0.9)	1 (0.5)	1.00

RMP.B1YP.JCLLIB2(AES2JEAB)
RMP.B1YO.HCJEREP(AES2JEAB)
* Frequencies are analyzed using a Fisher’s Exact test.
XAES0002

Table 14.41. Treatment-Emergent Non-Solicited Adverse Events Incidence by Body System All Randomized Patients Subchronic Treatment Phase (Study Periods III-V) B1Y-MC-HCJE (continued)

Body System: NERVOUS SYSTEM

Event Classification	Flx (N=109) n (%)	Placebo (N=110) n (%)	Total (N=219) n (%)	p-Value*
PATIENTS WITH >= 1 TESS	46 (42.2)	28 (25.5)	74 (33.8)	.010
PATIENTS WITH NO TESS	63 (57.8)	82 (74.5)	145 (66.2)	.010
DIZZINESS	11 (10.1)	8 (7.3)	19 (8.7)	.483
NERVOUSNESS	11 (10.1)	6 (5.5)	17 (7.8)	.218
ABNORMAL DREAMS	7 (6.4)	3 (2.7)	10 (4.6)	.215
INSOMNIA	6 (5.5)	5 (4.5)	11 (5.0)	.768
HOSTILITY	5 (4.6)	5 (4.5)	10 (4.6)	1.00
PERSONALITY DISORDER	5 (4.6)	2 (1.8)	7 (3.2)	.280
SOMNOLENCE	5 (4.6)	4 (3.6)	9 (4.1)	.748
AGITATION	4 (3.7)	0	4 (1.8)	.060
HYPERKINESIA	4 (3.7)	1 (0.9)	5 (2.3)	.212
AKATHISIA	3 (2.8)	0	3 (1.4)	.122
DEPRESSION	3 (2.8)	2 (1.8)	5 (2.3)	.683
SPEECH DISORDER	3 (2.8)	2 (1.8)	5 (2.3)	.683
TREMOR	3 (2.8)	1 (0.9)	4 (1.8)	.369
ACUTE BRAIN SYNDROME	2 (1.8)	0	2 (0.9)	.247
ANXIETY	2 (1.8)	0	2 (0.9)	.247
EUPHORIA	2 (1.8)	0	2 (0.9)	.247
SLEEP DISORDER	2 (1.8)	0	2 (0.9)	.247
THINKING ABNORMAL	2 (1.8)	1 (0.9)	3 (1.4)	.622
AMNESIA	1 (0.9)	1 (0.9)	2 (0.9)	1.00
APATHY	1 (0.9)	0	1 (0.5)	.498
BUCCOGLOSSAL SYNDROME	1 (0.9)	0	1 (0.5)	.498
DELUSIONS	1 (0.9)	0	1 (0.5)	.498
EMOTIONAL LABILITY	1 (0.9)	0	1 (0.5)	.498
HALLUCINATIONS	1 (0.9)	0	1 (0.5)	.498
HYPERTONIA	1 (0.9)	1 (0.9)	2 (0.9)	1.00
MANIC REACTION	1 (0.9)	0	1 (0.5)	.498
NEUROSIS	1 (0.9)	0	1 (0.5)	.498
HYPESTHESIA	0	1 (0.9)	1 (0.5)	1.00
VERTIGO	0	1 (0.9)	1 (0.5)	1.00

RMP.B1YP.JCLLIB2(AES2JEAB)
RMP.B1YO.HCJEREP(AES2JEAB)
* Frequencies are analyzed using a Fisher’s Exact test.
XAES0002

Table 14.41. Treatment-Emergent Non-Solicited Adverse Events Incidence by Body System All Randomized Patients Subchronic Treatment Phase (Study Periods III-V) B1Y-MC-HCJE (continued)

Body System: RESPIRATORY SYSTEM

Event Classification	Flx (N=109) n (%)	Placebo (N=110) n (%)	Total (N=219) n (%)	p-Value*
PATIENTS WITH >= 1 TESS	61 (56.0)	42 (38.2)	103 (47.0)	.010
PATIENTS WITH NO TESS	48 (44.0)	68 (61.8)	116 (53.0)	.010
RHINITIS	34 (31.2)	29 (26.4)	63 (28.8)	.458
PHARYNGITIS	21 (19.3)	14 (12.7)	35 (16.0)	.202
COUGH INCREASED	16 (14.7)	9 (8.2)	25 (11.4)	.143
EPISTAXIS	5 (4.6)	2 (1.8)	7 (3.2)	.280
SINUSITIS	4 (3.7)	2 (1.8)	6 (2.7)	.446
ASTHMA	3 (2.8)	0	3 (1.4)	.122
BRONCHITIS	2 (1.8)	2 (1.8)	4 (1.8)	1.00
YAWN	2 (1.8)	0	2 (0.9)	.247
DYSPNEA	1 (0.9)	0	1 (0.5)	.498
LARYNGITIS	1 (0.9)	1 (0.9)	2 (0.9)	1.00
LUNG DISORDER	1 (0.9)	0	1 (0.5)	.498
PNEUMONIA	1 (0.9)	0	1 (0.5)	.498
HYPOVENTILATION	0	1 (0.9)	1 (0.5)	1.00

RMP.B1YP.JCLLIB2(AES2JEAB)
RMP.B1YO.HCJEREP(AES2JEAB)
* Frequencies are analyzed using a Fisher’s Exact test.
XAES0002

Table 14.41. Treatment-Emergent Non-Solicited Adverse Events Incidence by Body System All Randomized Patients Subchronic Treatment Phase (Study Periods III-V) B1Y-MC-HCJE (continued)

Body System: SKIN AND APPENDAGES

Event Classification	Flx (N=109) n (%)	Placebo (N=110) n (%)	Total (N=219) n (%)	p-Value*
PATIENTS WITH >= 1 TESS	23 (21.1)	18 (16.4)	41 (18.7)	.391
PATIENTS WITH NO TESS	86 (78.9)	92 (83.6)	178 (81.3)	.391
RASH	13 (11.9)	10 (9.1)	23 (10.5)	.517
PRURITUS	6 (5.5)	6 (5.5)	12 (5.5)	1.00
CONTACT DERMATITIS	3 (2.8)	0	3 (1.4)	.122
DRY SKIN	2 (1.8)	3 (2.7)	5 (2.3)	1.00
SWEATING	2 (1.8)	0	2 (0.9)	.247
FUNGAL DERMATITIS	1 (0.9)	1 (0.9)	2 (0.9)	1.00
HERPES SIMPLEX	1 (0.9)	0	1 (0.5)	.498
MACULOPAPULAR RASH	1 (0.9)	1 (0.9)	2 (0.9)	1.00
VESICULOBULLOUS RASH	1 (0.9)	0	1 (0.5)	.498
ACNE	0	1 (0.9)	1 (0.5)	1.00
ALOPECIA	0	1 (0.9)	1 (0.5)	1.00
PUSTULAR RASH	0	1 (0.9)	1 (0.5)	1.00
SKIN DISCOLORATION	0	1 (0.9)	1 (0.5)	1.00
SKIN ULCER	0	1 (0.9)	1 (0.5)	1.00
SUBCUTANEOUS NODULE	0	1 (0.9)	1 (0.5)	1.00

RMP.B1YP.JCLLIB2(AES2JEAB)
RMP.B1YO.HCJEREP(AES2JEAB)
* Frequencies are analyzed using a Fisher’s Exact test.
XAES0002

Table 14.41. Treatment-Emergent Non-Solicited Adverse Events Incidence by Body System All Randomized Patients Subchronic Treatment Phase (Study Periods III-V) B1Y-MC-HCJE (continued)

Body System: SPECIAL SENSES

Event Classification	Flx (N=109) n (%)	Placebo (N=110) n (%)	Total (N=219) n (%)	p-Value*
PATIENTS WITH >= 1 TESS	16 (14.7)	4 (3.6)	20 (9.1)	.005
PATIENTS WITH NO TESS	93 (85.3)	106 (96.4)	199 (90.9)	.005
EAR PAIN	6 (5.5)	3 (2.7)	9 (4.1)	.332
EAR DISORDER	2 (1.8)	1 (0.9)	3 (1.4)	.622
EYE DISORDER	2 (1.8)	0	2 (0.9)	.247
OTITIS EXTERNA	2 (1.8)	1 (0.9)	3 (1.4)	.622
AMBLYOPIA	1 (0.9)	0	1 (0.5)	.498
EYE PAIN	1 (0.9)	0	1 (0.5)	.498
OTITIS MEDIA	1 (0.9)	0	1 (0.5)	.498
TINNITUS	1 (0.9)	0	1 (0.5)	.498

RMP.B1YP.JCLLIB2(AES2JEAB)
RMP.B1YO.HCJEREP(AES2JEAB)
* Frequencies are analyzed using a Fisher’s Exact test.
XAES0002

Table 14.41. Treatment-Emergent Non-Solicited Adverse Events Incidence by Body System All Randomized Patients Subchronic Treatment Phase (Study Periods III-V) B1Y-MC-HCJE (concluded)

Body System: UROGENITAL SYSTEM

Event Classification	Flx (N=109) n (%)	Placebo (N=110) n (%)	Total (N=219) n (%)	p-Value*
PATIENTS WITH >= 1 TESS	7 (6.4)	11 (10.0)	18 (8.2)	.462
PATIENTS WITH NO TESS	102 (93.6)	99 (90.0)	201 (91.8)	.462
DYSMENORRHEA	4 (3.7)	4 (3.6)	8 (3.7)	1.00
ENDOMETRIAL HYPERPLASIA	1 (0.9)	0	1 (0.5)	.498
URINARY FREQUENCY	1 (0.9)	2 (1.8)	3 (1.4)	1.00
URINARY TRACT INFECTION	1 (0.9)	1 (0.9)	2 (0.9)	1.00
BILIRUBINURIA	0	1 (0.9)	1 (0.5)	1.00
CYSTITIS	0	1 (0.9)	1 (0.5)	1.00
DYSURIA	0	1 (0.9)	1 (0.5)	1.00
LEUKORRHEA	0	1 (0.9)	1 (0.5)	1.00
MENORRHAGIA	0	1 (0.9)	1 (0.5)	1.00
METRORRHAGIA	0	1 (0.9)	1 (0.5)	1.00

RMP.B1YP.JCLLIB2(AES2JEAB)
RMP.B1YO.HCJEREP(AES2JEAB)
* Frequencies are analyzed using a Fisher's Exact test.
XAES0002

14.3.1.2.2. Treatment-Emergent Non-Solicited Adverse Events by Maximum Severity

The incidence of treatment-emergent non-solicited adverse events by maximum severity for the subchronic treatment phase is presented in Table 14.42. This analysis accurately measures the severity of adverse events and comparison to baseline events, and therefore points out clinically relevant changes in adverse events. Overall, the majority of reported treatment-emergent non-solicited adverse events were mild or moderate in severity. There were no statistically significant differences between treatment groups in the incidence of treatment-emergent adverse events classified as severe.

Table 14.42. Treatment-Emergent Non-Solicited Adverse Events Incidence by Maximum Severity All Randomized Patients Subchronic Treatment Phase (Study Periods III-V) B1Y-MC-HCJE

Maximum Severity	Flx (N=109) n (%)	Placebo (N=110) n (%)	Total (N=219) n (%)	p-Value*
PATIENTS WITH >= 1 TESS				
Mild	23 (21.1)	23 (20.9)	46 (21.0)	
Moderate	56 (51.4)	46 (41.8)	102 (46.6)	
Severe	22 (20.2)	18 (16.4)	40 (18.3)	.489
Total	101 (92.7)	87 (79.1)	188 (85.8)	.006
HEADACHE				
Mild	19 (17.4)	6 (5.5)	25 (11.4)	
Moderate	14 (12.8)	13 (11.8)	27 (12.3)	
Severe	4 (3.7)	2 (1.8)	6 (2.7)	.446
Total	37 (33.9)	21 (19.1)	58 (26.5)	.014
RHINITIS				
Mild	23 (21.1)	20 (18.2)	43 (19.6)	
Moderate	10 (9.2)	9 (8.2)	19 (8.7)	
Severe	1 (0.9)	0	1 (0.5)	.498
Total	34 (31.2)	29 (26.4)	63 (28.8)	.458
ABDOMINAL PAIN				
Mild	14 (12.8)	10 (9.1)	24 (11.0)	
Moderate	7 (6.4)	10 (9.1)	17 (7.8)	
Severe	1 (0.9)	2 (1.8)	3 (1.4)	1.00
Total	22 (20.2)	22 (20.0)	44 (20.1)	1.00
PHARYNGITIS				
Mild	11 (10.1)	9 (8.2)	20 (9.1)	
Moderate	9 (8.3)	5 (4.5)	14 (6.4)	
Severe	1 (0.9)	0	1 (0.5)	.498
Total	21 (19.3)	14 (12.7)	35 (16.0)	.202

RMP.B1YP.JCLLIB2(AES8JEAB)
RMP.B1YO.HCJEREP(AES8JEAB)
* Frequencies are analyzed using a Fisher's Exact test.
XAES0008

Table 14.42. Treatment-Emergent Non-Solicited Adverse Events Incidence by Maximum Severity All Randomized Patients Subchronic Treatment Phase (Study Periods III-V) B1Y-MC-HCJE (continued)

Maximum Severity	Flx (N=109) n (%)	Placebo (N=110) n (%)	Total (N=219) n (%)	p-Value*
ACCIDENTAL INJURY				
Mild	9 (8.3)	6 (5.5)	15 (6.8)	
Moderate	10 (9.2)	3 (2.7)	13 (5.9)	
Severe	0	1 (0.9)	1 (0.5)	1.00
Total	19 (17.4)	10 (9.1)	29 (13.2)	.076
COUGH INCREASED				
Mild	8 (7.3)	7 (6.4)	15 (6.8)	
Moderate	6 (5.5)	2 (1.8)	8 (3.7)	
Severe	2 (1.8)	0	2 (0.9)	.247
Total	16 (14.7)	9 (8.2)	25 (11.4)	.143
DIARRHEA				
Mild	6 (5.5)	9 (8.2)	15 (6.8)	
Moderate	6 (5.5)	4 (3.6)	10 (4.6)	
Severe	2 (1.8)	0	2 (0.9)	.247
Total	14 (12.8)	13 (11.8)	27 (12.3)	.840
RASH				
Mild	10 (9.2)	6 (5.5)	16 (7.3)	
Moderate	3 (2.8)	3 (2.7)	6 (2.7)	
Severe	0	1 (0.9)	1 (0.5)	1.00
Total	13 (11.9)	10 (9.1)	23 (10.5)	.517
DIZZINESS				
Mild	10 (9.2)	6 (5.5)	16 (7.3)	
Moderate	1 (0.9)	1 (0.9)	2 (0.9)	
Severe	0	1 (0.9)	1 (0.5)	1.00
Total	11 (10.1)	8 (7.3)	19 (8.7)	.483

RMP.B1YP.JCLLIB2(AES8JEAB)
RMP.B1YO.HCJEREP(AES8JEAB)
* Frequencies are analyzed using a Fisher’s Exact test.
XAES0008

Table 14.42. Treatment-Emergent Non-Solicited Adverse Events Incidence by Maximum Severity All Randomized Patients Subchronic Treatment Phase (Study Periods III-V) B1Y-MC-HCJE (continued)

Maximum Severity	Flx (N=109) n (%)	Placebo (N=110) n (%)	Total (N=219) n (%)	p-Value*
NERVOUSNESS				
Mild	4 (3.7)	1 (0.9)	5 (2.3)	
Moderate	4 (3.7)	3 (2.7)	7 (3.2)	
Severe	3 (2.8)	2 (1.8)	5 (2.3)	.683
Total	11 (10.1)	6 (5.5)	17 (7.8)	.218
VOMITING				
Mild	7 (6.4)	7 (6.4)	14 (6.4)	
Moderate	3 (2.8)	4 (3.6)	7 (3.2)	
Severe	1 (0.9)	1 (0.9)	2 (0.9)	1.00
Total	11 (10.1)	12 (10.9)	23 (10.5)	1.00
ANOREXIA				
Mild	7 (6.4)	6 (5.5)	13 (5.9)	
Moderate	3 (2.8)	3 (2.7)	6 (2.7)	
Severe	0	0	0	
Total	10 (9.2)	9 (8.2)	19 (8.7)	.815
ASTHENIA				
Mild	2 (1.8)	2 (1.8)	4 (1.8)	
Moderate	7 (6.4)	2 (1.8)	9 (4.1)	
Severe	1 (0.9)	3 (2.7)	4 (1.8)	.622
Total	10 (9.2)	7 (6.4)	17 (7.8)	.462
FEVER				
Mild	8 (7.3)	2 (1.8)	10 (4.6)	
Moderate	2 (1.8)	4 (3.6)	6 (2.7)	
Severe	0	2 (1.8)	2 (0.9)	.498
Total	10 (9.2)	8 (7.3)	18 (8.2)	.632

RMP.B1YP.JCLLIB2(AES8JEAB)
RMP.B1YO.HCJEREP(AES8JEAB)
* Frequencies are analyzed using a Fisher’s Exact test.
XAES0008

Table 14.42. Treatment-Emergent Non-Solicited Adverse Events Incidence by Maximum Severity All Randomized Patients Subchronic Treatment Phase (Study Periods III-V) B1Y-MC-HCJE (continued)

Maximum Severity	Flx (N=109) n	(%)	Placebo (N=110) n	(%)	Total (N=219) n	(%)	p-Value*
PAIN							
Mild	9	(8.3)	9	(8.2)	18	(8.2)	
Moderate	1	(0.9)	3	(2.7)	4	(1.8)	
Severe	0		0		0		
Total	10	(9.2)	12	(10.9)	22	(10.0)	.823
NAUSEA							
Mild	4	(3.7)	7	(6.4)	11	(5.0)	
Moderate	3	(2.8)	4	(3.6)	7	(3.2)	
Severe	2	(1.8)	0		2	(0.9)	.247
Total	9	(8.3)	11	(10.0)	20	(9.1)	.815
ABNORMAL DREAMS							
Mild	3	(2.8)	1	(0.9)	4	(1.8)	
Moderate	2	(1.8)	1	(0.9)	3	(1.4)	
Severe	2	(1.8)	1	(0.9)	3	(1.4)	.622
Total	7	(6.4)	3	(2.7)	10	(4.6)	.215
BACK PAIN							
Mild	6	(5.5)	4	(3.6)	10	(4.6)	
Moderate	0		0		0		
Severe	0		1	(0.9)	1	(0.5)	1.00
Total	6	(5.5)	5	(4.5)	11	(5.0)	.768
DRY MOUTH							
Mild	4	(3.7)	5	(4.5)	9	(4.1)	
Moderate	2	(1.8)	1	(0.9)	3	(1.4)	
Severe	0		0		0		
Total	6	(5.5)	6	(5.5)	12	(5.5)	1.00

RMP.B1YP.JCLLIB2(AES8JEAB)
RMP.B1YO.HCJEREP(AES8JEAB)
* Frequencies are analyzed using a Fisher’s Exact test.
XAES0008

Table 14.42. Treatment-Emergent Non-Solicited Adverse Events Incidence by Maximum Severity All Randomized Patients Subchronic Treatment Phase (Study Periods III-V) B1Y-MC-HCJE (continued)

Maximum Severity	Flx (N=109) n	(%)	Placebo (N=110) n	(%)	Total (N=219) n	(%)	p-Value*
EAR PAIN							
Mild	4	(3.7)	2	(1.8)	6	(2.7)	
Moderate	2	(1.8)	0		2	(0.9)	
Severe	0		1	(0.9)	1	(0.5)	1.00
Total	6	(5.5)	3	(2.7)	9	(4.1)	.332
INSOMNIA							
Mild	2	(1.8)	0		2	(0.9)	
Moderate	1	(0.9)	3	(2.7)	4	(1.8)	
Severe	3	(2.8)	2	(1.8)	5	(2.3)	.683
Total	6	(5.5)	5	(4.5)	11	(5.0)	.768
PRURITUS							
Mild	3	(2.8)	5	(4.5)	8	(3.7)	
Moderate	2	(1.8)	1	(0.9)	3	(1.4)	
Severe	1	(0.9)	0		1	(0.5)	.498
Total	6	(5.5)	6	(5.5)	12	(5.5)	1.00
EPISTAXIS							
Mild	2	(1.8)	0		2	(0.9)	
Moderate	3	(2.8)	2	(1.8)	5	(2.3)	
Severe	0		0		0		
Total	5	(4.6)	2	(1.8)	7	(3.2)	.280
HOSTILITY							
Mild	1	(0.9)	1	(0.9)	2	(0.9)	
Moderate	2	(1.8)	3	(2.7)	5	(2.3)	
Severe	2	(1.8)	1	(0.9)	3	(1.4)	.622
Total	5	(4.6)	5	(4.5)	10	(4.6)	1.00

RMP.B1YP.JCLLIB2(AES8JEAB)
RMP.B1YO.HCJEREP(AES8JEAB)
* Frequencies are analyzed using a Fisher’s Exact test.
XAES0008

Table 14.42. Treatment-Emergent Non-Solicited Adverse Events Incidence by Maximum Severity All Randomized Patients Subchronic Treatment Phase (Study Periods III-V) B1Y-MC-HCJE (continued)

Maximum Severity	Flx (N=109) n	(%)	Placebo (N=110) n	(%)	Total (N=219) n	(%)	p-Value*
INFECTION							
Mild	4	(3.7)	2	(1.8)	6	(2.7)	
Moderate	1	(0.9)	1	(0.9)	2	(0.9)	
Severe	0		2	(1.8)	2	(0.9)	.498
Total	5	(4.6)	5	(4.5)	10	(4.6)	1.00
PERSONALITY DISORDER							
Mild	2	(1.8)	1	(0.9)	3	(1.4)	
Moderate	2	(1.8)	1	(0.9)	3	(1.4)	
Severe	1	(0.9)	0		1	(0.5)	.498
Total	5	(4.6)	2	(1.8)	7	(3.2)	.280
SOMNOLENCE							
Mild	3	(2.8)	2	(1.8)	5	(2.3)	
Moderate	2	(1.8)	2	(1.8)	4	(1.8)	
Severe	0		0		0		
Total	5	(4.6)	4	(3.6)	9	(4.1)	.748
AGITATION							
Mild	2	(1.8)	0		2	(0.9)	
Moderate	0		0		0		
Severe	2	(1.8)	0		2	(0.9)	.247
Total	4	(3.7)	0		4	(1.8)	.060
ALLERGIC REACTION							
Mild	2	(1.8)	0		2	(0.9)	
Moderate	0		2	(1.8)	2	(0.9)	
Severe	2	(1.8)	0		2	(0.9)	.247
Total	4	(3.7)	2	(1.8)	6	(2.7)	.446

RMP.B1YP.JCLLIB2(AES8JEAB)
RMP.B1YO.HCJEREP(AES8JEAB)
* Frequencies are analyzed using a Fisher’s Exact test.
XAES0008

Table 14.42. Treatment-Emergent Non-Solicited Adverse Events Incidence by Maximum Severity All Randomized Patients Subchronic Treatment Phase (Study Periods III-V) B1Y-MC-HCJE (continued)

Maximum Severity	Flx (N=109) n	(%)	Placebo (N=110) n	(%)	Total (N=219) n	(%)	p-Value*
DYSMENORRHEA							
Mild	2	(1.8)	4	(3.6)	6	(2.7)	
Moderate	2	(1.8)	0		2	(0.9)	
Severe	0		0		0		
Total	4	(3.7)	4	(3.6)	8	(3.7)	1.00
DYSPEPSIA							
Mild	3	(2.8)	4	(3.6)	7	(3.2)	
Moderate	1	(0.9)	1	(0.9)	2	(0.9)	
Severe	0		0		0		
Total	4	(3.7)	5	(4.5)	9	(4.1)	1.00
ECCHYMOSIS							
Mild	1	(0.9)	1	(0.9)	2	(0.9)	
Moderate	3	(2.8)	1	(0.9)	4	(1.8)	
Severe	0		0		0		
Total	4	(3.7)	2	(1.8)	6	(2.7)	.446
FLU SYNDROME							
Mild	3	(2.8)	1	(0.9)	4	(1.8)	
Moderate	1	(0.9)	2	(1.8)	3	(1.4)	
Severe	0		0		0		
Total	4	(3.7)	3	(2.7)	7	(3.2)	.721
HYPERKINESIA							
Mild	1	(0.9)	0		1	(0.5)	
Moderate	1	(0.9)	1	(0.9)	2	(0.9)	
Severe	2	(1.8)	0		2	(0.9)	.247
Total	4	(3.7)	1	(0.9)	5	(2.3)	.212

RMP.B1YP.JCLLIB2(AES8JEAB)
RMP.B1YO.HCJEREP(AES8JEAB)
* Frequencies are analyzed using a Fisher’s Exact test.
XAES0008

Table 14.42. Treatment-Emergent Non-Solicited Adverse Events Incidence by Maximum Severity All Randomized Patients Subchronic Treatment Phase (Study Periods III-V) B1Y-MC-HCJE (continued)

Maximum Severity	Flx (N=109) n	(%)	Placebo (N=110) n	(%)	Total (N=219) n	(%)	p-Value*
PHOTOSENSITIVITY REACTION							
Mild	2	(1.8)	0		2	(0.9)	
Moderate	2	(1.8)	1	(0.9)	3	(1.4)	
Severe	0		0		0		
Total	4	(3.7)	1	(0.9)	5	(2.3)	.212
SINUSITIS							
Mild	0		0		0		
Moderate	4	(3.7)	2	(1.8)	6	(2.7)	
Severe	0		0		0		
Total	4	(3.7)	2	(1.8)	6	(2.7)	.446
AKATHISIA							
Mild	3	(2.8)	0		3	(1.4)	
Moderate	0		0		0		
Severe	0		0		0		
Total	3	(2.8)	0		3	(1.4)	.122
ASTHMA							
Mild	0		0		0		
Moderate	1	(0.9)	0		1	(0.5)	
Severe	2	(1.8)	0		2	(0.9)	.247
Total	3	(2.8)	0		3	(1.4)	.122
CHEST PAIN							
Mild	2	(1.8)	1	(0.9)	3	(1.4)	
Moderate	1	(0.9)	1	(0.9)	2	(0.9)	
Severe	0		0		0		
Total	3	(2.8)	2	(1.8)	5	(2.3)	.683

RMP.B1YP.JCLLIB2(AES8JEAB)
RMP.B1YO.HCJEREP(AES8JEAB)
* Frequencies are analyzed using a Fisher’s Exact test.
XAES0008

Table 14.42. Treatment-Emergent Non-Solicited Adverse Events Incidence by Maximum Severity All Randomized Patients Subchronic Treatment Phase (Study Periods III-V) B1Y-MC-HCJE (continued)

Maximum Severity	Flx (N=109) n	(%)	Placebo (N=110) n	(%)	Total (N=219) n	(%)	p-Value*
CONSTIPATION							
Mild	1	(0.9)	4	(3.6)	5	(2.3)	
Moderate	1	(0.9)	2	(1.8)	3	(1.4)	
Severe	1	(0.9)	0		1	(0.5)	.498
Total	3	(2.8)	6	(5.5)	9	(4.1)	.499
CONTACT DERMATITIS							
Mild	1	(0.9)	0		1	(0.5)	
Moderate	2	(1.8)	0		2	(0.9)	
Severe	0		0		0		
Total	3	(2.8)	0		3	(1.4)	.122
DEPRESSION							
Mild	0		0		0		
Moderate	1	(0.9)	2	(1.8)	3	(1.4)	
Severe	2	(1.8)	0		2	(0.9)	.247
Total	3	(2.8)	2	(1.8)	5	(2.3)	.683
MYALGIA							
Mild	2	(1.8)	3	(2.7)	5	(2.3)	
Moderate	1	(0.9)	3	(2.7)	4	(1.8)	
Severe	0		0		0		
Total	3	(2.8)	6	(5.5)	9	(4.1)	.499
NECK PAIN							
Mild	2	(1.8)	1	(0.9)	3	(1.4)	
Moderate	1	(0.9)	0		1	(0.5)	
Severe	0		0		0		
Total	3	(2.8)	1	(0.9)	4	(1.8)	.369

RMP.B1YP.JCLLIB2(AES8JEAB)
RMP.B1YO.HCJEREP(AES8JEAB)
* Frequencies are analyzed using a Fisher’s Exact test.
XAES0008

Table 14.42. Treatment-Emergent Non-Solicited Adverse Events Incidence by Maximum Severity All Randomized Patients Subchronic Treatment Phase (Study Periods III-V) B1Y-MC-HCJE (continued)

Maximum Severity	Flx (N=109) n	(%)	Placebo (N=110) n	(%)	Total (N=219) n	(%)	p-Value*
SPEECH DISORDER							
Mild	1	(0.9)	2	(1.8)	3	(1.4)	
Moderate	1	(0.9)	0		1	(0.5)	
Severe	1	(0.9)	0		1	(0.5)	.498
Total	3	(2.8)	2	(1.8)	5	(2.3)	.683
TREMOR							
Mild	2	(1.8)	1	(0.9)	3	(1.4)	
Moderate	1	(0.9)	0		1	(0.5)	
Severe	0		0		0		
Total	3	(2.8)	1	(0.9)	4	(1.8)	.369
ACUTE BRAIN SYNDROME							
Mild	0		0		0		
Moderate	2	(1.8)	0		2	(0.9)	
Severe	0		0		0		
Total	2	(1.8)	0		2	(0.9)	.247
ANXIETY							
Mild	0		0		0		
Moderate	1	(0.9)	0		1	(0.5)	
Severe	1	(0.9)	0		1	(0.5)	.498
Total	2	(1.8)	0		2	(0.9)	.247
BRONCHITIS							
Mild	0		0		0		
Moderate	2	(1.8)	2	(1.8)	4	(1.8)	
Severe	0		0		0		
Total	2	(1.8)	2	(1.8)	4	(1.8)	1.00

RMP.B1YP.JCLLIB2(AES8JEAB)
RMP.B1YO.HCJEREP(AES8JEAB)
* Frequencies are analyzed using a Fisher's Exact test.
XAES0008

Table 14.42. Treatment-Emergent Non-Solicited Adverse Events Incidence by Maximum Severity All Randomized Patients Subchronic Treatment Phase (Study Periods III-V) B1Y-MC-HCJE (continued)

Maximum Severity	Flx (N=109) n	(%)	Placebo (N=110) n	(%)	Total (N=219) n	(%)	p-Value*
CHILLS							
Mild	2	(1.8)	1	(0.9)	3	(1.4)	
Moderate	0		0		0		
Severe	0		0		0		
Total	2	(1.8)	1	(0.9)	3	(1.4)	.622
DRY SKIN							
Mild	2	(1.8)	2	(1.8)	4	(1.8)	
Moderate	0		1	(0.9)	1	(0.5)	
Severe	0		0		0		
Total	2	(1.8)	3	(2.7)	5	(2.3)	1.00
EAR DISORDER							
Mild	1	(0.9)	0		1	(0.5)	
Moderate	1	(0.9)	1	(0.9)	2	(0.9)	
Severe	0		0		0		
Total	2	(1.8)	1	(0.9)	3	(1.4)	.622
EUPHORIA							
Mild	1	(0.9)	0		1	(0.5)	
Moderate	1	(0.9)	0		1	(0.5)	
Severe	0		0		0		
Total	2	(1.8)	0		2	(0.9)	.247
EYE DISORDER							
Mild	2	(1.8)	0		2	(0.9)	
Moderate	0		0		0		
Severe	0		0		0		
Total	2	(1.8)	0		2	(0.9)	.247

RMP.B1YP.JCLLIB2(AES8JEAB)
RMP.B1YO.HCJEREP(AES8JEAB)
* Frequencies are analyzed using a Fisher’s Exact test.
XAES0008

Table 14.42. Treatment-Emergent Non-Solicited Adverse Events Incidence by Maximum Severity All Randomized Patients Subchronic Treatment Phase (Study Periods III-V) B1Y-MC-HCJE (continued)

Maximum Severity	Flx (N=109) n	(%)	Placebo (N=110) n	(%)	Total (N=219) n	(%)	p-Value*
GASTROENTERITIS							
Mild	2	(1.8)	0		2	(0.9)	
Moderate	0		0		0		
Severe	0		0		0		
Total	2	(1.8)	0		2	(0.9)	.247
INCREASED APPETITE							
Mild	1	(0.9)	3	(2.7)	4	(1.8)	
Moderate	1	(0.9)	0		1	(0.5)	
Severe	0		0		0		
Total	2	(1.8)	3	(2.7)	5	(2.3)	1.00
NECK RIGIDITY							
Mild	2	(1.8)	1	(0.9)	3	(1.4)	
Moderate	0		0		0		
Severe	0		0		0		
Total	2	(1.8)	1	(0.9)	3	(1.4)	.622
OTITIS EXTERNA							
Mild	1	(0.9)	0		1	(0.5)	
Moderate	1	(0.9)	1	(0.9)	2	(0.9)	
Severe	0		0		0		
Total	2	(1.8)	1	(0.9)	3	(1.4)	.622
SLEEP DISORDER							
Mild	2	(1.8)	0		2	(0.9)	
Moderate	0		0		0		
Severe	0		0		0		
Total	2	(1.8)	0		2	(0.9)	.247

RMP.B1YP.JCLLIB2(AES8JEAB)
RMP.B1YO.HCJEREP(AES8JEAB)
* Frequencies are analyzed using a Fisher’s Exact test.
XAES0008

Table 14.42. Treatment-Emergent Non-Solicited Adverse Events Incidence by Maximum Severity All Randomized Patients Subchronic Treatment Phase (Study Periods III-V) B1Y-MC-HCJE (continued)

Maximum Severity	Flx (N=109) n	(%)	Placebo (N=110) n	(%)	Total (N=219) n	(%)	p-Value*
SURGICAL PROCEDURE							
Mild	1	(0.9)	0		1	(0.5)	
Moderate	1	(0.9)	2	(1.8)	3	(1.4)	
Severe	0		0		0		
Total	2	(1.8)	2	(1.8)	4	(1.8)	1.00
SWEATING							
Mild	1	(0.9)	0		1	(0.5)	
Moderate	1	(0.9)	0		1	(0.5)	
Severe	0		0		0		
Total	2	(1.8)	0		2	(0.9)	.247
THINKING ABNORMAL							
Mild	2	(1.8)	1	(0.9)	3	(1.4)	
Moderate	0		0		0		
Severe	0		0		0		
Total	2	(1.8)	1	(0.9)	3	(1.4)	.622
THIRST							
Mild	2	(1.8)	2	(1.8)	4	(1.8)	
Moderate	0		0		0		
Severe	0		0		0		
Total	2	(1.8)	2	(1.8)	4	(1.8)	1.00
TOOTH DISORDER							
Mild	1	(0.9)	0		1	(0.5)	
Moderate	1	(0.9)	0		1	(0.5)	
Severe	0		0		0		
Total	2	(1.8)	0		2	(0.9)	.247

RMP.B1YP.JCLLIB2(AES8JEAB)
RMP.B1YO.HCJEREP(AES8JEAB)
* Frequencies are analyzed using a Fisher’s Exact test.
XAES0008

Table 14.42. Treatment-Emergent Non-Solicited Adverse Events Incidence by Maximum Severity All Randomized Patients Subchronic Treatment Phase (Study Periods III-V) B1Y-MC-HCJE (continued)

Maximum Severity	Flx (N=109) n	(%)	Placebo (N=110) n	(%)	Total (N=219) n	(%)	p-Value*
WEIGHT LOSS							
Mild	2	(1.8)	0		2	(0.9)	
Moderate	0		1	(0.9)	1	(0.5)	
Severe	0		0		0		
Total	2	(1.8)	1	(0.9)	3	(1.4)	.622
YAWN							
Mild	2	(1.8)	0		2	(0.9)	
Moderate	0		0		0		
Severe	0		0		0		
Total	2	(1.8)	0		2	(0.9)	.247
AMBLYOPIA							
Mild	1	(0.9)	0		1	(0.5)	
Moderate	0		0		0		
Severe	0		0		0		
Total	1	(0.9)	0		1	(0.5)	.498
AMNESIA							
Mild	1	(0.9)	1	(0.9)	2	(0.9)	
Moderate	0		0		0		
Severe	0		0		0		
Total	1	(0.9)	1	(0.9)	2	(0.9)	1.00
ANEMIA							
Mild	1	(0.9)	0		1	(0.5)	
Moderate	0		0		0		
Severe	0		0		0		
Total	1	(0.9)	0		1	(0.5)	.498

RMP.B1YP.JCLLIB2(AES8JEAB)
RMP.B1YO.HCJEREP(AES8JEAB)
* Frequencies are analyzed using a Fisher's Exact test.
XAES0008

Table 14.42. Treatment-Emergent Non-Solicited Adverse Events Incidence by Maximum Severity All Randomized Patients Subchronic Treatment Phase (Study Periods III-V) B1Y-MC-HCJE (continued)

Maximum Severity	Flx (N=109) n (%)	Placebo (N=110) n (%)	Total (N=219) n (%)	p-Value*
APATHY				
Mild	0	0	0	
Moderate	1 (0.9)	0	1 (0.5)	
Severe	0	0	0	
Total	1 (0.9)	0	1 (0.5)	.498
BRADYCARDIA				
Mild	1 (0.9)	1 (0.9)	2 (0.9)	
Moderate	0	0	0	
Severe	0	0	0	
Total	1 (0.9)	1 (0.9)	2 (0.9)	1.00
BUCCOGLOSSAL SYNDROME				
Mild	0	0	0	
Moderate	0	0	0	
Severe	1 (0.9)	0	1 (0.5)	.498
Total	1 (0.9)	0	1 (0.5)	.498
CARDIOVASCULAR DISORDER				
Mild	1 (0.9)	0	1 (0.5)	
Moderate	0	0	0	
Severe	0	0	0	
Total	1 (0.9)	0	1 (0.5)	.498
DELUSIONS				
Mild	0	0	0	
Moderate	0	0	0	
Severe	1 (0.9)	0	1 (0.5)	.498
Total	1 (0.9)	0	1 (0.5)	.498

RMP.B1YP.JCLLIB2(AES8JEAB)
RMP.B1YO.HCJEREP(AES8JEAB)
* Frequencies are analyzed using a Fisher’s Exact test.
XAES0008

Table 14.42. Treatment-Emergent Non-Solicited Adverse Events Incidence by Maximum Severity All Randomized Patients Subchronic Treatment Phase (Study Periods III-V) B1Y-MC-HCJE (continued)

Maximum Severity	Flx (N=109) n	(%)	Placebo (N=110) n	(%)	Total (N=219) n	(%)	p-Value*
DYSPHAGIA							
Mild	0		1	(0.9)	1	(0.5)	
Moderate	1	(0.9)	0		1	(0.5)	
Severe	0		0		0		
Total	1	(0.9)	1	(0.9)	2	(0.9)	1.00
DYSPNEA							
Mild	1	(0.9)	0		1	(0.5)	
Moderate	0		0		0		
Severe	0		0		0		
Total	1	(0.9)	0		1	(0.5)	.498
EMOTIONAL LABILITY							
Mild	0		0		0		
Moderate	1	(0.9)	0		1	(0.5)	
Severe	0		0		0		
Total	1	(0.9)	0		1	(0.5)	.498
ENDOCRINE DISORDER							
Mild	0		0		0		
Moderate	1	(0.9)	0		1	(0.5)	
Severe	0		0		0		
Total	1	(0.9)	0		1	(0.5)	.498
ENDOMETRIAL HYPERPLASIA							
Mild	0		0		0		
Moderate	1	(0.9)	0		1	(0.5)	
Severe	0		0		0		
Total	1	(0.9)	0		1	(0.5)	.498

RMP.B1YP.JCLLIB2(AES8JEAB)
RMP.B1YO.HCJEREP(AES8JEAB)
* Frequencies are analyzed using a Fisher’s Exact test.
XAES0008

Table 14.42. Treatment-Emergent Non-Solicited Adverse Events Incidence by Maximum Severity All Randomized Patients Subchronic Treatment Phase (Study Periods III-V) B1Y-MC-HCJE (continued)

Maximum Severity	Flx (N=109) n (%)	Placebo (N=110) n (%)	Total (N=219) n (%)	p-Value*
EYE PAIN				
Mild	1 (0.9)	0	1 (0.5)	
Moderate	0	0	0	
Severe	0	0	0	
Total	1 (0.9)	0	1 (0.5)	.498
FECAL INCONTINENCE				
Mild	0	0	0	
Moderate	1 (0.9)	0	1 (0.5)	
Severe	0	0	0	
Total	1 (0.9)	0	1 (0.5)	.498
FLATULENCE				
Mild	0	0	0	
Moderate	0	0	0	
Severe	1 (0.9)	0	1 (0.5)	.498
Total	1 (0.9)	0	1 (0.5)	.498
FUNGAL DERMATITIS				
Mild	0	1 (0.9)	1 (0.5)	
Moderate	1 (0.9)	0	1 (0.5)	
Severe	0	0	0	
Total	1 (0.9)	1 (0.9)	2 (0.9)	1.00
GASTROINTESTINAL DISORDER				
Mild	1 (0.9)	0	1 (0.5)	
Moderate	0	1 (0.9)	1 (0.5)	
Severe	0	0	0	
Total	1 (0.9)	1 (0.9)	2 (0.9)	1.00

RMP.B1YP.JCLLIB2(AES8JEAB)
RMP.B1YO.HCJEREP(AES8JEAB)
* Frequencies are analyzed using a Fisher’s Exact test.
XAES0008

Table 14.42. Treatment-Emergent Non-Solicited Adverse Events Incidence by Maximum Severity All Randomized Patients Subchronic Treatment Phase (Study Periods III-V) B1Y-MC-HCJE (continued)

Maximum Severity	Flx (N=109) n	(%)	Placebo (N=110) n	(%)	Total (N=219) n	(%)	p-Value*
HALLUCINATIONS							
Mild	1	(0.9)	0		1	(0.5)	
Moderate	0		0		0		
Severe	0		0		0		
Total	1	(0.9)	0		1	(0.5)	.498
HEPATITIS NONSPECIFIC							
Mild	0		0		0		
Moderate	1	(0.9)	0		1	(0.5)	
Severe	0		0		0		
Total	1	(0.9)	0		1	(0.5)	.498
HEPATOMEGALY							
Mild	1	(0.9)	1	(0.9)	2	(0.9)	
Moderate	0		0		0		
Severe	0		0		0		
Total	1	(0.9)	1	(0.9)	2	(0.9)	1.00
HERPES SIMPLEX							
Mild	0		0		0		
Moderate	1	(0.9)	0		1	(0.5)	
Severe	0		0		0		
Total	1	(0.9)	0		1	(0.5)	.498
HYPERCHOLESTEREMIA							
Mild	1	(0.9)	0		1	(0.5)	
Moderate	0		0		0		
Severe	0		0		0		
Total	1	(0.9)	0		1	(0.5)	.498

RMP.B1YP.JCLLIB2(AES8JEAB)
RMP.B1YO.HCJEREP(AES8JEAB)
* Frequencies are analyzed using a Fisher’s Exact test.
XAES0008

Table 14.42. Treatment-Emergent Non-Solicited Adverse Events Incidence by Maximum Severity All Randomized Patients Subchronic Treatment Phase (Study Periods III-V) B1Y-MC-HCJE (continued)

Maximum Severity	Flx (N=109) n	(%)	Placebo (N=110) n	(%)	Total (N=219) n	(%)	p-Value*
HYPERTONIA							
Mild	0		1	(0.9)	1	(0.5)	
Moderate	1	(0.9)	0		1	(0.5)	
Severe	0		0		0		
Total	1	(0.9)	1	(0.9)	2	(0.9)	1.00
HYPOTENSION							
Mild	1	(0.9)	0		1	(0.5)	
Moderate	0		0		0		
Severe	0		0		0		
Total	1	(0.9)	0		1	(0.5)	.498
INCREASED SALIVATION							
Mild	1	(0.9)	0		1	(0.5)	
Moderate	0		1	(0.9)	1	(0.5)	
Severe	0		0		0		
Total	1	(0.9)	1	(0.9)	2	(0.9)	1.00
INTENTIONAL INJURY							
Mild	1	(0.9)	0		1	(0.5)	
Moderate	0		0		0		
Severe	0		1	(0.9)	1	(0.5)	1.00
Total	1	(0.9)	1	(0.9)	2	(0.9)	1.00
JOINT DISORDER							
Mild	0		0		0		
Moderate	1	(0.9)	0		1	(0.5)	
Severe	0		0		0		
Total	1	(0.9)	0		1	(0.5)	.498

RMP.B1YP.JCLLIB2(AES8JEAB)
RMP.B1YO.HCJEREP(AES8JEAB)
* Frequencies are analyzed using a Fisher’s Exact test.
XAES0008

Table 14.42. Treatment-Emergent Non-Solicited Adverse Events Incidence by Maximum Severity All Randomized Patients Subchronic Treatment Phase (Study Periods III-V) B1Y-MC-HCJE (continued)

Maximum Severity	Flx (N=109) n	(%)	Placebo (N=110) n	(%)	Total (N=219) n	(%)	p-Value*
LARYNGITIS							
Mild	1	(0.9)	0		1	(0.5)	
Moderate	0		1	(0.9)	1	(0.5)	
Severe	0		0		0		
Total	1	(0.9)	1	(0.9)	2	(0.9)	1.00
LEG CRAMPS							
Mild	0		2	(1.8)	2	(0.9)	
Moderate	1	(0.9)	0		1	(0.5)	
Severe	0		1	(0.9)	1	(0.5)	1.00
Total	1	(0.9)	3	(2.7)	4	(1.8)	.622
LEUKOPENIA							
Mild	1	(0.9)	0		1	(0.5)	
Moderate	0		0		0		
Severe	0		0		0		
Total	1	(0.9)	0		1	(0.5)	.498
LUNG DISORDER							
Mild	1	(0.9)	0		1	(0.5)	
Moderate	0		0		0		
Severe	0		0		0		
Total	1	(0.9)	0		1	(0.5)	.498
LYMPHADENOPATHY							
Mild	1	(0.9)	1	(0.9)	2	(0.9)	
Moderate	0		0		0		
Severe	0		0		0		
Total	1	(0.9)	1	(0.9)	2	(0.9)	1.00

RMP.B1YP.JCLLIB2(AES8JEAB)
RMP.B1YO.HCJEREP(AES8JEAB)
* Frequencies are analyzed using a Fisher’s Exact test.
XAES0008

Table 14.42. Treatment-Emergent Non-Solicited Adverse Events Incidence by Maximum Severity All Randomized Patients Subchronic Treatment Phase (Study Periods III-V) B1Y-MC-HCJE (continued)

Maximum Severity	Flx (N=109) n	(%)	Placebo (N=110) n	(%)	Total (N=219) n	(%)	p-Value*
MACULOPAPULAR RASH							
Mild	0		0		0		
Moderate	1	(0.9)	1	(0.9)	2	(0.9)	
Severe	0		0		0		
Total	1	(0.9)	1	(0.9)	2	(0.9)	1.00
MANIC REACTION							
Mild	0		0		0		
Moderate	0		0		0		
Severe	1	(0.9)	0		1	(0.5)	.498
Total	1	(0.9)	0		1	(0.5)	.498
MIGRAINE							
Mild	0		0		0		
Moderate	0		0		0		
Severe	1	(0.9)	1	(0.9)	2	(0.9)	1.00
Total	1	(0.9)	1	(0.9)	2	(0.9)	1.00
NEUROSIS							
Mild	1	(0.9)	0		1	(0.5)	
Moderate	0		0		0		
Severe	0		0		0		
Total	1	(0.9)	0		1	(0.5)	.498
OTITIS MEDIA							
Mild	0		0		0		
Moderate	1	(0.9)	0		1	(0.5)	
Severe	0		0		0		
Total	1	(0.9)	0		1	(0.5)	.498

RMP.B1YP.JCLLIB2(AES8JEAB)
RMP.B1YO.HCJEREP(AES8JEAB)
* Frequencies are analyzed using a Fisher’s Exact test.
XAES0008

Table 14.42. Treatment-Emergent Non-Solicited Adverse Events Incidence by Maximum Severity All Randomized Patients Subchronic Treatment Phase (Study Periods III-V) B1Y-MC-HCJE (continued)

Maximum Severity	Flx (N=109) n	(%)	Placebo (N=110) n	(%)	Total (N=219) n	(%)	p-Value*
OVERDOSE							
Mild	1	(0.9)	0		1	(0.5)	
Moderate	0		1	(0.9)	1	(0.5)	
Severe	0		0		0		
Total	1	(0.9)	1	(0.9)	2	(0.9)	1.00
PALPITATION							
Mild	1	(0.9)	0		1	(0.5)	
Moderate	0		1	(0.9)	1	(0.5)	
Severe	0		0		0		
Total	1	(0.9)	1	(0.9)	2	(0.9)	1.00
PNEUMONIA							
Mild	1	(0.9)	0		1	(0.5)	
Moderate	0		0		0		
Severe	0		0		0		
Total	1	(0.9)	0		1	(0.5)	.498
RECTAL HEMORRHAGE							
Mild	1	(0.9)	0		1	(0.5)	
Moderate	0		0		0		
Severe	0		0		0		
Total	1	(0.9)	0		1	(0.5)	.498
SINUS BRADYCARDIA							
Mild	1	(0.9)	0		1	(0.5)	
Moderate	0		0		0		
Severe	0		0		0		
Total	1	(0.9)	0		1	(0.5)	.498

RMP.B1YP.JCLLIB2(AES8JEAB)
RMP.B1YO.HCJEREP(AES8JEAB)
* Frequencies are analyzed using a Fisher’s Exact test.
XAES0008

Table 14.42. Treatment-Emergent Non-Solicited Adverse Events Incidence by Maximum Severity All Randomized Patients Subchronic Treatment Phase (Study Periods III-V) B1Y-MC-HCJE (continued)

Maximum Severity	Flx (N=109) n	(%)	Placebo (N=110) n	(%)	Total (N=219) n	(%)	p-Value*
SYNCOPE							
Mild	0		0		0		
Moderate	1	(0.9)	0		1	(0.5)	
Severe	0		0		0		
Total	1	(0.9)	0		1	(0.5)	.498
TACHYCARDIA							
Mild	1	(0.9)	0		1	(0.5)	
Moderate	0		0		0		
Severe	0		0		0		
Total	1	(0.9)	0		1	(0.5)	.498
THYROID DISORDER							
Mild	1	(0.9)	0		1	(0.5)	
Moderate	0		0		0		
Severe	0		0		0		
Total	1	(0.9)	0		1	(0.5)	.498
TINNITUS							
Mild	1	(0.9)	0		1	(0.5)	
Moderate	0		0		0		
Severe	0		0		0		
Total	1	(0.9)	0		1	(0.5)	.498
ULCERATIVE STOMATITIS							
Mild	0		0		0		
Moderate	1	(0.9)	0		1	(0.5)	
Severe	0		0		0		
Total	1	(0.9)	0		1	(0.5)	.498

RMP.B1YP.JCLLIB2(AES8JEAB)
RMP.B1YO.HCJEREP(AES8JEAB)
* Frequencies are analyzed using a Fisher's Exact test.
XAES0008

Table 14.42. Treatment-Emergent Non-Solicited Adverse Events Incidence by Maximum Severity All Randomized Patients Subchronic Treatment Phase (Study Periods III-V) B1Y-MC-HCJE (continued)

Maximum Severity	Flx (N=109) n	(%)	Placebo (N=110) n	(%)	Total (N=219) n	(%)	p-Value*
URINARY FREQUENCY							
Mild	1	(0.9)	2	(1.8)	3	(1.4)	
Moderate	0		0		0		
Severe	0		0		0		
Total	1	(0.9)	2	(1.8)	3	(1.4)	1.00
URINARY TRACT INFECTION							
Mild	0		0		0		
Moderate	1	(0.9)	1	(0.9)	2	(0.9)	
Severe	0		0		0		
Total	1	(0.9)	1	(0.9)	2	(0.9)	1.00
VASODILATATION							
Mild	1	(0.9)	0		1	(0.5)	
Moderate	0		0		0		
Severe	0		0		0		
Total	1	(0.9)	0		1	(0.5)	.498
VESICULOBULLOUS RASH							
Mild	1	(0.9)	0		1	(0.5)	
Moderate	0		0		0		
Severe	0		0		0		
Total	1	(0.9)	0		1	(0.5)	.498
ABDOMINAL SYNDROME ACUTE							
Mild	0		0		0		
Moderate	0		0		0		
Severe	0		1	(0.9)	1	(0.5)	1.00
Total	0		1	(0.9)	1	(0.5)	1.00

RMP.B1YP.JCLLIB2(AES8JEAB)
RMP.B1YO.HCJEREP(AES8JEAB)
* Frequencies are analyzed using a Fisher's Exact test.
XAES0008

Table 14.42. Treatment-Emergent Non-Solicited Adverse Events Incidence by Maximum Severity All Randomized Patients Subchronic Treatment Phase (Study Periods III-V) B1Y-MC-HCJE (continued)

Maximum Severity	Flx (N=109) n	(%)	Placebo (N=110) n	(%)	Total (N=219) n	(%)	p-Value*
ACNE							
Mild	0		1	(0.9)	1	(0.5)	
Moderate	0		0		0		
Severe	0		0		0		
Total	0		1	(0.9)	1	(0.5)	1.00
ALOPECIA							
Mild	0		1	(0.9)	1	(0.5)	
Moderate	0		0		0		
Severe	0		0		0		
Total	0		1	(0.9)	1	(0.5)	1.00
APHTHOUS STOMATITIS							
Mild	0		1	(0.9)	1	(0.5)	
Moderate	0		0		0		
Severe	0		0		0		
Total	0		1	(0.9)	1	(0.5)	1.00
ARTHRALGIA							
Mild	0		1	(0.9)	1	(0.5)	
Moderate	0		0		0		
Severe	0		0		0		
Total	0		1	(0.9)	1	(0.5)	1.00
BILIRUBINURIA							
Mild	0		0		0		
Moderate	0		0		0		
Severe	0		1	(0.9)	1	(0.5)	1.00
Total	0		1	(0.9)	1	(0.5)	1.00

RMP.B1YP.JCLLIB2(AES8JEAB)
RMP.B1YO.HCJEREP(AES8JEAB)
* Frequencies are analyzed using a Fisher's Exact test.
XAES0008

Table 14.42. Treatment-Emergent Non-Solicited Adverse Events Incidence by Maximum Severity All Randomized Patients Subchronic Treatment Phase (Study Periods III-V) B1Y-MC-HCJE (continued)

Maximum Severity	Flx (N=109) n	(%)	Placebo (N=110) n	(%)	Total (N=219) n	(%)	p-Value*
CYSTITIS							
Mild	0		0		0		
Moderate	0		1	(0.9)	1	(0.5)	
Severe	0		0		0		
Total	0		1	(0.9)	1	(0.5)	1.00
DEHYDRATION							
Mild	0		2	(1.8)	2	(0.9)	
Moderate	0		0		0		
Severe	0		0		0		
Total	0		2	(1.8)	2	(0.9)	.498
DYSURIA							
Mild	0		0		0		
Moderate	0		1	(0.9)	1	(0.5)	
Severe	0		0		0		
Total	0		1	(0.9)	1	(0.5)	1.00
FACE EDEMA							
Mild	0		1	(0.9)	1	(0.5)	
Moderate	0		0		0		
Severe	0		0		0		
Total	0		1	(0.9)	1	(0.5)	1.00
HYPESTHESIA							
Mild	0		1	(0.9)	1	(0.5)	
Moderate	0		0		0		
Severe	0		0		0		
Total	0		1	(0.9)	1	(0.5)	1.00

RMP.B1YP.JCLLIB2(AES8JEAB)
RMP.B1YO.HCJEREP(AES8JEAB)
* Frequencies are analyzed using a Fisher’s Exact test.
XAES0008

Table 14.42. Treatment-Emergent Non-Solicited Adverse Events Incidence by Maximum Severity All Randomized Patients Subchronic Treatment Phase (Study Periods III-V) B1Y-MC-HCJE (continued)

Maximum Severity	Flx (N=109) n	(%)	Placebo (N=110) n	(%)	Total (N=219) n	(%)	p-Value*
HYPOVENTILATION							
Mild	0		1	(0.9)	1	(0.5)	
Moderate	0		0		0		
Severe	0		0		0		
Total	0		1	(0.9)	1	(0.5)	1.00
LEUKORRHEA							
Mild	0		0		0		
Moderate	0		1	(0.9)	1	(0.5)	
Severe	0		0		0		
Total	0		1	(0.9)	1	(0.5)	1.00
LYMPHOCYTOSIS							
Mild	0		0		0		
Moderate	0		0		0		
Severe	0		1	(0.9)	1	(0.5)	1.00
Total	0		1	(0.9)	1	(0.5)	1.00
MENORRHAGIA							
Mild	0		1	(0.9)	1	(0.5)	
Moderate	0		0		0		
Severe	0		0		0		
Total	0		1	(0.9)	1	(0.5)	1.00
METRORRHAGIA							
Mild	0		1	(0.9)	1	(0.5)	
Moderate	0		0		0		
Severe	0		0		0		
Total	0		1	(0.9)	1	(0.5)	1.00

RMP.B1YP.JCLLIB2(AES8JEAB)
RMP.B1YO.HCJEREP(AES8JEAB)
* Frequencies are analyzed using a Fisher’s Exact test.
XAES0008

Table 14.42. Treatment-Emergent Non-Solicited Adverse Events Incidence by Maximum Severity All Randomized Patients Subchronic Treatment Phase (Study Periods III-V) B1Y-MC-HCJE (continued)

Maximum Severity	Flx (N=109) n	(%)	Placebo (N=110) n	(%)	Total (N=219) n	(%)	p-Value*
MOUTH ULCERATION							
Mild	0		1	(0.9)	1	(0.5)	
Moderate	0		0		0		
Severe	0		0		0		
Total	0		1	(0.9)	1	(0.5)	1.00
PUSTULAR RASH							
Mild	0		0		0		
Moderate	0		1	(0.9)	1	(0.5)	
Severe	0		0		0		
Total	0		1	(0.9)	1	(0.5)	1.00
SKIN DISCOLORATION							
Mild	0		1	(0.9)	1	(0.5)	
Moderate	0		0		0		
Severe	0		0		0		
Total	0		1	(0.9)	1	(0.5)	1.00
SKIN ULCER							
Mild	0		1	(0.9)	1	(0.5)	
Moderate	0		0		0		
Severe	0		0		0		
Total	0		1	(0.9)	1	(0.5)	1.00
SPLENOMEGALY							
Mild	0		1	(0.9)	1	(0.5)	
Moderate	0		0		0		
Severe	0		0		0		
Total	0		1	(0.9)	1	(0.5)	1.00

RMP.B1YP.JCLLIB2(AES8JEAB)
RMP.B1YO.HCJEREP(AES8JEAB)
* Frequencies are analyzed using a Fisher’s Exact test.
XAES0008

Table 14.42. Treatment-Emergent Non-Solicited Adverse Events Incidence by Maximum Severity All Randomized Patients Subchronic Treatment Phase (Study Periods III-V) B1Y-MC-HCJE (concluded)

Maximum Severity	Flx (N=109) n	(%)	Placebo (N=110) n	(%)	Total (N=219) n	(%)	p-Value*
SUBCUTANEOUS NODULE							
Mild	0		1	(0.9)	1	(0.5)	
Moderate	0		0		0		
Severe	0		0		0		
Total	0		1	(0.9)	1	(0.5)	1.00
UNEXPECTED BENEFIT							
Mild	0		1	(0.9)	1	(0.5)	
Moderate	0		0		0		
Severe	0		0		0		
Total	0		1	(0.9)	1	(0.5)	1.00
VERTIGO							
Mild	0		0		0		
Moderate	0		1	(0.9)	1	(0.5)	
Severe	0		0		0		
Total	0		1	(0.9)	1	(0.5)	1.00
WEIGHT GAIN							
Mild	0		1	(0.9)	1	(0.5)	
Moderate	0		0		0		
Severe	0		0		0		
Total	0		1	(0.9)	1	(0.5)	1.00

RMP.B1YP.JCLLIB2(AES8JEAB)
RMP.B1YO.HCJEREP(AES8JEAB)
* Frequencies are analyzed using a Fisher's Exact test.
XAES0008

14.3.1.2.3. Treatment-Emergent Solicited Adverse Events

Treatment-emergent solicited adverse events are those events which first occurred or worsened (as defined by increase in intensity score on the Side-Effects Checklist) after initiation of treatment. Adverse events were coded using the terms specified on the Side-Effects Checklist.

For the primary analysis of the Side-Effects Checklist (see Table 12.5), the intensity score of "don't know = 4" was set to "not at all = 0." Treatment-emergent solicited adverse events during the acute treatment phase were also evaluated using a more conservative method of determining treatment-emergence (see Table 14.43). In this analysis, the intensity score of "don't know = 4" was set to "missing." "Missing" values for a known event were then assumed to have an intensity score based on whether the event occurred at baseline or postbaseline. Baseline events were assigned an intensity

score of 1 and postbaseline events were assigned an intensity score of 3. Treatment-emergence for these events was determined using these values.

One hundred eight (99%) fluoxetine-treated patients reported treatment-emergent solicited adverse events as compared with 102 (93%) placebo-treated patients (p=.035). Placebo-treated patients reported statistically significantly more events of trouble with pronouncing words (p=.027) and trouble with wetness in mouth (p=.011). These results are similar to those seen using the primary analysis of the Side-Effects Checklist.

Table 14.43. Treatment-Emergent Solicited Adverse Events - Method 2
Side-Effects Checklist
Incidence by Decreasing Frequency (Ordered by Fluoxetine)
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE

Event Classification	Flx (N=109) n (%)	Placebo (N=110) n (%)	Total (N=219) n (%)	p-Value*
PATIENTS WITH >= 1 TESS	108 (99.1)	102 (92.7)	210 (95.9)	.035
PATIENTS WITH NO TESS	1 (0.9)	8 (7.3)	9 (4.1)	.035
15. HEADACHE	60 (55.0)	47 (42.7)	107 (48.9)	.079
23. FEELING SLEEPY	56 (51.4)	50 (45.5)	106 (48.4)	.418
22. TIREDNESS	55 (50.5)	48 (43.6)	103 (47.0)	.345
14. COLD OR SNIFFLES	52 (47.7)	58 (52.7)	110 (50.2)	.500
26. GETTING ALONG WITH PARENTS	52 (47.7)	51 (46.4)	103 (47.0)	.893
07. STOMACHACHES	48 (44.0)	49 (44.5)	97 (44.3)	1.00
28. CRYING	48 (44.0)	47 (42.7)	95 (43.4)	.892
31. BEING SAD	48 (44.0)	38 (34.5)	86 (39.3)	.168
32. PAYING ATTENTION	47 (43.1)	39 (35.5)	86 (39.3)	.270
09. BEING SICK TO YOUR STOMACH	46 (42.2)	40 (36.4)	86 (39.3)	.408

1 Treatment-Emergent = was present at baseline (Visit 4) and worsened as defined by increase in score on the side-effects checklist at any postbaseline visit (Visits 5-15) or new occurrence after baseline.
Do not know = 4 values set to missing
RMP.B1YP.JCLLIB2(AES2JEKJ)
RMP.B1YO.HCJEREP(AES2JEKJ)
* Frequencies are analyzed using a Fisher’s Exact test.
XAES0002

Table 14.43. Treatment-Emergent Solicited Adverse Events - Method 2
Side-Effects Checklist
Incidence by Decreasing Frequency (Ordered by Fluoxetine)
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE (continued)

Event Classification	Flx (N=109) n (%)	Placebo (N=110) n (%)	Total (N=219) n (%)	p-Value*
24. SLEEPING	46 (42.2)	50 (45.5)	96 (43.8)	.683
29. GETTING MAD	46 (42.2)	51 (46.4)	97 (44.3)	.587
30. NOT BEING HAPPY	44 (40.4)	39 (35.5)	83 (37.9)	.488
16. DIZZINESS	39 (35.8)	33 (30.0)	72 (32.9)	.390
27. GETTING ALONG WITH KIDS	37 (33.9)	34 (30.9)	71 (32.4)	.667
03. DRY MOUTH AND LIPS	36 (33.0)	43 (39.1)	79 (36.1)	.399
01. EATING	34 (31.2)	39 (35.5)	73 (33.3)	.567
08. MUSCLE CRAMPS	34 (31.2)	43 (39.1)	77 (35.2)	.258
21. SITTING STILL	34 (31.2)	43 (39.1)	77 (35.2)	.258
12. ITCHY OR SCRATCHY SKIN	33 (30.3)	36 (32.7)	69 (31.5)	.771
06. DIARRHEA	30 (27.5)	25 (22.7)	55 (25.1)	.439
25. BAD DREAMS	30 (27.5)	37 (33.6)	67 (30.6)	.379

1 Treatment-Emergent = was present at baseline (Visit 4) and worsened as defined by increase in score on the side-effects checklist at any postbaseline visit (Visits 5-15) or new occurrence after baseline.
Do not know = 4 values set to missing
RMP.B1YP.JCLLIB2(AES2JEKJ)
RMP.B1YO.HCJEREP(AES2JEKJ)
* Frequencies are analyzed using a Fisher’s Exact test.
XAES0002

Table 14.43. Treatment-Emergent Solicited Adverse Events - Method 2
Side-Effects Checklist
Incidence by Decreasing Frequency (Ordered by Fluoxetine)
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE (concluded)

Event Classification	Flx (N=109) n (%)	Placebo (N=110) n (%)	Total (N=219) n (%)	p-Value*
18. SHAKINESS	28 (25.7)	23 (20.9)	51 (23.3)	.428
17. PLAYING SPORTS	21 (19.3)	23 (20.9)	44 (20.1)	.866
13. RASHES	20 (18.3)	26 (23.6)	46 (21.0)	.407
19. PRONOUNCING WORDS	19 (17.4)	34 (30.9)	53 (24.2)	.027
02. DRINKING	16 (14.7)	22 (20.0)	38 (17.4)	.373
20. DOING THINGS WITH YOUR HANDS	16 (14.7)	27 (24.5)	43 (19.6)	.088
04. WETNESS IN MOUTH	11 (10.1)	26 (23.6)	37 (16.9)	.011
05. CONSTIPATION	11 (10.1)	16 (14.5)	27 (12.3)	.412
11. URINATING	11 (10.1)	15 (13.6)	26 (11.9)	.532
10. WETTING THE BED	4 (3.7)	6 (5.5)	10 (4.6)	.748

1 Treatment-Emergent = was present at baseline (Visit 4) and worsened as defined by increase in score on the side-effects checklist at any postbaseline visit (Visits 5-15) or new occurrence after baseline.
Do not know = 4 values set to missing
RMP.B1YP.JCLLIB2(AES2JEKJ)
RMP.B1YO.HCJEREP(AES2JEKJ)
* Frequencies are analyzed using a Fisher’s Exact test.
XAES0002

14.3.1.2.4. Treatment-Emergent Solicited Adverse Events from the Side-Effects Checklist by Maximum Intensity

Treatment-emergent solicited adverse events were also analyzed by maximum intensity for the subchronic treatment phase (see Table 14.44). The Side-Effects Checklist measured intensity, rather than severity, as is typically done in Lilly-sponsored trials. An intensity score of "1," which meant the event occurred "just a little" (according to the Side-Effects Checklist) was mapped to the term "mild" for severity analysis in Lilly's system. Similarly, a score of "2" (pretty much) mapped to moderate, and a score of "3" (very much) mapped to severe.

Table 14.44 presents a summary of the incidence of treatment-emergent solicited adverse events by maximum intensity for the subchronic treatment phase. Statistically significant differences were observed in the reported intensity of three treatment-emergent solicited adverse events. A severe intensity of wetness in mouth was reported by 7 (6%) placebo-treated patients compared with 0 (0%) fluoxetine-treated patients (p=.014). A severe intensity of feeling sleepy was reported by 21 (19%) fluoxetine-treated patients compared with 8 (7%) placebo-treated patients (p=.010). Twenty-one (19%) patients in the fluoxetine treatment group reported a severe intensity of trouble paying attention compared with 8 (7%) patients in the placebo treatment group (p=.010).

Although statistically significant differences in the reported intensity (that is, frequency of some events captured on the Side-Effects Checklist) were reported, these changes tended to be small and did not result in patient discontinuation from the study.

Table 14.44. Treatment-Emergent Solicited Adverse Events Side-Effects Checklist Incidence by Maximum Intensity All Randomized Patients Subchronic Treatment Phase (Study Periods III-V) B1Y-MC-HCJE

Maximum Severity	Flx (N=109) n (%)	Placebo (N=110) n (%)	Total (N=219) n (%)	p-Value*
PATIENTS WITH >= 1 TESS				
Mild	16 (14.7)	9 (8.2)	25 (11.4)	
Moderate	20 (18.3)	35 (31.8)	55 (25.1)	
Severe	71 (65.1)	57 (51.8)	128 (58.4)	.055
Total	107 (98.2)	101 (91.8)	208 (95.0)	.059
01. EATING				
Mild	16 (14.7)	18 (16.4)	34 (15.5)	
Moderate	15 (13.8)	13 (11.8)	28 (12.8)	
Severe	3 (2.8)	8 (7.3)	11 (5.0)	.215
Total	34 (31.2)	39 (35.5)	73 (33.3)	.567
02. DRINKING				
Mild	6 (5.5)	9 (8.2)	15 (6.8)	
Moderate	4 (3.7)	8 (7.3)	12 (5.5)	
Severe	6 (5.5)	4 (3.6)	10 (4.6)	.538
Total	16 (14.7)	21 (19.1)	37 (16.9)	.471
03. DRY MOUTH AND LIPS				
Mild	19 (17.4)	20 (18.2)	39 (17.8)	
Moderate	10 (9.2)	10 (9.1)	20 (9.1)	
Severe	5 (4.6)	12 (10.9)	17 (7.8)	.128
Total	34 (31.2)	42 (38.2)	76 (34.7)	.321
04. WETNESS IN MOUTH				
Mild	5 (4.6)	13 (11.8)	18 (8.2)	
Moderate	6 (5.5)	4 (3.6)	10 (4.6)	
Severe	0	7 (6.4)	7 (3.2)	.014
Total	11 (10.1)	24 (21.8)	35 (16.0)	.026

1Treatment-Emergent = was present at baseline (Visit 4) and worsened as defined by increase in score on the side-effects checklist at any postbaseline visit (Visits 5-15) or new occurrence after baseline

RMP.B1YP.JCLLIB2(AES8JEAD)
RMP.B1YO.HCJEREP(AES8JEAD)
* Frequencies are analyzed using a Fisher's Exact test.
XAES0008

Table 14.44. Treatment-Emergent Solicited Adverse Events Side-Effects Checklist Incidence by Maximum Intensity All Randomized Patients Subchronic Treatment Phase (Study Periods III-V) B1Y-MC-HCJE (continued)

Maximum Severity	Flx (N=109) n (%)	Placebo (N=110) n (%)	Total (N=219) n (%)	p-Value*
05. CONSTIPATION				
Mild	7 (6.4)	7 (6.4)	14 (6.4)	
Moderate	1 (0.9)	5 (4.5)	6 (2.7)	
Severe	3 (2.8)	2 (1.8)	5 (2.3)	.683
Total	11 (10.1)	14 (12.7)	25 (11.4)	.672
06. DIARRHEA				
Mild	17 (15.6)	14 (12.7)	31 (14.2)	
Moderate	6 (5.5)	6 (5.5)	12 (5.5)	
Severe	5 (4.6)	3 (2.7)	8 (3.7)	.499
Total	28 (25.7)	23 (20.9)	51 (23.3)	.428
07. STOMACHACHES				
Mild	30 (27.5)	29 (26.4)	59 (26.9)	
Moderate	13 (11.9)	14 (12.7)	27 (12.3)	
Severe	5 (4.6)	6 (5.5)	11 (5.0)	1.00
Total	48 (44.0)	49 (44.5)	97 (44.3)	1.00
08. MUSCLE CRAMPS				
Mild	23 (21.1)	30 (27.3)	53 (24.2)	
Moderate	7 (6.4)	7 (6.4)	14 (6.4)	
Severe	5 (4.6)	5 (4.5)	10 (4.6)	1.00
Total	35 (32.1)	42 (38.2)	77 (35.2)	.396
09. BEING SICK TO YOUR STOMACH				
Mild	26 (23.9)	25 (22.7)	51 (23.3)	
Moderate	14 (12.8)	12 (10.9)	26 (11.9)	
Severe	4 (3.7)	2 (1.8)	6 (2.7)	.446
Total	44 (40.4)	39 (35.5)	83 (37.9)	.488

1Treatment-Emergent = was present at baseline (Visit 4) and worsened as defined by increase in score on the side-effects checklist at any postbaseline visit (Visits 5-15) or new occurrence after baseline

RMP.B1YP.JCLLIB2(AES8JEAD)
RMP.B1YO.HCJEREP(AES8JEAD)
* Frequencies are analyzed using a Fisher's Exact test.
XAES0008

Table 14.44. Treatment-Emergent Solicited Adverse Events Side-Effects Checklist Incidence by Maximum Intensity All Randomized Patients Subchronic Treatment Phase (Study Periods III-V) B1Y-MC-HCJE (continued)

Maximum Severity	Flx (N=109) n (%)	Placebo (N=110) n (%)	Total (N=219) n (%)	p-Value*
10. WETTING THE BED				
Mild	2 (1.8)	4 (3.6)	6 (2.7)	
Moderate	1 (0.9)	0	1 (0.5)	
Severe	0	1 (0.9)	1 (0.5)	1.00
Total	3 (2.8)	5 (4.5)	8 (3.7)	.721
11. URINATING				
Mild	6 (5.5)	6 (5.5)	12 (5.5)	
Moderate	3 (2.8)	5 (4.5)	8 (3.7)	
Severe	1 (0.9)	2 (1.8)	3 (1.4)	1.00
Total	10 (9.2)	13 (11.8)	23 (10.5)	.660
12. ITCHY OR SCRATCHY SKIN				
Mild	16 (14.7)	16 (14.5)	32 (14.6)	
Moderate	10 (9.2)	13 (11.8)	23 (10.5)	
Severe	6 (5.5)	7 (6.4)	13 (5.9)	1.00
Total	32 (29.4)	36 (32.7)	68 (31.1)	.662
13. RASHES				
Mild	12 (11.0)	16 (14.5)	28 (12.8)	
Moderate	4 (3.7)	5 (4.5)	9 (4.1)	
Severe	2 (1.8)	4 (3.6)	6 (2.7)	.683
Total	18 (16.5)	25 (22.7)	43 (19.6)	.308
14. COLD OR SNIFFLES				
Mild	24 (22.0)	23 (20.9)	47 (21.5)	
Moderate	14 (12.8)	19 (17.3)	33 (15.1)	
Severe	13 (11.9)	14 (12.7)	27 (12.3)	1.00
Total	51 (46.8)	56 (50.9)	107 (48.9)	.590

1Treatment-Emergent = was present at baseline (Visit 4) and worsened as defined by increase in score on the side-effects checklist at any postbaseline visit (Visits 5-15) or new occurrence after baseline

RMP.B1YP.JCLLIB2(AES8JEAD)
RMP.B1YO.HCJEREP(AES8JEAD)
* Frequencies are analyzed using a Fisher's Exact test.
XAES0008

Table 14.44. Treatment-Emergent Solicited Adverse Events Side-Effects Checklist Incidence by Maximum Intensity All Randomized Patients Subchronic Treatment Phase (Study Periods III-V) B1Y-MC-HCJE (continued)

Maximum Severity	Flx (N=109) n (%)	Placebo (N=110) n (%)	Total (N=219) n (%)	p-Value*
15. HEADACHE				
Mild	24 (22.0)	21 (19.1)	45 (20.5)	
Moderate	26 (23.9)	15 (13.6)	41 (18.7)	
Severe	7 (6.4)	8 (7.3)	15 (6.8)	1.00
Total	57 (52.3)	44 (40.0)	101 (46.1)	.079
16. DIZZINESS				
Mild	27 (24.8)	25 (22.7)	52 (23.7)	
Moderate	6 (5.5)	3 (2.7)	9 (4.1)	
Severe	5 (4.6)	4 (3.6)	9 (4.1)	.748
Total	38 (34.9)	32 (29.1)	70 (32.0)	.387
17. PLAYING SPORTS				
Mild	8 (7.3)	11 (10.0)	19 (8.7)	
Moderate	5 (4.6)	8 (7.3)	13 (5.9)	
Severe	6 (5.5)	2 (1.8)	8 (3.7)	.171
Total	19 (17.4)	21 (19.1)	40 (18.3)	.861
18. SHAKINESS				
Mild	16 (14.7)	19 (17.3)	35 (16.0)	
Moderate	4 (3.7)	3 (2.7)	7 (3.2)	
Severe	6 (5.5)	2 (1.8)	8 (3.7)	.171
Total	26 (23.9)	24 (21.8)	50 (22.8)	.750
19. PRONOUNCING WORDS				
Mild	14 (12.8)	22 (20.0)	36 (16.4)	
Moderate	2 (1.8)	8 (7.3)	10 (4.6)	
Severe	2 (1.8)	3 (2.7)	5 (2.3)	1.00
Total	18 (16.5)	33 (30.0)	51 (23.3)	.025

1Treatment-Emergent = was present at baseline (Visit 4) and worsened as defined by increase in score on the side-effects checklist at any postbaseline visit (Visits 5-15) or new occurrence after baseline

RMP.B1YP.JCLLIB2(AES8JEAD)
RMP.B1YO.HCJEREP(AES8JEAD)
* Frequencies are analyzed using a Fisher's Exact test.
XAES0008

Table 14.44. Treatment-Emergent Solicited Adverse Events Side-Effects Checklist Incidence by Maximum Intensity All Randomized Patients Subchronic Treatment Phase (Study Periods III-V) B1Y-MC-HCJE (continued)

Maximum Severity	Flx (N=109) n (%)	Placebo (N=110) n (%)	Total (N=219) n (%)	p-Value*
20. DOING THINGS WITH YOUR HANDS				
Mild	9 (8.3)	15 (13.6)	24 (11.0)	
Moderate	4 (3.7)	7 (6.4)	11 (5.0)	
Severe	2 (1.8)	3 (2.7)	5 (2.3)	1.00
Total	15 (13.8)	25 (22.7)	40 (18.3)	.115
21. SITTING STILL				
Mild	11 (10.1)	22 (20.0)	33 (15.1)	
Moderate	14 (12.8)	16 (14.5)	30 (13.7)	
Severe	9 (8.3)	5 (4.5)	14 (6.4)	.285
Total	34 (31.2)	43 (39.1)	77 (35.2)	.258
22. TIREDNESS				
Mild	22 (20.2)	17 (15.5)	39 (17.8)	
Moderate	12 (11.0)	18 (16.4)	30 (13.7)	
Severe	21 (19.3)	13 (11.8)	34 (15.5)	.140
Total	55 (50.5)	48 (43.6)	103 (47.0)	.345
23. FEELING SLEEPY				
Mild	18 (16.5)	22 (20.0)	40 (18.3)	
Moderate	17 (15.6)	19 (17.3)	36 (16.4)	
Severe	21 (19.3)	8 (7.3)	29 (13.2)	.010
Total	56 (51.4)	49 (44.5)	105 (47.9)	.345
24. SLEEPING				
Mild	16 (14.7)	17 (15.5)	33 (15.1)	
Moderate	15 (13.8)	18 (16.4)	33 (15.1)	
Severe	14 (12.8)	15 (13.6)	29 (13.2)	1.00
Total	45 (41.3)	50 (45.5)	95 (43.4)	.586

1Treatment-Emergent = was present at baseline (Visit 4) and worsened as defined by increase in score on the side-effects checklist at any postbaseline visit (Visits 5-15) or new occurrence after baseline

RMP.B1YP.JCLLIB2(AES8JEAD)
RMP.B1YO.HCJEREP(AES8JEAD)
* Frequencies are analyzed using a Fisher's Exact test.
XAES0008

Table 14.44. Treatment-Emergent Solicited Adverse Events Side-Effects Checklist Incidence by Maximum Intensity All Randomized Patients Subchronic Treatment Phase (Study Periods III-V) B1Y-MC-HCJE (continued)

Maximum Severity	Flx (N=109) n (%)	Placebo (N=110) n (%)	Total (N=219) n (%)	p-Value*
25. BAD DREAMS				
Mild	19 (17.4)	26 (23.6)	45 (20.5)	
Moderate	5 (4.6)	5 (4.5)	10 (4.6)	
Severe	6 (5.5)	4 (3.6)	10 (4.6)	.538
Total	30 (27.5)	35 (31.8)	65 (29.7)	.555
26. GETTING ALONG WITH PARENTS				
Mild	9 (8.3)	22 (20.0)	31 (14.2)	
Moderate	20 (18.3)	13 (11.8)	33 (15.1)	
Severe	22 (20.2)	13 (11.8)	35 (16.0)	.100
Total	51 (46.8)	48 (43.6)	99 (45.2)	.685
27. GETTING ALONG WITH KIDS				
Mild	12 (11.0)	15 (13.6)	27 (12.3)	
Moderate	14 (12.8)	9 (8.2)	23 (10.5)	
Severe	8 (7.3)	9 (8.2)	17 (7.8)	1.00
Total	34 (31.2)	33 (30.0)	67 (30.6)	.884
28. CRYING				
Mild	26 (23.9)	23 (20.9)	49 (22.4)	
Moderate	13 (11.9)	17 (15.5)	30 (13.7)	
Severe	8 (7.3)	4 (3.6)	12 (5.5)	.252
Total	47 (43.1)	44 (40.0)	91 (41.6)	.682
29. GETTING MAD				
Mild	16 (14.7)	24 (21.8)	40 (18.3)	
Moderate	16 (14.7)	15 (13.6)	31 (14.2)	
Severe	13 (11.9)	12 (10.9)	25 (11.4)	.835
Total	45 (41.3)	51 (46.4)	96 (43.8)	.497

1Treatment-Emergent = was present at baseline (Visit 4) and worsened as defined by increase in score on the side-effects checklist at any postbaseline visit (Visits 5-15) or new occurrence after baseline

RMP.B1YP.JCLLIB2(AES8JEAD)
RMP.B1YO.HCJEREP(AES8JEAD)
* Frequencies are analyzed using a Fisher's Exact test.
XAES0008

Table 14.44. Treatment-Emergent Solicited Adverse Events Side-Effects Checklist Incidence by Maximum Intensity All Randomized Patients Subchronic Treatment Phase (Study Periods III-V) B1Y-MC-HCJE (concluded)

Maximum Severity	Flx (N=109) n (%)	Placebo (N=110) n (%)	Total (N=219) n (%)	p-Value*
30. NOT BEING HAPPY				
Mild	13 (11.9)	16 (14.5)	29 (13.2)	
Moderate	19 (17.4)	14 (12.7)	33 (15.1)	
Severe	12 (11.0)	9 (8.2)	21 (9.6)	.501
Total	44 (40.4)	39 (35.5)	83 (37.9)	.488
31. BEING SAD				
Mild	19 (17.4)	17 (15.5)	36 (16.4)	
Moderate	15 (13.8)	13 (11.8)	28 (12.8)	
Severe	13 (11.9)	6 (5.5)	19 (8.7)	.099
Total	47 (43.1)	36 (32.7)	83 (37.9)	.127
32. PAYING ATTENTION				
Mild	9 (8.3)	16 (14.5)	25 (11.4)	
Moderate	17 (15.6)	13 (11.8)	30 (13.7)	
Severe	21 (19.3)	8 (7.3)	29 (13.2)	.010
Total	47 (43.1)	37 (33.6)	84 (38.4)	.166

1Treatment-Emergent = was present at baseline (Visit 4) and worsened as defined by increase in score on the side-effects checklist at any postbaseline visit (Visits 5-15) or new occurrence after baseline
RMP.B1YP.JCLLIB2(AES8JEAD)
RMP.B1YO.HCJEREP(AES8JEAD)
* Frequencies are analyzed using a Fisher's Exact test.
XAES0008

14.3.1.3. Adverse Events in All Randomized Patients Entering Study Period V

This section summarizes the adverse events experienced by all randomized patients entering Study Period V. These analyses include all patients who did not discontinue prior to Visit 11. When determining treatment-emergent events for these analyses, baseline was defined as Visits 4 through 10. Comparisons were made between patients receiving all doses of fluoxetine (20 to 60 mg/day) and patients receiving placebo treatment.

14.3.1.3.1. Non-Solicited Events

Table 14.45 presents a summary of treatment-emergent non-solicited adverse events reported by all patients entering Study Period V.

Of the 158 patients entering Study Period V, 95 (60%) patients reported treatment-emergent non-solicited adverse events and 63 (40%) did not. The adverse event of

constipation was reported significantly more often (p=.033) by placebo-treated patients (6%) compared with fluoxetine-treated patients (0%). No other event occurred in statistically significantly different percentages of patients in the two treatment groups.

Table 14.45. Treatment-Emergent Non-Solicited Adverse Events Incidence by Decreasing Frequency (Ordered by Fluoxetine) All Patients Entering Study Period V Study Period V, B1Y-MC-HCJE

Event Classification	Flx (N=90) n (%)	Placebo (N=68) n (%)	Total (N=158) n (%)	p-Value*
PATIENTS WITH >= 1 TESS	52 (57.8)	43 (63.2)	95 (60.1)	.515
PATIENTS WITH NO TESS	38 (42.2)	25 (36.8)	63 (39.9)	.515
RHINITIS	11 (12.2)	8 (11.8)	19 (12.0)	1.00
COUGH INCREASED	8 (8.9)	2 (2.9)	10 (6.3)	.189
ACCIDENTAL INJURY	7 (7.8)	2 (2.9)	9 (5.7)	.302
ABDOMINAL PAIN	5 (5.6)	6 (8.8)	11 (7.0)	.532
PHARYNGITIS	5 (5.6)	5 (7.4)	10 (6.3)	.746
HEADACHE	4 (4.4)	5 (7.4)	9 (5.7)	.500
BACK PAIN	3 (3.3)	0	3 (1.9)	.260
DIARRHEA	3 (3.3)	2 (2.9)	5 (3.2)	1.00
FEVER	3 (3.3)	3 (4.4)	6 (3.8)	1.00
HOSTILITY	3 (3.3)	0	3 (1.9)	.260
INFECTION	3 (3.3)	3 (4.4)	6 (3.8)	1.00
NERVOUSNESS	3 (3.3)	0	3 (1.9)	.260
PERSONALITY DISORDER	3 (3.3)	1 (1.5)	4 (2.5)	.635
RASH	3 (3.3)	6 (8.8)	9 (5.7)	.175
VOMITING	3 (3.3)	4 (5.9)	7 (4.4)	.465
ALLERGIC REACTION	2 (2.2)	0	2 (1.3)	.507
ASTHENIA	2 (2.2)	1 (1.5)	3 (1.9)	1.00
CONTACT DERMATITIS	2 (2.2)	0	2 (1.3)	.507
DRY MOUTH	2 (2.2)	2 (2.9)	4 (2.5)	1.00
EAR PAIN	2 (2.2)	0	2 (1.3)	.507
HYPERKINESIA	2 (2.2)	1 (1.5)	3 (1.9)	1.00
INCREASED APPETITE	2 (2.2)	0	2 (1.3)	.507
INSOMNIA	2 (2.2)	0	2 (1.3)	.507
MYALGIA	2 (2.2)	1 (1.5)	3 (1.9)	1.00
NECK RIGIDITY	2 (2.2)	1 (1.5)	3 (1.9)	1.00
PAIN	2 (2.2)	3 (4.4)	5 (3.2)	.652
PHOTOSENSITIVITY REACTION	2 (2.2)	1 (1.5)	3 (1.9)	1.00
PRURITUS	2 (2.2)	1 (1.5)	3 (1.9)	1.00
SOMNOLENCE	2 (2.2)	1 (1.5)	3 (1.9)	1.00
THINKING ABNORMAL	2 (2.2)	0	2 (1.3)	.507
ABNORMAL DREAMS	1 (1.1)	0	1 (0.6)	1.00
ACUTE BRAIN SYNDROME	1 (1.1)	0	1 (0.6)	1.00
AGITATION	1 (1.1)	0	1 (0.6)	1.00
AKATHISIA	1 (1.1)	0	1 (0.6)	1.00
AMBLYOPIA	1 (1.1)	0	1 (0.6)	1.00
AMNESIA	1 (1.1)	0	1 (0.6)	1.00
ANEMIA	1 (1.1)	0	1 (0.6)	1.00
ANOREXIA	1 (1.1)	3 (4.4)	4 (2.5)	.315
ASTHMA	1 (1.1)	0	1 (0.6)	1.00

RMP.B1YP.JCLLIB2(AES2JEKP)
RMP.B1YO.HCJEREP(AES2JEKP)
* Frequencies are analyzed using a Fisher's Exact test.
XAES0002

Table 14.45. Treatment-Emergent Non-Solicited Adverse Events Incidence by Decreasing Frequency (Ordered by Fluoxetine) All Patients Entering Study Period V Study Period V, B1Y-MC-HCJE (continued)

Event Classification	Flx (N=90) n	(%)	Placebo (N=68) n	(%)	Total (N=158) n	(%)	p-Value*
BRADYCARDIA	1	(1.1)	0		1	(0.6)	1.00
BRONCHITIS	1	(1.1)	2	(2.9)	3	(1.9)	.578
CARDIOVASCULAR DISORDER	1	(1.1)	0		1	(0.6)	1.00
DEPRESSION	1	(1.1)	1	(1.5)	2	(1.3)	1.00
DIZZINESS	1	(1.1)	4	(5.9)	5	(3.2)	.166
DYSPEPSIA	1	(1.1)	1	(1.5)	2	(1.3)	1.00
EAR DISORDER	1	(1.1)	0		1	(0.6)	1.00
ECCHYMOSIS	1	(1.1)	0		1	(0.6)	1.00
ENDOCRINE DISORDER	1	(1.1)	0		1	(0.6)	1.00
EUPHORIA	1	(1.1)	0		1	(0.6)	1.00
GASTROINTESTINAL DISORDER	1	(1.1)	0		1	(0.6)	1.00
HYPERCHOLESTEREMIA	1	(1.1)	0		1	(0.6)	1.00
INCREASED SALIVATION	1	(1.1)	1	(1.5)	2	(1.3)	1.00
INTENTIONAL INJURY	1	(1.1)	0		1	(0.6)	1.00
LARYNGITIS	1	(1.1)	0		1	(0.6)	1.00
LEUKOPENIA	1	(1.1)	0		1	(0.6)	1.00
LYMPHADENOPATHY	1	(1.1)	1	(1.5)	2	(1.3)	1.00
OTITIS MEDIA	1	(1.1)	0		1	(0.6)	1.00
RECTAL HEMORRHAGE	1	(1.1)	0		1	(0.6)	1.00
SINUS BRADYCARDIA	1	(1.1)	0		1	(0.6)	1.00
SINUSITIS	1	(1.1)	0		1	(0.6)	1.00
SPEECH DISORDER	1	(1.1)	0		1	(0.6)	1.00
SURGICAL PROCEDURE	1	(1.1)	1	(1.5)	2	(1.3)	1.00
SWEATING	1	(1.1)	0		1	(0.6)	1.00
THYROID DISORDER	1	(1.1)	0		1	(0.6)	1.00
TOOTH DISORDER	1	(1.1)	0		1	(0.6)	1.00
ULCERATIVE STOMATITIS	1	(1.1)	0		1	(0.6)	1.00
VESICULOBULLOUS RASH	1	(1.1)	0		1	(0.6)	1.00
YAWN	1	(1.1)	0		1	(0.6)	1.00
BILIRUBINURIA	0		1	(1.5)	1	(0.6)	.430
CHILLS	0		1	(1.5)	1	(0.6)	.430
CONSTIPATION	0		4	(5.9)	4	(2.5)	.033
DRY SKIN	0		2	(2.9)	2	(1.3)	.184
DYSMENORRHEA	0		1	(1.5)	1	(0.6)	.430
EPISTAXIS	0		1	(1.5)	1	(0.6)	.430
HEPATOMEGALY	0		1	(1.5)	1	(0.6)	.430
LEG CRAMPS	0		2	(2.9)	2	(1.3)	.184
LYMPHOCYTOSIS	0		1	(1.5)	1	(0.6)	.430
MENORRHAGIA	0		1	(1.5)	1	(0.6)	.430
NAUSEA	0		3	(4.4)	3	(1.9)	.078
NECK PAIN	0		1	(1.5)	1	(0.6)	.430

RMP.B1YP.JCLLIB2(AES2JEKP)
RMP.B1YO.HCJEREP(AES2JEKP)
* Frequencies are analyzed using a Fisher’s Exact test.
XAES0002

Table 14.45. Treatment-Emergent Non-Solicited Adverse Events Incidence by Decreasing Frequency (Ordered by Fluoxetine) All Patients Entering Study Period V Study Period V, B1Y-MC-HCJE (concluded)

Event Classification	Flx (N=90) n (%)	Placebo (N=68) n (%)	Total (N=158) n (%)	p-Value*
OVERDOSE	0	1 (1.5)	1 (0.6)	.430
PUSTULAR RASH	0	1 (1.5)	1 (0.6)	.430
SPLENOMEGALY	0	1 (1.5)	1 (0.6)	.430
TREMOR	0	1 (1.5)	1 (0.6)	.430
VERTIGO	0	1 (1.5)	1 (0.6)	.430

RMP.B1YP.JCLLIB2(AES2JEKP)
RMP.B1YO.HCJEREP(AES2JEKP)
* Frequencies are analyzed using a Fisher's Exact test.
XAES0002

14.3.1.3.2. Solicited Events

Table 14.46 presents a summary of the incidence of treatment-emergent solicited adverse events for all randomized patients entering Study Period V.

One hundred fifty-eight patients entered Study Period V. Of these, 106 (67%) patients reported at least one treatment-emergent solicited adverse event. The adverse event of rashes was reported statistically significantly (p=.005) more often by placebo-treated patients (12%) as compared with fluoxetine-treated patients (1%). The adverse event of wetness in mouth was reported statistically significantly (p=.043) more often by placebo-treated patients (9%) as compared with fluoxetine-treated patients (1%). No other event occurred in statistically significantly different percentages of patients in the two treatment groups.

Table 14.46. Treatment-Emergent Solicited Adverse Events
Side-Effects Checklist
Incidence by Decreasing Frequency (Ordered by Fluoxetine)
All Patients Entering Study Period V
Study Period V, B1Y-MC-HCJE

Event Classification	Flx (N=90) n (%)	Placebo (N=68) n (%)	Total (N=158) n (%)	p-Value*
PATIENTS WITH >= 1 TESS	55 (61.1)	51 (75.0)	106 (67.1)	.087
PATIENTS WITH NO TESS	35 (38.9)	17 (25.0)	52 (32.9)	.087
07. STOMACHACHES	14 (15.6)	7 (10.3)	21 (13.3)	.357
15. HEADACHE	13 (14.4)	7 (10.3)	20 (12.7)	.479
14. COLD OR SNIFFLES	11 (12.2)	11 (16.2)	22 (13.9)	.495
26. GETTING ALONG WITH PARENTS	10 (11.1)	7 (10.3)	17 (10.8)	1.00
08. MUSCLE CRAMPS	8 (8.9)	11 (16.2)	19 (12.0)	.217
22. TIREDNESS	8 (8.9)	3 (4.4)	11 (7.0)	.353
28. CRYING	8 (8.9)	6 (8.8)	14 (8.9)	1.00
09. BEING SICK TO YOUR STOMACH	7 (7.8)	7 (10.3)	14 (8.9)	.586

1 Treatment-Emergent Solicited= was present at baseline (highest score for item of visits 4-10) and worsened as defined by increase in score on the side-effescts checklist at any postbaseline visit (visits 11-15) or new occurrence after baseline.
Do not know = 4 value set to Not at all = 0
RMP.B1YP.JCLLIB2(AES2JEKO)
RMP.B1YO.HCJEREP(AES2JEKO)
* Frequencies are analyzed using a Fisher’s Exact test.
XAES0002

Table 14.46. Treatment-Emergent Solicited Adverse Events
Side-Effects Checklist
Incidence by Decreasing Frequency (Ordered by Fluoxetine)
All Patients Entering Study Period V
Study Period V, B1Y-MC-HCJE (continued)

Event Classification	Flx (N=90) n (%)	Placebo (N=68) n (%)	Total (N=158) n (%)	p-Value*
16. DIZZINESS	7 (7.8)	10 (14.7)	17 (10.8)	.199
29. GETTING MAD	7 (7.8)	8 (11.8)	15 (9.5)	.423
30. NOT BEING HAPPY	7 (7.8)	5 (7.4)	12 (7.6)	1.00
31. BEING SAD	7 (7.8)	4 (5.9)	11 (7.0)	.759
32. PAYING ATTENTION	7 (7.8)	10 (14.7)	17 (10.8)	.199
06. DIARRHEA	6 (6.7)	5 (7.4)	11 (7.0)	1.00
12. ITCHY OR SCRATCHY SKIN	6 (6.7)	7 (10.3)	13 (8.2)	.560
18. SHAKINESS	6 (6.7)	1 (1.5)	7 (4.4)	.240
23. FEELING SLEEPY	6 (6.7)	4 (5.9)	10 (6.3)	1.00
24. SLEEPING	6 (6.7)	7 (10.3)	13 (8.2)	.560

1 Treatment-Emergent Solicited= was present at baseline (highest score for item of visits 4-10) and worsened as defined by increase in score on the side-effescts checklist at any postbaseline visit (visits 11-15) or new occurrence after baseline.
Do not know = 4 value set to Not at all = 0
RMP.B1YP.JCLLIB2(AES2JEKO)
RMP.B1YO.HCJEREP(AES2JEKO)
* Frequencies are analyzed using a Fisher’s Exact test.
XAES0002

Table 14.46. Treatment-Emergent Solicited Adverse Events
Side-Effects Checklist
Incidence by Decreasing Frequency (Ordered by Fluoxetine)
All Patients Entering Study Period V
Study Period V, B1Y-MC-HCJE (continued)

Event Classification	Flx (N=90) n (%)	Placebo (N=68) n (%)	Total (N=158) n (%)	p-Value*
19. PRONOUNCING WORDS	5 (5.6)	6 (8.8)	11 (7.0)	.532
21. SITTING STILL	5 (5.6)	2 (2.9)	7 (4.4)	.700
27. GETTING ALONG WITH KIDS	5 (5.6)	3 (4.4)	8 (5.1)	1.00
01. EATING	4 (4.4)	4 (5.9)	8 (5.1)	.726
25. BAD DREAMS	4 (4.4)	9 (13.2)	13 (8.2)	.076
02. DRINKING	2 (2.2)	1 (1.5)	3 (1.9)	1.00
03. DRY MOUTH AND LIPS	2 (2.2)	5 (7.4)	7 (4.4)	.141
05. CONSTIPATION	2 (2.2)	4 (5.9)	6 (3.8)	.404
17. PLAYING SPORTS	2 (2.2)	2 (2.9)	4 (2.5)	1.00
20. DOING THINGS WITH YOUR HANDS	2 (2.2)	6 (8.8)	8 (5.1)	.076

1 Treatment-Emergent Solicited= was present at baseline (highest score for item of visits 4-10) and worsened as defined by increase in score on the side-effescts checklist at any postbaseline visit (visits 11-15) or new occurrence after baseline.
Do not know = 4 value set to Not at all = 0
RMP.B1YP.JCLLIB2(AES2JEKO)
RMP.B1YO.HCJEREP(AES2JEKO)
* Frequencies are analyzed using a Fisher’s Exact test.
XAES0002

Table 14.46. Treatment-Emergent Solicited Adverse Events
Side-Effects Checklist
Incidence by Decreasing Frequency (Ordered by Fluoxetine)
All Patients Entering Study Period V
Study Period V, B1Y-MC-HCJE (concluded)

Event Classification	Flx (N=90) n (%)	Placebo (N=68) n (%)	Total (N=158) n (%)	p-Value*
04. WETNESS IN MOUTH	1 (1.1)	6 (8.8)	7 (4.4)	.043
13. RASHES	1 (1.1)	8 (11.8)	9 (5.7)	.005
11. URINATING	0	1 (1.5)	1 (0.6)	.430

1 Treatment-Emergent Solicited= was present at baseline (highest score for item of visits 4-10)
and worsened as defined by increase in score on the side-effescts checklist at any postbaseline visit
(visits 11-15) or new occurrence after baseline.
Do not know = 4 value set to Not at all = 0
RMP.B1YP.JCLLIB2(AES2JEKO)
RMP.B1YO.HCJEREP(AES2JEKO)
* Frequencies are analyzed using a Fisher’s Exact test.
XAES0002

14.3.2. Subgroup Analyses

14.3.2.1. Acute Treatment Phase (Study Periods III-IV)

14.3.2.1.1. By Age

Table 14.47 presents the incidence of treatment-emergent non-solicited adverse events analyzed by age subgroups for the acute treatment phase.

There were no statistically significant differences observed between treatment groups for either age subgroup for any treatment-emergent non-solicited adverse event.

Table 14.47. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Age Category
All Randomized Patients
Acute Treatment Phase (Study Periods III-IV)
B1Y-MC-HCJE

AGE	Flx 20 N	Flx 20 n (%)	Placebo N	Placebo n (%)	Total N	Total n (%)	p-Value*
PATIENTS WITH >= 1 TESS							
8 - < 13	61	53 (86.9)	61	44 (72.1)	122	97 (79.5)	.071
13 - < 18	48	41 (85.4)	49	36 (73.5)	97	77 (79.4)	.210
Total	109	94 (86.2)	110	80 (72.7)	219	174 (79.5)	.019
PATIENTS WITH NO TESS							
8 - < 13	61	8 (13.1)	61	17 (27.9)	122	25 (20.5)	.071
13 - < 18	48	7 (14.6)	49	13 (26.5)	97	20 (20.6)	.210
Total	109	15 (13.8)	110	30 (27.3)	219	45 (20.5)	.019

RMP.B1YP.JCLLIB2(AES6JEAC)
RMP.B1YO.HCJEREP(AES6JEAC)
AGE: Patient Age
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.47. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Age Category
All Randomized Patients
Acute Treatment Phase (Study Periods III-IV)
B1Y-MC-HCJE (continued)

AGE	Flx 20 N	Flx 20 n (%)	Placebo N	Placebo n (%)	Total N	Total n (%)	p-Value*
HEADACHE							
8 - < 13	61	18 (29.5)	61	9 (14.8)	122	27 (22.1)	.080
13 - < 18	48	15 (31.3)	49	9 (18.4)	97	24 (24.7)	.164
Total	109	33 (30.3)	110	18 (16.4)	219	51 (23.3)	.017
RHINITIS							
8 - < 13	61	11 (18.0)	61	11 (18.0)	122	22 (18.0)	1.00
13 - < 18	48	13 (27.1)	49	10 (20.4)	97	23 (23.7)	.482
Total	109	24 (22.0)	110	21 (19.1)	219	45 (20.5)	.619

RMP.B1YP.JCLLIB2(AES6JEAC)
RMP.B1YO.HCJEREP(AES6JEAC)
AGE: Patient Age
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.47. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Age Category
All Randomized Patients
Acute Treatment Phase (Study Periods III-IV)
B1Y-MC-HCJE (continued)

	Flx 20		Placebo		Total		p-Value*
AGE	N	n (%)	N	n (%)	N	n (%)	
ABDOMINAL PAIN							
8 - < 13	61	11 (18.0)	61	10 (16.4)	122	21 (17.2)	1.00
13 - < 18	48	6 (12.5)	49	6 (12.2)	97	12 (12.4)	1.00
Total	109	17 (15.6)	110	16 (14.5)	219	33 (15.1)	.852
PHARYNGITIS							
8 - < 13	61	10 (16.4)	61	4 (6.6)	122	14 (11.5)	.154
13 - < 18	48	6 (12.5)	49	5 (10.2)	97	11 (11.3)	.759
Total	109	16 (14.7)	110	9 (8.2)	219	25 (11.4)	.143

RMP.B1YP.JCLLIB2(AES6JEAC)
RMP.B1YO.HCJEREP(AES6JEAC)
AGE: Patient Age
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.47. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Age Category
All Randomized Patients
Acute Treatment Phase (Study Periods III-IV)
B1Y-MC-HCJE (continued)

	Flx 20		Placebo		Total		p-Value*
AGE	N	n (%)	N	n (%)	N	n (%)	
ACCIDENTAL INJURY							
8 - < 13	61	10 (16.4)	61	5 (8.2)	122	15 (12.3)	.270
13 - < 18	48	3 (6.3)	49	3 (6.1)	97	6 (6.2)	1.00
Total	109	13 (11.9)	110	8 (7.3)	219	21 (9.6)	.261
DIARRHEA							
8 - < 13	61	9 (14.8)	61	7 (11.5)	122	16 (13.1)	.789
13 - < 18	48	2 (4.2)	49	4 (8.2)	97	6 (6.2)	.678
Total	109	11 (10.1)	110	11 (10.0)	219	22 (10.0)	1.00

RMP.B1YP.JCLLIB2(AES6JEAC)
RMP.B1YO.HCJEREP(AES6JEAC)
AGE: Patient Age
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.47. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Age Category
All Randomized Patients
Acute Treatment Phase (Study Periods III-IV)
B1Y-MC-HCJE (continued)

	Flx 20			Placebo			Total			p-Value*
AGE	N	n	(%)	N	n	(%)	N	n	(%)	
DIZZINESS										
8 - < 13	61	8	(13.1)	61	3	(4.9)	122	11	(9.0)	.205
13 - < 18	48	2	(4.2)	49	1	(2.0)	97	3	(3.1)	.617
Total	109	10	(9.2)	110	4	(3.6)	219	14	(6.4)	.106
RASH										
8 - < 13	61	7	(11.5)	61	3	(4.9)	122	10	(8.2)	.323
13 - < 18	48	3	(6.3)	49	1	(2.0)	97	4	(4.1)	.362
Total	109	10	(9.2)	110	4	(3.6)	219	14	(6.4)	.106

RMP.B1YP.JCLLIB2(AES6JEAC)
RMP.B1YO.HCJEREP(AES6JEAC)
AGE: Patient Age
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.47. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Age Category
All Randomized Patients
Acute Treatment Phase (Study Periods III-IV)
B1Y-MC-HCJE (continued)

	Flx 20			Placebo			Total			p-Value*
AGE	N	n	(%)	N	n	(%)	N	n	(%)	
ANOREXIA										
8 - < 13	61	6	(9.8)	61	3	(4.9)	122	9	(7.4)	.491
13 - < 18	48	3	(6.3)	49	3	(6.1)	97	6	(6.2)	1.00
Total	109	9	(8.3)	110	6	(5.5)	219	15	(6.8)	.437
COUGH INCREASED										
8 - < 13	61	8	(13.1)	61	3	(4.9)	122	11	(9.0)	.205
13 - < 18	48	1	(2.1)	49	4	(8.2)	97	5	(5.2)	.362
Total	109	9	(8.3)	110	7	(6.4)	219	16	(7.3)	.615

RMP.B1YP.JCLLIB2(AES6JEAC)
RMP.B1YO.HCJEREP(AES6JEAC)
AGE: Patient Age
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.47. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Age Category
All Randomized Patients
Acute Treatment Phase (Study Periods III-IV)
B1Y-MC-HCJE (continued)

	Flx 20			Placebo			Total			p-Value*
AGE	N	n	(%)	N	n	(%)	N	n	(%)	
NAUSEA										
8 - < 13	61	6	(9.8)	61	5	(8.2)	122	11	(9.0)	1.00
13 - < 18	48	3	(6.3)	49	3	(6.1)	97	6	(6.2)	1.00
Total	109	9	(8.3)	110	8	(7.3)	219	17	(7.8)	.806
NERVOUSNESS										
8 - < 13	61	6	(9.8)	61	3	(4.9)	122	9	(7.4)	.491
13 - < 18	48	3	(6.3)	49	3	(6.1)	97	6	(6.2)	1.00
Total	109	9	(8.3)	110	6	(5.5)	219	15	(6.8)	.437

RMP.B1YP.JCLLIB2(AES6JEAC)
RMP.B1YO.HCJEREP(AES6JEAC)
AGE: Patient Age
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.47. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Age Category
All Randomized Patients
Acute Treatment Phase (Study Periods III-IV)
B1Y-MC-HCJE (continued)

	Flx 20			Placebo			Total			p-Value*
AGE	N	n	(%)	N	n	(%)	N	n	(%)	
ASTHENIA										
8 - < 13	61	4	(6.6)	61	4	(6.6)	122	8	(6.6)	1.00
13 - < 18	48	4	(8.3)	49	2	(4.1)	97	6	(6.2)	.436
Total	109	8	(7.3)	110	6	(5.5)	219	14	(6.4)	.594
PAIN										
8 - < 13	61	5	(8.2)	61	3	(4.9)	122	8	(6.6)	.717
13 - < 18	48	3	(6.3)	49	6	(12.2)	97	9	(9.3)	.487
Total	109	8	(7.3)	110	9	(8.2)	219	17	(7.8)	1.00

RMP.B1YP.JCLLIB2(AES6JEAC)
RMP.B1YO.HCJEREP(AES6JEAC)
AGE: Patient Age
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.47. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Age Category
All Randomized Patients
Acute Treatment Phase (Study Periods III-IV)
B1Y-MC-HCJE (continued)

	Flx 20		Placebo		Total		p-Value*
AGE	N	n (%)	N	n (%)	N	n (%)	
VOMITING							
8 - < 13	61	8 (13.1)	61	3 (4.9)	122	11 (9.0)	.205
13 - < 18	48	0	49	5 (10.2)	97	5 (5.2)	.056
Total	109	8 (7.3)	110	8 (7.3)	219	16 (7.3)	1.00
FEVER							
8 - < 13	61	5 (8.2)	61	4 (6.6)	122	9 (7.4)	1.00
13 - < 18	48	2 (4.2)	49	1 (2.0)	97	3 (3.1)	.617
Total	109	7 (6.4)	110	5 (4.5)	219	12 (5.5)	.569

RMP.B1YP.JCLLIB2(AES6JEAC)
RMP.B1YO.HCJEREP(AES6JEAC)
AGE: Patient Age
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.47. Treatment-Emergent Non-Solicited Adverse Events Subgroup Analysis by Age Category All Randomized Patients Acute Treatment Phase (Study Periods III-IV) B1Y-MC-HCJE (continued)

	Flx 20			Placebo			Total			p-Value*
AGE	N	n	(%)	N	n	(%)	N	n	(%)	
ABNORMAL DREAMS										
8 - < 13	61	2	(3.3)	61	1	(1.6)	122	3	(2.5)	1.00
13 - < 18	48	4	(8.3)	49	2	(4.1)	97	6	(6.2)	.436
Total	109	6	(5.5)	110	3	(2.7)	219	9	(4.1)	.332
EPISTAXIS										
8 - < 13	61	4	(6.6)	61	1	(1.6)	122	5	(4.1)	.365
13 - < 18	48	1	(2.1)	49	0		97	1	(1.0)	.495
Total	109	5	(4.6)	110	1	(0.9)	219	6	(2.7)	.119

RMP.B1YP.JCLLIB2(AES6JEAC)
RMP.B1YO.HCJEREP(AES6JEAC)
AGE: Patient Age
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.47. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Age Category
All Randomized Patients
Acute Treatment Phase (Study Periods III-IV)
B1Y-MC-HCJE (continued)

	Flx 20			Placebo			Total			p-Value*
AGE	N	n	(%)	N	n	(%)	N	n	(%)	
DRY MOUTH										
8 - < 13	61	2	(3.3)	61	2	(3.3)	122	4	(3.3)	1.00
13 - < 18	48	2	(4.2)	49	3	(6.1)	97	5	(5.2)	1.00
Total	109	4	(3.7)	110	5	(4.5)	219	9	(4.1)	1.00
DYSMENORRHEA										
8 - < 13	61	1	(1.6)	61	0		122	1	(0.8)	1.00
13 - < 18	48	3	(6.3)	49	3	(6.1)	97	6	(6.2)	1.00
Total	109	4	(3.7)	110	3	(2.7)	219	7	(3.2)	.721

RMP.B1YP.JCLLIB2(AES6JEAC)
RMP.B1YO.HCJEREP(AES6JEAC)
AGE: Patient Age
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.47. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Age Category
All Randomized Patients
Acute Treatment Phase (Study Periods III-IV)
B1Y-MC-HCJE (continued)

	Flx 20			Placebo			Total			p-Value*
AGE	N	n	(%)	N	n	(%)	N	n	(%)	
EAR PAIN										
8 - < 13	61	4	(6.6)	61	3	(4.9)	122	7	(5.7)	1.00
13 - < 18	48	0		49	0		97	0		
Total	109	4	(3.7)	110	3	(2.7)	219	7	(3.2)	.721
FLU SYNDROME										
8 - < 13	61	2	(3.3)	61	2	(3.3)	122	4	(3.3)	1.00
13 - < 18	48	2	(4.2)	49	1	(2.0)	97	3	(3.1)	.617
Total	109	4	(3.7)	110	3	(2.7)	219	7	(3.2)	.721

RMP.B1YP.JCLLIB2(AES6JEAC)
RMP.B1YO.HCJEREP(AES6JEAC)
AGE: Patient Age
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.47. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Age Category
All Randomized Patients
Acute Treatment Phase (Study Periods III-IV)
B1Y-MC-HCJE (continued)

	Flx 20			Placebo			Total			p-Value*
AGE	N	n	(%)	N	n	(%)	N	n	(%)	
INSOMNIA										
8 - < 13	61	3	(4.9)	61	4	(6.6)	122	7	(5.7)	1.00
13 - < 18	48	1	(2.1)	49	1	(2.0)	97	2	(2.1)	1.00
Total	109	4	(3.7)	110	5	(4.5)	219	9	(4.1)	1.00
PRURITUS										
8 - < 13	61	3	(4.9)	61	2	(3.3)	122	5	(4.1)	1.00
13 - < 18	48	1	(2.1)	49	3	(6.1)	97	4	(4.1)	.617
Total	109	4	(3.7)	110	5	(4.5)	219	9	(4.1)	1.00

RMP.B1YP.JCLLIB2(AES6JEAC)
RMP.B1YO.HCJEREP(AES6JEAC)
AGE: Patient Age
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.47. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Age Category
All Randomized Patients
Acute Treatment Phase (Study Periods III-IV)
B1Y-MC-HCJE (continued)

	Flx 20			Placebo			Total			p-Value*
AGE	N	n	(%)	N	n	(%)	N	n	(%)	
AGITATION										
8 - < 13	61	3	(4.9)	61	0		122	3	(2.5)	.244
13 - < 18	48	0		49	0		97	0		
Total	109	3	(2.8)	110	0		219	3	(1.4)	.122
BACK PAIN										
8 - < 13	61	2	(3.3)	61	1	(1.6)	122	3	(2.5)	1.00
13 - < 18	48	1	(2.1)	49	4	(8.2)	97	5	(5.2)	.362
Total	109	3	(2.8)	110	5	(4.5)	219	8	(3.7)	.721

RMP.B1YP.JCLLIB2(AES6JEAC)
RMP.B1YO.HCJEREP(AES6JEAC)
AGE: Patient Age
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.47. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Age Category
All Randomized Patients
Acute Treatment Phase (Study Periods III-IV)
B1Y-MC-HCJE (continued)

	Flx 20			Placebo			Total			p-Value*
AGE	N	n	(%)	N	n	(%)	N	n	(%)	
CHEST PAIN										
8 - < 13	61	1	(1.6)	61	1	(1.6)	122	2	(1.6)	1.00
13 - < 18	48	2	(4.2)	49	1	(2.0)	97	3	(3.1)	.617
Total	109	3	(2.8)	110	2	(1.8)	219	5	(2.3)	.683
CONSTIPATION										
8 - < 13	61	3	(4.9)	61	0		122	3	(2.5)	.244
13 - < 18	48	0		49	2	(4.1)	97	2	(2.1)	.495
Total	109	3	(2.8)	110	2	(1.8)	219	5	(2.3)	.683

RMP.B1YP.JCLLIB2(AES6JEAC)
RMP.B1YO.HCJEREP(AES6JEAC)
AGE: Patient Age
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.47. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Age Category
All Randomized Patients
Acute Treatment Phase (Study Periods III-IV)
B1Y-MC-HCJE (continued)

	Flx 20			Placebo			Total			p-Value*
AGE	N	n	(%)	N	n	(%)	N	n	(%)	
DYSPEPSIA										
8 - < 13	61	2	(3.3)	61	2	(3.3)	122	4	(3.3)	1.00
13 - < 18	48	1	(2.1)	49	2	(4.1)	97	3	(3.1)	1.00
Total	109	3	(2.8)	110	4	(3.6)	219	7	(3.2)	1.00
ECCHYMOSIS										
8 - < 13	61	2	(3.3)	61	2	(3.3)	122	4	(3.3)	1.00
13 - < 18	48	1	(2.1)	49	0		97	1	(1.0)	.495
Total	109	3	(2.8)	110	2	(1.8)	219	5	(2.3)	.683

RMP.B1YP.JCLLIB2(AES6JEAC)
RMP.B1YO.HCJEREP(AES6JEAC)
AGE: Patient Age
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.47. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Age Category
All Randomized Patients
Acute Treatment Phase (Study Periods III-IV)
B1Y-MC-HCJE (continued)

	Flx 20			Placebo			Total			p-Value*
AGE	N	n	(%)	N	n	(%)	N	n	(%)	
NECK PAIN										
8 - < 13	61	3	(4.9)	61	0		122	3	(2.5)	.244
13 - < 18	48	0		49	0		97	0		
Total	109	3	(2.8)	110	0		219	3	(1.4)	.122
SINUSITIS										
8 - < 13	61	2	(3.3)	61	1	(1.6)	122	3	(2.5)	1.00
13 - < 18	48	1	(2.1)	49	1	(2.0)	97	2	(2.1)	1.00
Total	109	3	(2.8)	110	2	(1.8)	219	5	(2.3)	.683

RMP.B1YP.JCLLIB2(AES6JEAC)
RMP.B1YO.HCJEREP(AES6JEAC)
AGE: Patient Age
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.47. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Age Category
All Randomized Patients
Acute Treatment Phase (Study Periods III-IV)
B1Y-MC-HCJE (continued)

	Flx 20			Placebo			Total			p-Value*
AGE	N	n	(%)	N	n	(%)	N	n	(%)	
SOMNOLENCE										
8 - < 13	61	2	(3.3)	61	1	(1.6)	122	3	(2.5)	1.00
13 - < 18	48	1	(2.1)	49	2	(4.1)	97	3	(3.1)	1.00
Total	109	3	(2.8)	110	3	(2.7)	219	6	(2.7)	1.00
TREMOR										
8 - < 13	61	0		61	0		122	0		
13 - < 18	48	3	(6.3)	49	0		97	3	(3.1)	.117
Total	109	3	(2.8)	110	0		219	3	(1.4)	.122

RMP.B1YP.JCLLIB2(AES6JEAC)
RMP.B1YO.HCJEREP(AES6JEAC)
AGE: Patient Age
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.47. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Age Category
All Randomized Patients
Acute Treatment Phase (Study Periods III-IV)
B1Y-MC-HCJE (continued)

	Flx 20			Placebo			Total			p-Value*
AGE	N	n	(%)	N	n	(%)	N	n	(%)	
AKATHISIA										
8 - < 13	61	1	(1.6)	61	0		122	1	(0.8)	1.00
13 - < 18	48	1	(2.1)	49	0		97	1	(1.0)	.495
Total	109	2	(1.8)	110	0		219	2	(0.9)	.247
ALLERGIC REACTION										
8 - < 13	61	1	(1.6)	61	1	(1.6)	122	2	(1.6)	1.00
13 - < 18	48	1	(2.1)	49	1	(2.0)	97	2	(2.1)	1.00
Total	109	2	(1.8)	110	2	(1.8)	219	4	(1.8)	1.00

RMP.B1YP.JCLLIB2(AES6JEAC)
RMP.B1YO.HCJEREP(AES6JEAC)
AGE: Patient Age
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.47. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Age Category
All Randomized Patients
Acute Treatment Phase (Study Periods III-IV)
B1Y-MC-HCJE (continued)

	Flx 20			Placebo			Total			p-Value*
AGE	N	n	(%)	N	n	(%)	N	n	(%)	
ANXIETY										
8 - < 13	61	2	(3.3)	61	0		122	2	(1.6)	.496
13 - < 18	48	0		49	0		97	0		
Total	109	2	(1.8)	110	0		219	2	(0.9)	.247
ASTHMA										
8 - < 13	61	1	(1.6)	61	0		122	1	(0.8)	1.00
13 - < 18	48	1	(2.1)	49	0		97	1	(1.0)	.495
Total	109	2	(1.8)	110	0		219	2	(0.9)	.247

RMP.B1YP.JCLLIB2(AES6JEAC)
RMP.B1YO.HCJEREP(AES6JEAC)
AGE: Patient Age
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.47. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Age Category
All Randomized Patients
Acute Treatment Phase (Study Periods III-IV)
B1Y-MC-HCJE (continued)

	Flx 20			Placebo			Total			p-Value*
AGE	N	n	(%)	N	n	(%)	N	n	(%)	
CHILLS										
8 - < 13	61	1	(1.6)	61	0		122	1	(0.8)	1.00
13 - < 18	48	1	(2.1)	49	0		97	1	(1.0)	.495
Total	109	2	(1.8)	110	0		219	2	(0.9)	.247
DEPRESSION										
8 - < 13	61	0		61	1	(1.6)	122	1	(0.8)	1.00
13 - < 18	48	2	(4.2)	49	0		97	2	(2.1)	.242
Total	109	2	(1.8)	110	1	(0.9)	219	3	(1.4)	.622

RMP.B1YP.JCLLIB2(AES6JEAC)
RMP.B1YO.HCJEREP(AES6JEAC)
AGE: Patient Age
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.47. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Age Category
All Randomized Patients
Acute Treatment Phase (Study Periods III-IV)
B1Y-MC-HCJE (continued)

	Flx 20			Placebo			Total			p-Value*
AGE	N	n	(%)	N	n	(%)	N	n	(%)	
DRY SKIN										
8 - < 13	61	2	(3.3)	61	1	(1.6)	122	3	(2.5)	1.00
13 - < 18	48	0		49	0		97	0		
Total	109	2	(1.8)	110	1	(0.9)	219	3	(1.4)	.622
EYE DISORDER										
8 - < 13	61	2	(3.3)	61	0		122	2	(1.6)	.496
13 - < 18	48	0		49	0		97	0		
Total	109	2	(1.8)	110	0		219	2	(0.9)	.247

RMP.B1YP.JCLLIB2(AES6JEAC)
RMP.B1YO.HCJEREP(AES6JEAC)
AGE: Patient Age
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.47. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Age Category
All Randomized Patients
Acute Treatment Phase (Study Periods III-IV)
B1Y-MC-HCJE (continued)

	Flx 20			Placebo			Total			p-Value*
AGE	N	n	(%)	N	n	(%)	N	n	(%)	
GASTROENTERITIS										
8 - < 13	61	1	(1.6)	61	0		122	1	(0.8)	1.00
13 - < 18	48	1	(2.1)	49	0		97	1	(1.0)	.495
Total	109	2	(1.8)	110	0		219	2	(0.9)	.247
HOSTILITY										
8 - < 13	61	2	(3.3)	61	3	(4.9)	122	5	(4.1)	1.00
13 - < 18	48	0		49	2	(4.1)	97	2	(2.1)	.495
Total	109	2	(1.8)	110	5	(4.5)	219	7	(3.2)	.446

RMP.B1YP.JCLLIB2(AES6JEAC)
RMP.B1YO.HCJEREP(AES6JEAC)
AGE: Patient Age
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.47. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Age Category
All Randomized Patients
Acute Treatment Phase (Study Periods III-IV)
B1Y-MC-HCJE (continued)

	Flx 20			Placebo			Total			p-Value*
AGE	N	n	(%)	N	n	(%)	N	n	(%)	
HYPERKINESIA										
8 - < 13	61	2	(3.3)	61	0		122	2	(1.6)	.496
13 - < 18	48	0		49	0		97	0		
Total	109	2	(1.8)	110	0		219	2	(0.9)	.247
INFECTION										
8 - < 13	61	1	(1.6)	61	2	(3.3)	122	3	(2.5)	1.00
13 - < 18	48	1	(2.1)	49	0		97	1	(1.0)	.495
Total	109	2	(1.8)	110	2	(1.8)	219	4	(1.8)	1.00

RMP.B1YP.JCLLIB2(AES6JEAC)
RMP.B1YO.HCJEREP(AES6JEAC)
AGE: Patient Age
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.47. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Age Category
All Randomized Patients
Acute Treatment Phase (Study Periods III-IV)
B1Y-MC-HCJE (continued)

	Flx 20			Placebo			Total			p-Value*
AGE	N	n	(%)	N	n	(%)	N	n	(%)	
OTITIS EXTERNA										
8 - < 13	61	1	(1.6)	61	1	(1.6)	122	2	(1.6)	1.00
13 - < 18	48	1	(2.1)	49	0		97	1	(1.0)	.495
Total	109	2	(1.8)	110	1	(0.9)	219	3	(1.4)	.622
PERSONALITY DISORDER										
8 - < 13	61	1	(1.6)	61	1	(1.6)	122	2	(1.6)	1.00
13 - < 18	48	1	(2.1)	49	0		97	1	(1.0)	.495
Total	109	2	(1.8)	110	1	(0.9)	219	3	(1.4)	.622

RMP.B1YP.JCLLIB2(AES6JEAC)
RMP.B1YO.HCJEREP(AES6JEAC)
AGE: Patient Age
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.47. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Age Category
All Randomized Patients
Acute Treatment Phase (Study Periods III-IV)
B1Y-MC-HCJE (continued)

	Flx 20			Placebo			Total			p-Value*
AGE	N	n	(%)	N	n	(%)	N	n	(%)	
PHOTOSENSITIVITY REACTION										
8 - < 13	61	2	(3.3)	61	0		122	2	(1.6)	.496
13 - < 18	48	0		49	0		97	0		
Total	109	2	(1.8)	110	0		219	2	(0.9)	.247
SLEEP DISORDER										
8 - < 13	61	2	(3.3)	61	0		122	2	(1.6)	.496
13 - < 18	48	0		49	0		97	0		
Total	109	2	(1.8)	110	0		219	2	(0.9)	.247

RMP.B1YP.JCLLIB2(AES6JEAC)
RMP.B1YO.HCJEREP(AES6JEAC)
AGE: Patient Age
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.47. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Age Category
All Randomized Patients
Acute Treatment Phase (Study Periods III-IV)
B1Y-MC-HCJE (continued)

	Flx 20			Placebo			Total			p-Value*
AGE	N	n	(%)	N	n	(%)	N	n	(%)	
SPEECH DISORDER										
8 - < 13	61	1	(1.6)	61	0		122	1	(0.8)	1.00
13 - < 18	48	1	(2.1)	49	2	(4.1)	97	3	(3.1)	1.00
Total	109	2	(1.8)	110	2	(1.8)	219	4	(1.8)	1.00
THIRST										
8 - < 13	61	2	(3.3)	61	2	(3.3)	122	4	(3.3)	1.00
13 - < 18	48	0		49	0		97	0		
Total	109	2	(1.8)	110	2	(1.8)	219	4	(1.8)	1.00

RMP.B1YP.JCLLIB2(AES6JEAC)
RMP.B1YO.HCJEREP(AES6JEAC)
AGE: Patient Age
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.47. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Age Category
All Randomized Patients
Acute Treatment Phase (Study Periods III-IV)
B1Y-MC-HCJE (continued)

	Flx 20			Placebo			Total			p-Value*
AGE	N	n	(%)	N	n	(%)	N	n	(%)	
WEIGHT LOSS										
8 - < 13	61	1	(1.6)	61	0		122	1	(0.8)	1.00
13 - < 18	48	1	(2.1)	49	1	(2.0)	97	2	(2.1)	1.00
Total	109	2	(1.8)	110	1	(0.9)	219	3	(1.4)	.622
ACUTE BRAIN SYNDROME										
8 - < 13	61	0		61	0		122	0		
13 - < 18	48	1	(2.1)	49	0		97	1	(1.0)	.495
Total	109	1	(0.9)	110	0		219	1	(0.5)	.498

RMP.B1YP.JCLLIB2(AES6JEAC)
RMP.B1YO.HCJEREP(AES6JEAC)
AGE: Patient Age
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.47. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Age Category
All Randomized Patients
Acute Treatment Phase (Study Periods III-IV)
B1Y-MC-HCJE (continued)

	Flx 20			Placebo			Total			p-Value*
AGE	N	n	(%)	N	n	(%)	N	n	(%)	
APATHY										
8 - < 13	61	0		61	0		122	0		
13 - < 18	48	1	(2.1)	49	0		97	1	(1.0)	.495
Total	109	1	(0.9)	110	0		219	1	(0.5)	.498
BRONCHITIS										
8 - < 13	61	1	(1.6)	61	0		122	1	(0.8)	1.00
13 - < 18	48	0		49	0		97	0		
Total	109	1	(0.9)	110	0		219	1	(0.5)	.498

RMP.B1YP.JCLLIB2(AES6JEAC)
RMP.B1YO.HCJEREP(AES6JEAC)
AGE: Patient Age
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.47. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Age Category
All Randomized Patients
Acute Treatment Phase (Study Periods III-IV)
B1Y-MC-HCJE (continued)

	Flx 20			Placebo			Total			p-Value*
AGE	N	n	(%)	N	n	(%)	N	n	(%)	
BUCCOGLOSSAL SYNDROME										
8 - < 13	61	0		61	0		122	0		
13 - < 18	48	1	(2.1)	49	0		97	1	(1.0)	.495
Total	109	1	(0.9)	110	0		219	1	(0.5)	.498
CONTACT DERMATITIS										
8 - < 13	61	1	(1.6)	61	0		122	1	(0.8)	1.00
13 - < 18	48	0		49	0		97	0		
Total	109	1	(0.9)	110	0		219	1	(0.5)	.498

RMP.B1YP.JCLLIB2(AES6JEAC)
RMP.B1YO.HCJEREP(AES6JEAC)
AGE: Patient Age
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.47. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Age Category
All Randomized Patients
Acute Treatment Phase (Study Periods III-IV)
B1Y-MC-HCJE (continued)

	Flx 20			Placebo			Total			p-Value*
AGE	N	n	(%)	N	n	(%)	N	n	(%)	
DELUSIONS										
8 - < 13	61	1	(1.6)	61	0		122	1	(0.8)	1.00
13 - < 18	48	0		49	0		97	0		
Total	109	1	(0.9)	110	0		219	1	(0.5)	.498
DYSPHAGIA										
8 - < 13	61	1	(1.6)	61	0		122	1	(0.8)	1.00
13 - < 18	48	0		49	1	(2.0)	97	1	(1.0)	1.00
Total	109	1	(0.9)	110	1	(0.9)	219	2	(0.9)	1.00

RMP.B1YP.JCLLIB2(AES6JEAC)
RMP.B1YO.HCJEREP(AES6JEAC)
AGE: Patient Age
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.47. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Age Category
All Randomized Patients
Acute Treatment Phase (Study Periods III-IV)
B1Y-MC-HCJE (continued)

	Flx 20			Placebo			Total			p-Value*
AGE	N	n	(%)	N	n	(%)	N	n	(%)	
DYSPNEA										
8 - < 13	61	1	(1.6)	61	0		122	1	(0.8)	1.00
13 - < 18	48	0		49	0		97	0		
Total	109	1	(0.9)	110	0		219	1	(0.5)	.498
EAR DISORDER										
8 - < 13	61	1	(1.6)	61	1	(1.6)	122	2	(1.6)	1.00
13 - < 18	48	0		49	0		97	0		
Total	109	1	(0.9)	110	1	(0.9)	219	2	(0.9)	1.00

RMP.B1YP.JCLLIB2(AES6JEAC)
RMP.B1YO.HCJEREP(AES6JEAC)
AGE: Patient Age
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.47. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Age Category
All Randomized Patients
Acute Treatment Phase (Study Periods III-IV)
B1Y-MC-HCJE (continued)

	Flx 20			Placebo			Total			p-Value*
AGE	N	n	(%)	N	n	(%)	N	n	(%)	
EMOTIONAL LABILITY										
8 - < 13	61	1	(1.6)	61	0		122	1	(0.8)	1.00
13 - < 18	48	0		49	0		97	0		
Total	109	1	(0.9)	110	0		219	1	(0.5)	.498
ENDOMETRIAL HYPERPLASIA										
8 - < 13	61	0		61	0		122	0		
13 - < 18	48	1	(2.1)	49	0		97	1	(1.0)	.495
Total	109	1	(0.9)	110	0		219	1	(0.5)	.498

RMP.B1YP.JCLLIB2(AES6JEAC)
RMP.B1YO.HCJEREP(AES6JEAC)
AGE: Patient Age
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.47. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Age Category
All Randomized Patients
Acute Treatment Phase (Study Periods III-IV)
B1Y-MC-HCJE (continued)

	Flx 20			Placebo			Total			p-Value*
AGE	N	n	(%)	N	n	(%)	N	n	(%)	
EUPHORIA										
8 - < 13	61	1	(1.6)	61	0		122	1	(0.8)	1.00
13 - < 18	48	0		49	0		97	0		
Total	109	1	(0.9)	110	0		219	1	(0.5)	.498
EYE PAIN										
8 - < 13	61	1	(1.6)	61	0		122	1	(0.8)	1.00
13 - < 18	48	0		49	0		97	0		
Total	109	1	(0.9)	110	0		219	1	(0.5)	.498

RMP.B1YP.JCLLIB2(AES6JEAC)
RMP.B1YO.HCJEREP(AES6JEAC)
AGE: Patient Age
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.47. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Age Category
All Randomized Patients
Acute Treatment Phase (Study Periods III-IV)
B1Y-MC-HCJE (continued)

	Flx 20			Placebo			Total			p-Value*
AGE	N	n	(%)	N	n	(%)	N	n	(%)	
FECAL INCONTINENCE										
8 - < 13	61	1	(1.6)	61	0		122	1	(0.8)	1.00
13 - < 18	48	0		49	0		97	0		
Total	109	1	(0.9)	110	0		219	1	(0.5)	.498
FLATULENCE										
8 - < 13	61	1	(1.6)	61	0		122	1	(0.8)	1.00
13 - < 18	48	0		49	0		97	0		
Total	109	1	(0.9)	110	0		219	1	(0.5)	.498

RMP.B1YP.JCLLIB2(AES6JEAC)
RMP.B1YO.HCJEREP(AES6JEAC)
AGE: Patient Age
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.47. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Age Category
All Randomized Patients
Acute Treatment Phase (Study Periods III-IV)
B1Y-MC-HCJE (continued)

	Flx 20			Placebo			Total			p-Value*
AGE	N	n	(%)	N	n	(%)	N	n	(%)	
FUNGAL DERMATITIS										
8 - < 13	61	1	(1.6)	61	1	(1.6)	122	2	(1.6)	1.00
13 - < 18	48	0		49	0		97	0		
Total	109	1	(0.9)	110	1	(0.9)	219	2	(0.9)	1.00
HALLUCINATIONS										
8 - < 13	61	1	(1.6)	61	0		122	1	(0.8)	1.00
13 - < 18	48	0		49	0		97	0		
Total	109	1	(0.9)	110	0		219	1	(0.5)	.498

RMP.B1YP.JCLLIB2(AES6JEAC)
RMP.B1YO.HCJEREP(AES6JEAC)
AGE: Patient Age
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.47. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Age Category
All Randomized Patients
Acute Treatment Phase (Study Periods III-IV)
B1Y-MC-HCJE (continued)

	Flx 20			Placebo			Total			p-Value*
AGE	N	n	(%)	N	n	(%)	N	n	(%)	
HEPATITIS NONSPECIFIC										
8 - < 13	61	1	(1.6)	61	0		122	1	(0.8)	1.00
13 - < 18	48	0		49	0		97	0		
Total	109	1	(0.9)	110	0		219	1	(0.5)	.498
HEPATOMEGALY										
8 - < 13	61	1	(1.6)	61	0		122	1	(0.8)	1.00
13 - < 18	48	0		49	0		97	0		
Total	109	1	(0.9)	110	0		219	1	(0.5)	.498

RMP.B1YP.JCLLIB2(AES6JEAC)
RMP.B1YO.HCJEREP(AES6JEAC)
AGE: Patient Age
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.47. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Age Category
All Randomized Patients
Acute Treatment Phase (Study Periods III-IV)
B1Y-MC-HCJE (continued)

	Flx 20			Placebo			Total			p-Value*
AGE	N	n	(%)	N	n	(%)	N	n	(%)	
HERPES SIMPLEX										
8 - < 13	61	0		61	0		122	0		
13 - < 18	48	1	(2.1)	49	0		97	1	(1.0)	.495
Total	109	1	(0.9)	110	0		219	1	(0.5)	.498
HYPERTONIA										
8 - < 13	61	1	(1.6)	61	1	(1.6)	122	2	(1.6)	1.00
13 - < 18	48	0		49	0		97	0		
Total	109	1	(0.9)	110	1	(0.9)	219	2	(0.9)	1.00

RMP.B1YP.JCLLIB2(AES6JEAC)
RMP.B1YO.HCJEREP(AES6JEAC)
AGE: Patient Age
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.47. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Age Category
All Randomized Patients
Acute Treatment Phase (Study Periods III-IV)
B1Y-MC-HCJE (continued)

	Flx 20			Placebo			Total			p-Value*
AGE	N	n	(%)	N	n	(%)	N	n	(%)	
HYPOTENSION										
8 - < 13	61	0		61	0		122	0		
13 - < 18	48	1	(2.1)	49	0		97	1	(1.0)	.495
Total	109	1	(0.9)	110	0		219	1	(0.5)	.498
JOINT DISORDER										
8 - < 13	61	1	(1.6)	61	0		122	1	(0.8)	1.00
13 - < 18	48	0		49	0		97	0		
Total	109	1	(0.9)	110	0		219	1	(0.5)	.498

RMP.B1YP.JCLLIB2(AES6JEAC)
RMP.B1YO.HCJEREP(AES6JEAC)
AGE: Patient Age
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.47. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Age Category
All Randomized Patients
Acute Treatment Phase (Study Periods III-IV)
B1Y-MC-HCJE (continued)

	Flx 20			Placebo			Total			p-Value*
AGE	N	n	(%)	N	n	(%)	N	n	(%)	
LEG CRAMPS										
8 - < 13	61	1	(1.6)	61	0		122	1	(0.8)	1.00
13 - < 18	48	0		49	1	(2.0)	97	1	(1.0)	1.00
Total	109	1	(0.9)	110	1	(0.9)	219	2	(0.9)	1.00
LUNG DISORDER										
8 - < 13	61	1	(1.6)	61	0		122	1	(0.8)	1.00
13 - < 18	48	0		49	0		97	0		
Total	109	1	(0.9)	110	0		219	1	(0.5)	.498

RMP.B1YP.JCLLIB2(AES6JEAC)
RMP.B1YO.HCJEREP(AES6JEAC)
AGE: Patient Age
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.47. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Age Category
All Randomized Patients
Acute Treatment Phase (Study Periods III-IV)
B1Y-MC-HCJE (continued)

	Flx 20			Placebo			Total			p-Value*
AGE	N	n	(%)	N	n	(%)	N	n	(%)	
MACULOPAPULAR RASH										
8 - < 13	61	0		61	0		122	0		
13 - < 18	48	1	(2.1)	49	1	(2.0)	97	2	(2.1)	1.00
Total	109	1	(0.9)	110	1	(0.9)	219	2	(0.9)	1.00
MANIC REACTION										
8 - < 13	61	1	(1.6)	61	0		122	1	(0.8)	1.00
13 - < 18	48	0		49	0		97	0		
Total	109	1	(0.9)	110	0		219	1	(0.5)	.498

RMP.B1YP.JCLLIB2(AES6JEAC)
RMP.B1YO.HCJEREP(AES6JEAC)
AGE: Patient Age
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.47. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Age Category
All Randomized Patients
Acute Treatment Phase (Study Periods III-IV)
B1Y-MC-HCJE (continued)

	Flx 20			Placebo			Total			p-Value*
AGE	N	n	(%)	N	n	(%)	N	n	(%)	
MIGRAINE										
8 - < 13	61	1	(1.6)	61	1	(1.6)	122	2	(1.6)	1.00
13 - < 18	48	0		49	0		97	0		
Total	109	1	(0.9)	110	1	(0.9)	219	2	(0.9)	1.00
MYALGIA										
8 - < 13	61	1	(1.6)	61	3	(4.9)	122	4	(3.3)	.619
13 - < 18	48	0		49	2	(4.1)	97	2	(2.1)	.495
Total	109	1	(0.9)	110	5	(4.5)	219	6	(2.7)	.212

RMP.B1YP.JCLLIB2(AES6JEAC)
RMP.B1YO.HCJEREP(AES6JEAC)
AGE: Patient Age
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.47. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Age Category
All Randomized Patients
Acute Treatment Phase (Study Periods III-IV)
B1Y-MC-HCJE (continued)

	Flx 20			Placebo			Total			p-Value*
AGE	N	n	(%)	N	n	(%)	N	n	(%)	
NEUROSIS										
8 - < 13	61	1	(1.6)	61	0		122	1	(0.8)	1.00
13 - < 18	48	0		49	0		97	0		
Total	109	1	(0.9)	110	0		219	1	(0.5)	.498
OVERDOSE										
8 - < 13	61	1	(1.6)	61	0		122	1	(0.8)	1.00
13 - < 18	48	0		49	0		97	0		
Total	109	1	(0.9)	110	0		219	1	(0.5)	.498

RMP.B1YP.JCLLIB2(AES6JEAC)
RMP.B1YO.HCJEREP(AES6JEAC)
AGE: Patient Age
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.47. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Age Category
All Randomized Patients
Acute Treatment Phase (Study Periods III-IV)
B1Y-MC-HCJE (continued)

	Flx 20			Placebo			Total			p-Value*
AGE	N	n	(%)	N	n	(%)	N	n	(%)	
PALPITATION										
8 - < 13	61	0		61	0		122	0		
13 - < 18	48	1	(2.1)	49	1	(2.0)	97	2	(2.1)	1.00
Total	109	1	(0.9)	110	1	(0.9)	219	2	(0.9)	1.00
PNEUMONIA										
8 - < 13	61	1	(1.6)	61	0		122	1	(0.8)	1.00
13 - < 18	48	0		49	0		97	0		
Total	109	1	(0.9)	110	0		219	1	(0.5)	.498

RMP.B1YP.JCLLIB2(AES6JEAC)
RMP.B1YO.HCJEREP(AES6JEAC)
AGE: Patient Age
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.47. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Age Category
All Randomized Patients
Acute Treatment Phase (Study Periods III-IV)
B1Y-MC-HCJE (continued)

	Flx 20			Placebo			Total			p-Value*
AGE	N	n	(%)	N	n	(%)	N	n	(%)	
SURGICAL PROCEDURE										
8 - < 13	61	0		61	0		122	0		
13 - < 18	48	1	(2.1)	49	1	(2.0)	97	2	(2.1)	1.00
Total	109	1	(0.9)	110	1	(0.9)	219	2	(0.9)	1.00
SWEATING										
8 - < 13	61	1	(1.6)	61	0		122	1	(0.8)	1.00
13 - < 18	48	0		49	0		97	0		
Total	109	1	(0.9)	110	0		219	1	(0.5)	.498

RMP.B1YP.JCLLIB2(AES6JEAC)
RMP.B1YO.HCJEREP(AES6JEAC)
AGE: Patient Age
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.47. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Age Category
All Randomized Patients
Acute Treatment Phase (Study Periods III-IV)
B1Y-MC-HCJE (continued)

	Flx 20			Placebo			Total			p-Value*
AGE	N	n	(%)	N	n	(%)	N	n	(%)	
SYNCOPE										
8 - < 13	61	0		61	0		122	0		
13 - < 18	48	1	(2.1)	49	0		97	1	(1.0)	.495
Total	109	1	(0.9)	110	0		219	1	(0.5)	.498
TACHYCARDIA										
8 - < 13	61	0		61	0		122	0		
13 - < 18	48	1	(2.1)	49	0		97	1	(1.0)	.495
Total	109	1	(0.9)	110	0		219	1	(0.5)	.498

RMP.B1YP.JCLLIB2(AES6JEAC)
RMP.B1YO.HCJEREP(AES6JEAC)
AGE: Patient Age
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.47. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Age Category
All Randomized Patients
Acute Treatment Phase (Study Periods III-IV)
B1Y-MC-HCJE (continued)

	Flx 20			Placebo			Total			p-Value*
AGE	N	n	(%)	N	n	(%)	N	n	(%)	
TINNITUS										
8 - < 13	61	0		61	0		122	0		
13 - < 18	48	1	(2.1)	49	0		97	1	(1.0)	.495
Total	109	1	(0.9)	110	0		219	1	(0.5)	.498
TOOTH DISORDER										
8 - < 13	61	0		61	0		122	0		
13 - < 18	48	1	(2.1)	49	0		97	1	(1.0)	.495
Total	109	1	(0.9)	110	0		219	1	(0.5)	.498

RMP.B1YP.JCLLIB2(AES6JEAC)
RMP.B1YO.HCJEREP(AES6JEAC)
AGE: Patient Age
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.47. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Age Category
All Randomized Patients
Acute Treatment Phase (Study Periods III-IV)
B1Y-MC-HCJE (continued)

	Flx 20			Placebo			Total			p-Value*
AGE	N	n	(%)	N	n	(%)	N	n	(%)	
URINARY FREQUENCY										
8 - < 13	61	1	(1.6)	61	1	(1.6)	122	2	(1.6)	1.00
13 - < 18	48	0		49	1	(2.0)	97	1	(1.0)	1.00
Total	109	1	(0.9)	110	2	(1.8)	219	3	(1.4)	1.00
URINARY TRACT INFECTION										
8 - < 13	61	1	(1.6)	61	0		122	1	(0.8)	1.00
13 - < 18	48	0		49	1	(2.0)	97	1	(1.0)	1.00
Total	109	1	(0.9)	110	1	(0.9)	219	2	(0.9)	1.00

RMP.B1YP.JCLLIB2(AES6JEAC)
RMP.B1YO.HCJEREP(AES6JEAC)
AGE: Patient Age
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.47. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Age Category
All Randomized Patients
Acute Treatment Phase (Study Periods III-IV)
B1Y-MC-HCJE (continued)

	Flx 20			Placebo			Total			p-Value*
AGE	N	n	(%)	N	n	(%)	N	n	(%)	
VASODILATATION										
8 - < 13	61	0		61	0		122	0		
13 - < 18	48	1	(2.1)	49	0		97	1	(1.0)	.495
Total	109	1	(0.9)	110	0		219	1	(0.5)	.498
YAWN										
8 - < 13	61	1	(1.6)	61	0		122	1	(0.8)	1.00
13 - < 18	48	0		49	0		97	0		
Total	109	1	(0.9)	110	0		219	1	(0.5)	.498

RMP.B1YP.JCLLIB2(AES6JEAC)
RMP.B1YO.HCJEREP(AES6JEAC)
AGE: Patient Age
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.47. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Age Category
All Randomized Patients
Acute Treatment Phase (Study Periods III-IV)
B1Y-MC-HCJE (continued)

	Flx 20			Placebo			Total			p-Value*
AGE	N	n	(%)	N	n	(%)	N	n	(%)	
ABDOMINAL SYNDROME ACUTE										
8 - < 13	61	0		61	1	(1.6)	122	1	(0.8)	1.00
13 - < 18	48	0		49	0		97	0		
Total	109	0		110	1	(0.9)	219	1	(0.5)	1.00
ACNE										
8 - < 13	61	0		61	1	(1.6)	122	1	(0.8)	1.00
13 - < 18	48	0		49	0		97	0		
Total	109	0		110	1	(0.9)	219	1	(0.5)	1.00

RMP.B1YP.JCLLIB2(AES6JEAC)
RMP.B1YO.HCJEREP(AES6JEAC)
AGE: Patient Age
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.47. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Age Category
All Randomized Patients
Acute Treatment Phase (Study Periods III-IV)
B1Y-MC-HCJE (continued)

	Flx 20			Placebo			Total			p-Value*
AGE	N	n	(%)	N	n	(%)	N	n	(%)	
ALOPECIA										
8 - < 13	61	0		61	0		122	0		
13 - < 18	48	0		49	1	(2.0)	97	1	(1.0)	1.00
Total	109	0		110	1	(0.9)	219	1	(0.5)	1.00
AMNESIA										
8 - < 13	61	0		61	0		122	0		
13 - < 18	48	0		49	1	(2.0)	97	1	(1.0)	1.00
Total	109	0		110	1	(0.9)	219	1	(0.5)	1.00

RMP.B1YP.JCLLIB2(AES6JEAC)
RMP.B1YO.HCJEREP(AES6JEAC)
AGE: Patient Age
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.47. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Age Category
All Randomized Patients
Acute Treatment Phase (Study Periods III-IV)
B1Y-MC-HCJE (continued)

	Flx 20			Placebo			Total			p-Value*
AGE	N	n	(%)	N	n	(%)	N	n	(%)	
APHTHOUS STOMATITIS										
8 - < 13	61	0		61	1	(1.6)	122	1	(0.8)	1.00
13 - < 18	48	0		49	0		97	0		
Total	109	0		110	1	(0.9)	219	1	(0.5)	1.00
ARTHRALGIA										
8 - < 13	61	0		61	1	(1.6)	122	1	(0.8)	1.00
13 - < 18	48	0		49	0		97	0		
Total	109	0		110	1	(0.9)	219	1	(0.5)	1.00

RMP.B1YP.JCLLIB2(AES6JEAC)
RMP.B1YO.HCJEREP(AES6JEAC)
AGE: Patient Age
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.47. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Age Category
All Randomized Patients
Acute Treatment Phase (Study Periods III-IV)
B1Y-MC-HCJE (continued)

	Flx 20			Placebo			Total			p-Value*
AGE	N	n	(%)	N	n	(%)	N	n	(%)	
BRADYCARDIA										
8 - < 13	61	0		61	1	(1.6)	122	1	(0.8)	1.00
13 - < 18	48	0		49	0		97	0		
Total	109	0		110	1	(0.9)	219	1	(0.5)	1.00
CYSTITIS										
8 - < 13	61	0		61	0		122	0		
13 - < 18	48	0		49	1	(2.0)	97	1	(1.0)	1.00
Total	109	0		110	1	(0.9)	219	1	(0.5)	1.00

RMP.B1YP.JCLLIB2(AES6JEAC)
RMP.B1YO.HCJEREP(AES6JEAC)
AGE: Patient Age
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.47. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Age Category
All Randomized Patients
Acute Treatment Phase (Study Periods III-IV)
B1Y-MC-HCJE (continued)

	Flx 20			Placebo			Total			p-Value*
AGE	N	n	(%)	N	n	(%)	N	n	(%)	
DEHYDRATION										
8 - < 13	61	0		61	2	(3.3)	122	2	(1.6)	.496
13 - < 18	48	0		49	0		97	0		
Total	109	0		110	2	(1.8)	219	2	(0.9)	.498
DYSURIA										
8 - < 13	61	0		61	1	(1.6)	122	1	(0.8)	1.00
13 - < 18	48	0		49	0		97	0		
Total	109	0		110	1	(0.9)	219	1	(0.5)	1.00

RMP.B1YP.JCLLIB2(AES6JEAC)
RMP.B1YO.HCJEREP(AES6JEAC)
AGE: Patient Age
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.47. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Age Category
All Randomized Patients
Acute Treatment Phase (Study Periods III-IV)
B1Y-MC-HCJE (continued)

	Flx 20			Placebo			Total			p-Value*
AGE	N	n	(%)	N	n	(%)	N	n	(%)	
FACE EDEMA										
8 - < 13	61	0		61	0		122	0		
13 - < 18	48	0		49	1	(2.0)	97	1	(1.0)	1.00
Total	109	0		110	1	(0.9)	219	1	(0.5)	1.00
GASTROINTESTINAL DISORDER										
8 - < 13	61	0		61	1	(1.6)	122	1	(0.8)	1.00
13 - < 18	48	0		49	0		97	0		
Total	109	0		110	1	(0.9)	219	1	(0.5)	1.00

RMP.B1YP.JCLLIB2(AES6JEAC)
RMP.B1YO.HCJEREP(AES6JEAC)
AGE: Patient Age
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.47. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Age Category
All Randomized Patients
Acute Treatment Phase (Study Periods III-IV)
B1Y-MC-HCJE (continued)

	Flx 20			Placebo			Total			p-Value*
AGE	N	n	(%)	N	n	(%)	N	n	(%)	
HYPESTHESIA										
8 - < 13	61	0		61	1	(1.6)	122	1	(0.8)	1.00
13 - < 18	48	0		49	0		97	0		
Total	109	0		110	1	(0.9)	219	1	(0.5)	1.00
HYPOVENTILATION										
8 - < 13	61	0		61	1	(1.6)	122	1	(0.8)	1.00
13 - < 18	48	0		49	0		97	0		
Total	109	0		110	1	(0.9)	219	1	(0.5)	1.00

RMP.B1YP.JCLLIB2(AES6JEAC)
RMP.B1YO.HCJEREP(AES6JEAC)
AGE: Patient Age
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.47. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Age Category
All Randomized Patients
Acute Treatment Phase (Study Periods III-IV)
B1Y-MC-HCJE (continued)

	Flx 20			Placebo			Total			p-Value*
AGE	N	n	(%)	N	n	(%)	N	n	(%)	
INCREASED APPETITE										
8 - < 13	61	0		61	2	(3.3)	122	2	(1.6)	.496
13 - < 18	48	0		49	1	(2.0)	97	1	(1.0)	1.00
Total	109	0		110	3	(2.7)	219	3	(1.4)	.247
INTENTIONAL INJURY										
8 - < 13	61	0		61	0		122	0		
13 - < 18	48	0		49	1	(2.0)	97	1	(1.0)	1.00
Total	109	0		110	1	(0.9)	219	1	(0.5)	1.00

RMP.B1YP.JCLLIB2(AES6JEAC)
RMP.B1YO.HCJEREP(AES6JEAC)
AGE: Patient Age
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.47. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Age Category
All Randomized Patients
Acute Treatment Phase (Study Periods III-IV)
B1Y-MC-HCJE (continued)

	Flx 20			Placebo			Total			p-Value*
AGE	N	n	(%)	N	n	(%)	N	n	(%)	
LARYNGITIS										
8 - < 13	61	0		61	1	(1.6)	122	1	(0.8)	1.00
13 - < 18	48	0		49	0		97	0		
Total	109	0		110	1	(0.9)	219	1	(0.5)	1.00
LEUKORRHEA										
8 - < 13	61	0		61	1	(1.6)	122	1	(0.8)	1.00
13 - < 18	48	0		49	0		97	0		
Total	109	0		110	1	(0.9)	219	1	(0.5)	1.00

RMP.B1YP.JCLLIB2(AES6JEAC)
RMP.B1YO.HCJEREP(AES6JEAC)
AGE: Patient Age
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.47. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Age Category
All Randomized Patients
Acute Treatment Phase (Study Periods III-IV)
B1Y-MC-HCJE (continued)

	Flx 20			Placebo			Total			p-Value*
AGE	N	n	(%)	N	n	(%)	N	n	(%)	
METRORRHAGIA										
8 - < 13	61	0		61	0		122	0		
13 - < 18	48	0		49	1	(2.0)	97	1	(1.0)	1.00
Total	109	0		110	1	(0.9)	219	1	(0.5)	1.00
MOUTH ULCERATION										
8 - < 13	61	0		61	1	(1.6)	122	1	(0.8)	1.00
13 - < 18	48	0		49	0		97	0		
Total	109	0		110	1	(0.9)	219	1	(0.5)	1.00

RMP.B1YP.JCLLIB2(AES6JEAC)
RMP.B1YO.HCJEREP(AES6JEAC)
AGE: Patient Age
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.47. Treatment-Emergent Non-Solicited Adverse Events Subgroup Analysis by Age Category All Randomized Patients Acute Treatment Phase (Study Periods III-IV) B1Y-MC-HCJE (continued)

	Flx 20		Placebo		Total		p-Value*
AGE	N	n (%)	N	n (%)	N	n (%)	
SKIN DISCOLORATION							
8 - < 13	61	0	61	1 (1.6)	122	1 (0.8)	1.00
13 - < 18	48	0	49	0	97	0	
Total	109	0	110	1 (0.9)	219	1 (0.5)	1.00
SKIN ULCER							
8 - < 13	61	0	61	1 (1.6)	122	1 (0.8)	1.00
13 - < 18	48	0	49	0	97	0	
Total	109	0	110	1 (0.9)	219	1 (0.5)	1.00

RMP.B1YP.JCLLIB2(AES6JEAC)
RMP.B1YO.HCJEREP(AES6JEAC)
AGE: Patient Age
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.47. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Age Category
All Randomized Patients
Acute Treatment Phase (Study Periods III-IV)
B1Y-MC-HCJE (continued)

	Flx 20			Placebo			Total			p-Value*
AGE	N	n	(%)	N	n	(%)	N	n	(%)	
SUBCUTANEOUS NODULE										
8 - < 13	61	0		61	1	(1.6)	122	1	(0.8)	1.00
13 - < 18	48	0		49	0		97	0		
Total	109	0		110	1	(0.9)	219	1	(0.5)	1.00
THINKING ABNORMAL										
8 - < 13	61	0		61	1	(1.6)	122	1	(0.8)	1.00
13 - < 18	48	0		49	0		97	0		
Total	109	0		110	1	(0.9)	219	1	(0.5)	1.00

RMP.B1YP.JCLLIB2(AES6JEAC)
RMP.B1YO.HCJEREP(AES6JEAC)
AGE: Patient Age
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.47. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Age Category
All Randomized Patients
Acute Treatment Phase (Study Periods III-IV)
B1Y-MC-HCJE (concluded)

	Flx 20			Placebo			Total			p-Value*
AGE	N	n	(%)	N	n	(%)	N	n	(%)	
UNEXPECTED BENEFIT										
8 - < 13	61	0		61	0		122	0		
13 - < 18	48	0		49	1	(2.0)	97	1	(1.0)	1.00
Total	109	0		110	1	(0.9)	219	1	(0.5)	1.00
WEIGHT GAIN										
8 - < 13	61	0		61	1	(1.6)	122	1	(0.8)	1.00
13 - < 18	48	0		49	0		97	0		
Total	109	0		110	1	(0.9)	219	1	(0.5)	1.00

RMP.B1YP.JCLLIB2(AES6JEAC)
RMP.B1YO.HCJEREP(AES6JEAC)
AGE: Patient Age
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.48 presents the incidence of treatment-emergent solicited adverse events from the Side-Effects Checklist analyzed by age subgroups during the acute treatment phase.

Statistically significant differences across age subgroups were observed for two treatment-emergent solicited adverse events when testing for the homogeneity of odds ratios using the Breslow-Day test. The Breslow-Day test for trouble with eating was statistically significant (p=.040); however, neither of the between-treatment group comparisons were statistically significant for age subgroups. The Breslow-Day test for trouble doing things with your hands was also statistically significant (p=.002). The between-treatment group comparison was significant for adolescents (p=.004), but not for children. This event occurred more frequently in placebo-treated adolescents (22%) as compared with fluoxetine-treated adolescents (2%).

Table 14.48. Treatment-Emergent Solicited Adverse Events
Side Effects Checklist Subgroup Analysis by Age
Significant (p<.05) Difference in Odds Ratio
All Randomized Patients
Acute Treatment Phase (Study Periods III-IV)
B1Y-MC-HCJE

SECL Event - Have you had trouble with:	AGE	Flx 20 N	Flx 20 n	Flx 20 (%)	Placebo N	Placebo n	Placebo (%)	p-Values: Homogeneity of Odds Ratio p-Value*	p-Values: Between Group Comparison p-Value**
01. EATING	8 - <13	61	19	(31.1)	61	14	(23.0)	.040	.415
	13 - <=18	48	12	(25.0)	49	21	(42.9)		.087
02. DRINKING	8 - <13	61	9	(14.8)	61	13	(21.3)	.911	.481
	13 - <=18	48	5	(10.4)	49	7	(14.3)		.759
03. DRY MOUTH AND LIPS	8 - <13	61	15	(24.6)	61	18	(29.5)	.972	.684
	13 - <=18	48	17	(35.4)	49	20	(40.8)		.677
04. WETNESS IN MOUTH	8 - <13	61	6	(9.8)	61	10	(16.4)	.705	.422
	13 - <=18	48	4	(8.3)	49	9	(18.4)		.233
05. CONSTIPATION	8 - <13	61	6	(9.8)	61	6	(9.8)	.773	1.00
	13 - <=18	48	3	(6.3)	49	4	(8.2)		1.00
06. DIARRHEA	8 - <13	61	15	(24.6)	61	12	(19.7)	.718	.663
	13 - <=18	48	7	(14.6)	49	7	(14.3)		1.00
07. STOMACHACHES	8 - <13	61	24	(39.3)	61	25	(41.0)	.510	1.00
	13 - <=18	48	13	(27.1)	49	18	(36.7)		.385

* The homogeneity of odds ratio p-Value is derived from the Breslow-Day test.
**The between group comparison within strata p-Value is from the Fisher's Exact Test.
Treatment-Emergent Solicited = was present at baseline and worsened as defined by increase in score on the side-effects checklist or new occurrence after baseline.
RMP.B1YP.SASPGM(CUSJESG1)
RMP.B1YO.HCJEREP(CUSTJEML)

Table 14.48. Treatment-Emergent Solicited Adverse Events
Side Effects Checklist Subgroup Analysis by Age
Significant (p<.05) Difference in Odds Ratio
All Randomized Patients
Acute Treatment Phase (Study Periods III-IV)
B1Y-MC-HCJE (continued)

SECL Event - Have you had trouble with:	AGE	Flx 20 N	Flx 20 n	Flx 20 (%)	Placebo N	Placebo n	Placebo (%)	p-Values: Homogeneity of Odds Ratio p-Value*	p-Values: Between Group Comparison p-Value**
08. MUSCLE CRAMPS	8 - <13	61	15	(24.6)	61	18	(29.5)	.838	.684
	13 - <=18	48	12	(25.0)	49	16	(32.7)		.503
09. BEING SICK TO YOUR STOMACH	8 - <13	61	24	(39.3)	61	17	(27.9)	.317	.250
	13 - <=18	48	15	(31.3)	49	16	(32.7)		1.00
10. WETTING THE BED	8 - <13	61	3	(4.9)	61	4	(6.6)	.414	1.00
	13 - <=18	48	0		49	1	(2.0)		1.00
11. URINATING	8 - <13	61	5	(8.2)	61	6	(9.8)	.984	1.00
	13 - <=18	48	5	(10.4)	49	6	(12.2)		1.00
12. ITCHY OR SCRATCHY SKIN	8 - <13	61	14	(23.0)	61	17	(27.9)	.886	.678
	13 - <=18	48	13	(27.1)	49	15	(30.6)		.823
13. RASHES	8 - <13	61	13	(21.3)	61	9	(14.8)	.085	.481
	13 - <=18	48	4	(8.3)	49	9	(18.4)		.233
14. COLD OR SNIFFLES	8 - <13	61	21	(34.4)	61	24	(39.3)	.656	.708
	13 - <=18	48	20	(41.7)	49	26	(53.1)		.312

* The homogeneity of odds ratio p-Value is derived from the Breslow-Day test.
**The between group comparison within strata p-Value is from the Fisher’s Exact Test.
Treatment-Emergent Solicited = was present at baseline and worsened as defined by increase in score on the side-effects checklist or new occurrence after baseline.
RMP.B1YP.SASPGM(CUSJESG1)
RMP.B1YO.HCJEREP(CUSTJEML)

Table 14.48. Treatment-Emergent Solicited Adverse Events
Side Effects Checklist Subgroup Analysis by Age
Significant (p<.05) Difference in Odds Ratio
All Randomized Patients
Acute Treatment Phase (Study Periods III-IV)
B1Y-MC-HCJE (continued)

SECL Event - Have you had trouble with:	AGE	Flx 20 N	Flx 20 n	Flx 20 (%)	Placebo N	Placebo n	Placebo (%)	p-Values: Homogeneity of Odds Ratio p-Value*	p-Values: Between Group Comparison p-Value**
15. HEADACHE	8 - <13	61	31	(50.8)	61	25	(41.0)	.743	.364
	13 - <=18	48	18	(37.5)	49	16	(32.7)		.674
16. DIZZINESS	8 - <13	61	16	(26.2)	61	11	(18.0)	.830	.383
	13 - <=18	48	18	(37.5)	49	12	(24.5)		.192
17. PLAYING SPORTS	8 - <13	61	10	(16.4)	61	9	(14.8)	.371	1.00
	13 - <=18	48	7	(14.6)	49	11	(22.4)		.435
18. SHAKINESS	8 - <13	61	9	(14.8)	61	11	(18.0)	.694	.807
	13 - <=18	48	12	(25.0)	49	12	(24.5)		1.00
19. PRONOUNCING WORDS	8 - <13	61	9	(14.8)	61	14	(23.0)	.220	.355
	13 - <=18	48	4	(8.3)	49	14	(28.6)		.017
20. DOING THINGS WITH YOUR HANDS	8 - <13	61	12	(19.7)	61	8	(13.1)	.002	.464
	13 - <=18	48	1	(2.1)	49	11	(22.4)		.004
21. SITTING STILL	8 - <13	61	18	(29.5)	61	23	(37.7)	.642	.444
	13 - <=18	48	12	(25.0)	49	19	(38.8)		.192

* The homogeneity of odds ratio p-Value is derived from the Breslow-Day test.
**The between group comparison within strata p-Value is from the Fisher's Exact Test.
Treatment-Emergent Solicited = was present at baseline and worsened as defined by increase in score on the side-effects checklist or new occurrence after baseline.
RMP.B1YP.SASPGM(CUSJESG1)
RMP.B1YO.HCJEREP(CUSTJEML)

Table 14.48. Treatment-Emergent Solicited Adverse Events
Side Effects Checklist Subgroup Analysis by Age
Significant (p<.05) Difference in Odds Ratio
All Randomized Patients
Acute Treatment Phase (Study Periods III-IV)
B1Y-MC-HCJE (continued)

SECL Event - Have you had trouble with:	AGE	Flx 20 N	Flx 20 n	Flx 20 (%)	Placebo N	Placebo n	Placebo (%)	p-Values: Homogeneity of Odds Ratio p-Value*	p-Values: Between Group Comparison p-Value**
22. TIREDNESS	8 - <13	61	30	(49.2)	61	24	(39.3)	.333	.362
	13 - <=18	48	20	(41.7)	49	22	(44.9)		.838
23. FEELING SLEEPY	8 - <13	61	30	(49.2)	61	24	(39.3)	.417	.362
	13 - <=18	48	22	(45.8)	49	23	(46.9)		1.00
24. SLEEPING	8 - <13	61	20	(32.8)	61	24	(39.3)	.789	.572
	13 - <=18	48	19	(39.6)	49	21	(42.9)		.837
25. BAD DREAMS	8 - <13	61	13	(21.3)	61	12	(19.7)	.788	1.00
	13 - <=18	48	14	(29.2)	49	15	(30.6)		1.00
26. GETTING ALONG WITH PARENTS	8 - <13	61	22	(36.1)	61	20	(32.8)	.433	.849
	13 - <=18	48	21	(43.8)	49	25	(51.0)		.544
27. GETTING ALONG WITH KIDS	8 - <13	61	20	(32.8)	61	17	(27.9)	.609	.694
	13 - <=18	48	13	(27.1)	49	14	(28.6)		1.00
28. CRYING	8 - <13	61	24	(39.3)	61	21	(34.4)	.424	.708
	13 - <=18	48	15	(31.3)	49	18	(36.7)		.669

* The homogeneity of odds ratio p-Value is derived from the Breslow-Day test.
**The between group comparison within strata p-Value is from the Fisher's Exact Test.
Treatment-Emergent Solicited = was present at baseline and worsened as defined by increase in score on the side-effects checklist or new occurrence after baseline.
RMP.B1YP.SASPGM(CUSJESG1)
RMP.B1YO.HCJEREP(CUSTJEML)

Table 14.48. Treatment-Emergent Solicited Adverse Events
Side Effects Checklist Subgroup Analysis by Age
Significant (p<.05) Difference in Odds Ratio
All Randomized Patients
Acute Treatment Phase (Study Periods III-IV)
B1Y-MC-HCJE (concluded)

SECL Event - Have you had trouble with:	AGE	Flx 20 N	Flx 20 n	Flx 20 (%)	Placebo N	Placebo n	Placebo (%)	p-Values: Homogeneity of Odds Ratio p-Value*	p-Values: Between Group Comparison p-Value**
29. GETTING MAD	8 - <13	61	20	(32.8)	61	25	(41.0)	.691	.453
	13 - <=18	48	20	(41.7)	49	22	(44.9)		.838
30. NOT BEING HAPPY	8 - <13	61	22	(36.1)	61	21	(34.4)	.453	1.00
	13 - <=18	48	18	(37.5)	49	13	(26.5)		.281
31. BEING SAD	8 - <13	61	26	(42.6)	61	16	(26.2)	.169	.086
	13 - <=18	48	15	(31.3)	49	16	(32.7)		1.00
32. PAYING ATTENTION	8 - <13	61	20	(32.8)	61	16	(26.2)	.472	.552
	13 - <=18	48	23	(47.9)	49	15	(30.6)		.098

* The homogeneity of odds ratio p-Value is derived from the Breslow-Day test.
**The between group comparison within strata p-Value is from the Fisher's Exact Test.
Treatment-Emergent Solicited = was present at baseline and worsened as defined by increase in score on the side-effects checklist or new occurrence after baseline.
RMP.B1YP.SASPGM(CUSJESG1)
RMP.B1YO.HCJEREP(CUSTJEML)

14.3.2.1.2. By Gender

Table 14.49 presents the incidence of treatment-emergent non-solicited adverse events examined by gender subgroups for the acute treatment phase.

There was a statistically significant difference between treatment groups in the number of females reporting treatment-emergent non-solicited adverse events (p=.017). Overall, more fluoxetine-treated females (89%) reported at least one treatment-emergent non-solicited adverse event than placebo-treated females (69%). Despite the overall difference in reporting frequencies, there were no statistically significant differences between gender subgroups for any individual treatment-emergent non-solicited adverse event. There was a trend towards significance in the reporting of headache in females (p=.052), with more fluoxetine-treated females (37%) reporting the event than placebo-treated females (19%).

Table 14.49. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Gender
All Randomized Patients
Acute Treatment Phase (Study Periods III-IV)
B1Y-MC-HCJE

	Flx 20		Placebo		Total		p-Value*
Gender	N	n (%)	N	n (%)	N	n (%)	
PATIENTS WITH >= 1 TESS							
Female	54	48 (88.9)	54	37 (68.5)	108	85 (78.7)	.017
Male	55	46 (83.6)	56	43 (76.8)	111	89 (80.2)	.476
Total	109	94 (86.2)	110	80 (72.7)	219	174 (79.5)	.019
PATIENTS WITH NO TESS							
Female	54	6 (11.1)	54	17 (31.5)	108	23 (21.3)	.017
Male	55	9 (16.4)	56	13 (23.2)	111	22 (19.8)	.476
Total	109	15 (13.8)	110	30 (27.3)	219	45 (20.5)	.019

RMP.B1YP.JCLLIB2(AES6JEAA)
RMP.B1YO.HCJEREP(AES6JEAA)
Gender: Patient Gender
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
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Table 14.49. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Gender
All Randomized Patients
Acute Treatment Phase (Study Periods III-IV)
B1Y-MC-HCJE (continued)

	Flx 20		Placebo		Total		p-Value*
Gender	N	n (%)	N	n (%)	N	n (%)	
HEADACHE							
Female	54	20 (37.0)	54	10 (18.5)	108	30 (27.8)	.052
Male	55	13 (23.6)	56	8 (14.3)	111	21 (18.9)	.234
Total	109	33 (30.3)	110	18 (16.4)	219	51 (23.3)	.017
RHINITIS							
Female	54	13 (24.1)	54	11 (20.4)	108	24 (22.2)	.817
Male	55	11 (20.0)	56	10 (17.9)	111	21 (18.9)	.812
Total	109	24 (22.0)	110	21 (19.1)	219	45 (20.5)	.619

RMP.B1YP.JCLLIB2(AES6JEAA)
RMP.B1YO.HCJEREP(AES6JEAA)
Gender: Patient Gender
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.49. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Gender
All Randomized Patients
Acute Treatment Phase (Study Periods III-IV)
B1Y-MC-HCJE (continued)

	Flx 20		Placebo		Total		p-Value*
Gender	N	n (%)	N	n (%)	N	n (%)	
ABDOMINAL PAIN							
Female	54	11 (20.4)	54	8 (14.8)	108	19 (17.6)	.614
Male	55	6 (10.9)	56	8 (14.3)	111	14 (12.6)	.776
Total	109	17 (15.6)	110	16 (14.5)	219	33 (15.1)	.852
PHARYNGITIS							
Female	54	11 (20.4)	54	7 (13.0)	108	18 (16.7)	.439
Male	55	5 (9.1)	56	2 (3.6)	111	7 (6.3)	.271
Total	109	16 (14.7)	110	9 (8.2)	219	25 (11.4)	.143

RMP.B1YP.JCLLIB2(AES6JEAA)
RMP.B1YO.HCJEREP(AES6JEAA)
Gender: Patient Gender
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.49. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Gender
All Randomized Patients
Acute Treatment Phase (Study Periods III-IV)
B1Y-MC-HCJE (continued)

	Flx 20		Placebo		Total		p-Value*
Gender	N	n (%)	N	n (%)	N	n (%)	
ACCIDENTAL INJURY							
Female	54	3 (5.6)	54	4 (7.4)	108	7 (6.5)	1.00
Male	55	10 (18.2)	56	4 (7.1)	111	14 (12.6)	.094
Total	109	13 (11.9)	110	8 (7.3)	219	21 (9.6)	.261
DIARRHEA							
Female	54	3 (5.6)	54	6 (11.1)	108	9 (8.3)	.489
Male	55	8 (14.5)	56	5 (8.9)	111	13 (11.7)	.392
Total	109	11 (10.1)	110	11 (10.0)	219	22 (10.0)	1.00

RMP.B1YP.JCLLIB2(AES6JEAA)
RMP.B1YO.HCJEREP(AES6JEAA)
Gender: Patient Gender
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.49. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Gender
All Randomized Patients
Acute Treatment Phase (Study Periods III-IV)
B1Y-MC-HCJE (continued)

	Flx 20			Placebo			Total			p-Value*
Gender	N	n	(%)	N	n	(%)	N	n	(%)	
DIZZINESS										
Female	54	5	(9.3)	54	3	(5.6)	108	8	(7.4)	.716
Male	55	5	(9.1)	56	1	(1.8)	111	6	(5.4)	.113
Total	109	10	(9.2)	110	4	(3.6)	219	14	(6.4)	.106
RASH										
Female	54	5	(9.3)	54	2	(3.7)	108	7	(6.5)	.437
Male	55	5	(9.1)	56	2	(3.6)	111	7	(6.3)	.271
Total	109	10	(9.2)	110	4	(3.6)	219	14	(6.4)	.106

RMP.B1YP.JCLLIB2(AES6JEAA)
RMP.B1YO.HCJEREP(AES6JEAA)
Gender: Patient Gender
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.49. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Gender
All Randomized Patients
Acute Treatment Phase (Study Periods III-IV)
B1Y-MC-HCJE (continued)

	Flx 20			Placebo			Total			p-Value*
Gender	N	n	(%)	N	n	(%)	N	n	(%)	
ANOREXIA										
Female	54	6	(11.1)	54	4	(7.4)	108	10	(9.3)	.742
Male	55	3	(5.5)	56	2	(3.6)	111	5	(4.5)	.679
Total	109	9	(8.3)	110	6	(5.5)	219	15	(6.8)	.437
COUGH INCREASED										
Female	54	3	(5.6)	54	2	(3.7)	108	5	(4.6)	1.00
Male	55	6	(10.9)	56	5	(8.9)	111	11	(9.9)	.761
Total	109	9	(8.3)	110	7	(6.4)	219	16	(7.3)	.615

RMP.B1YP.JCLLIB2(AES6JEAA)
RMP.B1YO.HCJEREP(AES6JEAA)
Gender: Patient Gender
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.49. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Gender
All Randomized Patients
Acute Treatment Phase (Study Periods III-IV)
B1Y-MC-HCJE (continued)

	Flx 20			Placebo			Total			p-Value*
Gender	N	n	(%)	N	n	(%)	N	n	(%)	
NAUSEA										
Female	54	2	(3.7)	54	4	(7.4)	108	6	(5.6)	.678
Male	55	7	(12.7)	56	4	(7.1)	111	11	(9.9)	.360
Total	109	9	(8.3)	110	8	(7.3)	219	17	(7.8)	.806
NERVOUSNESS										
Female	54	2	(3.7)	54	3	(5.6)	108	5	(4.6)	1.00
Male	55	7	(12.7)	56	3	(5.4)	111	10	(9.0)	.203
Total	109	9	(8.3)	110	6	(5.5)	219	15	(6.8)	.437

RMP.B1YP.JCLLIB2(AES6JEAA)
RMP.B1YO.HCJEREP(AES6JEAA)
Gender: Patient Gender
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.49. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Gender
All Randomized Patients
Acute Treatment Phase (Study Periods III-IV)
B1Y-MC-HCJE (continued)

	Flx 20			Placebo			Total			p-Value*
Gender	N	n	(%)	N	n	(%)	N	n	(%)	
ASTHENIA										
Female	54	5	(9.3)	54	3	(5.6)	108	8	(7.4)	.716
Male	55	3	(5.5)	56	3	(5.4)	111	6	(5.4)	1.00
Total	109	8	(7.3)	110	6	(5.5)	219	14	(6.4)	.594
PAIN										
Female	54	5	(9.3)	54	4	(7.4)	108	9	(8.3)	1.00
Male	55	3	(5.5)	56	5	(8.9)	111	8	(7.2)	.716
Total	109	8	(7.3)	110	9	(8.2)	219	17	(7.8)	1.00

RMP.B1YP.JCLLIB2(AES6JEAA)
RMP.B1YO.HCJEREP(AES6JEAA)
Gender: Patient Gender
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.49. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Gender
All Randomized Patients
Acute Treatment Phase (Study Periods III-IV)
B1Y-MC-HCJE (continued)

	Flx 20			Placebo			Total			p-Value*
Gender	N	n	(%)	N	n	(%)	N	n	(%)	
VOMITING										
Female	54	3	(5.6)	54	4	(7.4)	108	7	(6.5)	1.00
Male	55	5	(9.1)	56	4	(7.1)	111	9	(8.1)	.742
Total	109	8	(7.3)	110	8	(7.3)	219	16	(7.3)	1.00
FEVER										
Female	54	4	(7.4)	54	3	(5.6)	108	7	(6.5)	1.00
Male	55	3	(5.5)	56	2	(3.6)	111	5	(4.5)	.679
Total	109	7	(6.4)	110	5	(4.5)	219	12	(5.5)	.569

RMP.B1YP.JCLLIB2(AES6JEAA)
RMP.B1YO.HCJEREP(AES6JEAA)
Gender: Patient Gender
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.49. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Gender
All Randomized Patients
Acute Treatment Phase (Study Periods III-IV)
B1Y-MC-HCJE (continued)

	Flx 20			Placebo			Total			p-Value*
Gender	N	n	(%)	N	n	(%)	N	n	(%)	
ABNORMAL DREAMS										
Female	54	4	(7.4)	54	1	(1.9)	108	5	(4.6)	.363
Male	55	2	(3.6)	56	2	(3.6)	111	4	(3.6)	1.00
Total	109	6	(5.5)	110	3	(2.7)	219	9	(4.1)	.332
EPISTAXIS										
Female	54	2	(3.7)	54	1	(1.9)	108	3	(2.8)	1.00
Male	55	3	(5.5)	56	0		111	3	(2.7)	.118
Total	109	5	(4.6)	110	1	(0.9)	219	6	(2.7)	.119

RMP.B1YP.JCLLIB2(AES6JEAA)
RMP.B1YO.HCJEREP(AES6JEAA)
Gender: Patient Gender
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.49. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Gender
All Randomized Patients
Acute Treatment Phase (Study Periods III-IV)
B1Y-MC-HCJE (continued)

	Flx 20			Placebo			Total			p-Value*
Gender	N	n	(%)	N	n	(%)	N	n	(%)	
DRY MOUTH										
Female	54	0		54	2	(3.7)	108	2	(1.9)	.495
Male	55	4	(7.3)	56	3	(5.4)	111	7	(6.3)	.716
Total	109	4	(3.7)	110	5	(4.5)	219	9	(4.1)	1.00
DYSMENORRHEA										
Female	54	4	(7.4)	54	3	(5.6)	108	7	(6.5)	1.00
Male	55	0		56	0		111	0		
Total	109	4	(3.7)	110	3	(2.7)	219	7	(3.2)	.721

RMP.B1YP.JCLLIB2(AES6JEAA)
RMP.B1YO.HCJEREP(AES6JEAA)
Gender: Patient Gender
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.49. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Gender
All Randomized Patients
Acute Treatment Phase (Study Periods III-IV)
B1Y-MC-HCJE (continued)

	Flx 20			Placebo			Total			p-Value*
Gender	N	n	(%)	N	n	(%)	N	n	(%)	
EAR PAIN										
Female	54	2	(3.7)	54	2	(3.7)	108	4	(3.7)	1.00
Male	55	2	(3.6)	56	1	(1.8)	111	3	(2.7)	.618
Total	109	4	(3.7)	110	3	(2.7)	219	7	(3.2)	.721
FLU SYNDROME										
Female	54	2	(3.7)	54	0		108	2	(1.9)	.495
Male	55	2	(3.6)	56	3	(5.4)	111	5	(4.5)	1.00
Total	109	4	(3.7)	110	3	(2.7)	219	7	(3.2)	.721

RMP.B1YP.JCLLIB2(AES6JEAA)
RMP.B1YO.HCJEREP(AES6JEAA)
Gender: Patient Gender
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.49. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Gender
All Randomized Patients
Acute Treatment Phase (Study Periods III-IV)
B1Y-MC-HCJE (continued)

	Flx 20			Placebo			Total			p-Value*
Gender	N	n	(%)	N	n	(%)	N	n	(%)	
INSOMNIA										
Female	54	1	(1.9)	54	0		108	1	(0.9)	1.00
Male	55	3	(5.5)	56	5	(8.9)	111	8	(7.2)	.716
Total	109	4	(3.7)	110	5	(4.5)	219	9	(4.1)	1.00
PRURITUS										
Female	54	2	(3.7)	54	1	(1.9)	108	3	(2.8)	1.00
Male	55	2	(3.6)	56	4	(7.1)	111	6	(5.4)	.679
Total	109	4	(3.7)	110	5	(4.5)	219	9	(4.1)	1.00

RMP.B1YP.JCLLIB2(AES6JEAA)
RMP.B1YO.HCJEREP(AES6JEAA)
Gender: Patient Gender
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.49. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Gender
All Randomized Patients
Acute Treatment Phase (Study Periods III-IV)
B1Y-MC-HCJE (continued)

	Flx 20			Placebo			Total			p-Value*
Gender	N	n	(%)	N	n	(%)	N	n	(%)	
AGITATION										
Female	54	1	(1.9)	54	0		108	1	(0.9)	1.00
Male	55	2	(3.6)	56	0		111	2	(1.8)	.243
Total	109	3	(2.8)	110	0		219	3	(1.4)	.122
BACK PAIN										
Female	54	3	(5.6)	54	5	(9.3)	108	8	(7.4)	.716
Male	55	0		56	0		111	0		
Total	109	3	(2.8)	110	5	(4.5)	219	8	(3.7)	.721

RMP.B1YP.JCLLIB2(AES6JEAA)
RMP.B1YO.HCJEREP(AES6JEAA)
Gender: Patient Gender
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.49. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Gender
All Randomized Patients
Acute Treatment Phase (Study Periods III-IV)
B1Y-MC-HCJE (continued)

	Flx 20			Placebo			Total			p-Value*
Gender	N	n	(%)	N	n	(%)	N	n	(%)	
CHEST PAIN										
Female	54	2	(3.7)	54	1	(1.9)	108	3	(2.8)	1.00
Male	55	1	(1.8)	56	1	(1.8)	111	2	(1.8)	1.00
Total	109	3	(2.8)	110	2	(1.8)	219	5	(2.3)	.683
CONSTIPATION										
Female	54	1	(1.9)	54	0		108	1	(0.9)	1.00
Male	55	2	(3.6)	56	2	(3.6)	111	4	(3.6)	1.00
Total	109	3	(2.8)	110	2	(1.8)	219	5	(2.3)	.683

RMP.B1YP.JCLLIB2(AES6JEAA)
RMP.B1YO.HCJEREP(AES6JEAA)
Gender: Patient Gender
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.49. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Gender
All Randomized Patients
Acute Treatment Phase (Study Periods III-IV)
B1Y-MC-HCJE (continued)

	Flx 20			Placebo			Total			p-Value*
Gender	N	n	(%)	N	n	(%)	N	n	(%)	
DYSPEPSIA										
Female	54	1	(1.9)	54	2	(3.7)	108	3	(2.8)	1.00
Male	55	2	(3.6)	56	2	(3.6)	111	4	(3.6)	1.00
Total	109	3	(2.8)	110	4	(3.6)	219	7	(3.2)	1.00
ECCHYMOSIS										
Female	54	2	(3.7)	54	1	(1.9)	108	3	(2.8)	1.00
Male	55	1	(1.8)	56	1	(1.8)	111	2	(1.8)	1.00
Total	109	3	(2.8)	110	2	(1.8)	219	5	(2.3)	.683

RMP.B1YP.JCLLIB2(AES6JEAA)
RMP.B1YO.HCJEREP(AES6JEAA)
Gender: Patient Gender
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.49. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Gender
All Randomized Patients
Acute Treatment Phase (Study Periods III-IV)
B1Y-MC-HCJE (continued)

	Flx 20			Placebo			Total			p-Value*
Gender	N	n	(%)	N	n	(%)	N	n	(%)	
NECK PAIN										
Female	54	2	(3.7)	54	0		108	2	(1.9)	.495
Male	55	1	(1.8)	56	0		111	1	(0.9)	.495
Total	109	3	(2.8)	110	0		219	3	(1.4)	.122
SINUSITIS										
Female	54	2	(3.7)	54	1	(1.9)	108	3	(2.8)	1.00
Male	55	1	(1.8)	56	1	(1.8)	111	2	(1.8)	1.00
Total	109	3	(2.8)	110	2	(1.8)	219	5	(2.3)	.683

RMP.B1YP.JCLLIB2(AES6JEAA)
RMP.B1YO.HCJEREP(AES6JEAA)
Gender: Patient Gender
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.49. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Gender
All Randomized Patients
Acute Treatment Phase (Study Periods III-IV)
B1Y-MC-HCJE (continued)

	Flx 20			Placebo			Total			p-Value*
Gender	N	n	(%)	N	n	(%)	N	n	(%)	
SOMNOLENCE										
Female	54	1	(1.9)	54	0		108	1	(0.9)	1.00
Male	55	2	(3.6)	56	3	(5.4)	111	5	(4.5)	1.00
Total	109	3	(2.8)	110	3	(2.7)	219	6	(2.7)	1.00
TREMOR										
Female	54	2	(3.7)	54	0		108	2	(1.9)	.495
Male	55	1	(1.8)	56	0		111	1	(0.9)	.495
Total	109	3	(2.8)	110	0		219	3	(1.4)	.122

RMP.B1YP.JCLLIB2(AES6JEAA)
RMP.B1YO.HCJEREP(AES6JEAA)
Gender: Patient Gender
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.49. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Gender
All Randomized Patients
Acute Treatment Phase (Study Periods III-IV)
B1Y-MC-HCJE (continued)

	Flx 20			Placebo			Total			p-Value*
Gender	N	n	(%)	N	n	(%)	N	n	(%)	
AKATHISIA										
Female	54	1	(1.9)	54	0		108	1	(0.9)	1.00
Male	55	1	(1.8)	56	0		111	1	(0.9)	.495
Total	109	2	(1.8)	110	0		219	2	(0.9)	.247
ALLERGIC REACTION										
Female	54	2	(3.7)	54	0		108	2	(1.9)	.495
Male	55	0		56	2	(3.6)	111	2	(1.8)	.495
Total	109	2	(1.8)	110	2	(1.8)	219	4	(1.8)	1.00

RMP.B1YP.JCLLIB2(AES6JEAA)
RMP.B1YO.HCJEREP(AES6JEAA)
Gender: Patient Gender
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.49. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Gender
All Randomized Patients
Acute Treatment Phase (Study Periods III-IV)
B1Y-MC-HCJE (continued)

	Flx 20			Placebo			Total			p-Value*
Gender	N	n	(%)	N	n	(%)	N	n	(%)	
ANXIETY										
Female	54	2	(3.7)	54	0		108	2	(1.9)	.495
Male	55	0		56	0		111	0		
Total	109	2	(1.8)	110	0		219	2	(0.9)	.247
ASTHMA										
Female	54	0		54	0		108	0		
Male	55	2	(3.6)	56	0		111	2	(1.8)	.243
Total	109	2	(1.8)	110	0		219	2	(0.9)	.247

RMP.B1YP.JCLLIB2(AES6JEAA)
RMP.B1YO.HCJEREP(AES6JEAA)
Gender: Patient Gender
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.49. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Gender
All Randomized Patients
Acute Treatment Phase (Study Periods III-IV)
B1Y-MC-HCJE (continued)

	Flx 20			Placebo			Total			p-Value*
Gender	N	n	(%)	N	n	(%)	N	n	(%)	
CHILLS										
Female	54	1	(1.9)	54	0		108	1	(0.9)	1.00
Male	55	1	(1.8)	56	0		111	1	(0.9)	.495
Total	109	2	(1.8)	110	0		219	2	(0.9)	.247
DEPRESSION										
Female	54	2	(3.7)	54	0		108	2	(1.9)	.495
Male	55	0		56	1	(1.8)	111	1	(0.9)	1.00
Total	109	2	(1.8)	110	1	(0.9)	219	3	(1.4)	.622

RMP.B1YP.JCLLIB2(AES6JEAA)
RMP.B1YO.HCJEREP(AES6JEAA)
Gender: Patient Gender
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.49. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Gender
All Randomized Patients
Acute Treatment Phase (Study Periods III-IV)
B1Y-MC-HCJE (continued)

	Flx 20			Placebo			Total			p-Value*
Gender	N	n	(%)	N	n	(%)	N	n	(%)	
DRY SKIN										
Female	54	2	(3.7)	54	0		108	2	(1.9)	.495
Male	55	0		56	1	(1.8)	111	1	(0.9)	1.00
Total	109	2	(1.8)	110	1	(0.9)	219	3	(1.4)	.622
EYE DISORDER										
Female	54	2	(3.7)	54	0		108	2	(1.9)	.495
Male	55	0		56	0		111	0		
Total	109	2	(1.8)	110	0		219	2	(0.9)	.247

RMP.B1YP.JCLLIB2(AES6JEAA)
RMP.B1YO.HCJEREP(AES6JEAA)
Gender: Patient Gender
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.49. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Gender
All Randomized Patients
Acute Treatment Phase (Study Periods III-IV)
B1Y-MC-HCJE (continued)

	Flx 20			Placebo			Total			p-Value*
Gender	N	n	(%)	N	n	(%)	N	n	(%)	
GASTROENTERITIS										
Female	54	1	(1.9)	54	0		108	1	(0.9)	1.00
Male	55	1	(1.8)	56	0		111	1	(0.9)	.495
Total	109	2	(1.8)	110	0		219	2	(0.9)	.247
HOSTILITY										
Female	54	0		54	1	(1.9)	108	1	(0.9)	1.00
Male	55	2	(3.6)	56	4	(7.1)	111	6	(5.4)	.679
Total	109	2	(1.8)	110	5	(4.5)	219	7	(3.2)	.446

RMP.B1YP.JCLLIB2(AES6JEAA)
RMP.B1YO.HCJEREP(AES6JEAA)
Gender: Patient Gender
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.49. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Gender
All Randomized Patients
Acute Treatment Phase (Study Periods III-IV)
B1Y-MC-HCJE (continued)

	Flx 20			Placebo			Total			p-Value*
Gender	N	n	(%)	N	n	(%)	N	n	(%)	
HYPERKINESIA										
Female	54	1	(1.9)	54	0		108	1	(0.9)	1.00
Male	55	1	(1.8)	56	0		111	1	(0.9)	.495
Total	109	2	(1.8)	110	0		219	2	(0.9)	.247
INFECTION										
Female	54	1	(1.9)	54	1	(1.9)	108	2	(1.9)	1.00
Male	55	1	(1.8)	56	1	(1.8)	111	2	(1.8)	1.00
Total	109	2	(1.8)	110	2	(1.8)	219	4	(1.8)	1.00

RMP.B1YP.JCLLIB2(AES6JEAA)
RMP.B1YO.HCJEREP(AES6JEAA)
Gender: Patient Gender
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.49. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Gender
All Randomized Patients
Acute Treatment Phase (Study Periods III-IV)
B1Y-MC-HCJE (continued)

	Flx 20			Placebo			Total			p-Value*
Gender	N	n	(%)	N	n	(%)	N	n	(%)	
OTITIS EXTERNA										
Female	54	1	(1.9)	54	0		108	1	(0.9)	1.00
Male	55	1	(1.8)	56	1	(1.8)	111	2	(1.8)	1.00
Total	109	2	(1.8)	110	1	(0.9)	219	3	(1.4)	.622
PERSONALITY DISORDER										
Female	54	1	(1.9)	54	0		108	1	(0.9)	1.00
Male	55	1	(1.8)	56	1	(1.8)	111	2	(1.8)	1.00
Total	109	2	(1.8)	110	1	(0.9)	219	3	(1.4)	.622

RMP.B1YP.JCLLIB2(AES6JEAA)
RMP.B1YO.HCJEREP(AES6JEAA)
Gender: Patient Gender
* Frequencies are analyzed using a Fisher’s Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.49. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Gender
All Randomized Patients
Acute Treatment Phase (Study Periods III-IV)
B1Y-MC-HCJE (continued)

	Flx 20			Placebo			Total			p-Value*
Gender	N	n	(%)	N	n	(%)	N	n	(%)	
PHOTOSENSITIVITY REACTION										
Female	54	1	(1.9)	54	0		108	1	(0.9)	1.00
Male	55	1	(1.8)	56	0		111	1	(0.9)	.495
Total	109	2	(1.8)	110	0		219	2	(0.9)	.247
SLEEP DISORDER										
Female	54	2	(3.7)	54	0		108	2	(1.9)	.495
Male	55	0		56	0		111	0		
Total	109	2	(1.8)	110	0		219	2	(0.9)	.247

RMP.B1YP.JCLLIB2(AES6JEAA)
RMP.B1YO.HCJEREP(AES6JEAA)
Gender: Patient Gender
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.49. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Gender
All Randomized Patients
Acute Treatment Phase (Study Periods III-IV)
B1Y-MC-HCJE (continued)

	Flx 20			Placebo			Total			p-Value*
Gender	N	n	(%)	N	n	(%)	N	n	(%)	
SPEECH DISORDER										
Female	54	0		54	1	(1.9)	108	1	(0.9)	1.00
Male	55	2	(3.6)	56	1	(1.8)	111	3	(2.7)	.618
Total	109	2	(1.8)	110	2	(1.8)	219	4	(1.8)	1.00
THIRST										
Female	54	2	(3.7)	54	1	(1.9)	108	3	(2.8)	1.00
Male	55	0		56	1	(1.8)	111	1	(0.9)	1.00
Total	109	2	(1.8)	110	2	(1.8)	219	4	(1.8)	1.00

RMP.B1YP.JCLLIB2(AES6JEAA)
RMP.B1YO.HCJEREP(AES6JEAA)
Gender: Patient Gender
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.49. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Gender
All Randomized Patients
Acute Treatment Phase (Study Periods III-IV)
B1Y-MC-HCJE (continued)

	Flx 20			Placebo			Total			p-Value*
Gender	N	n	(%)	N	n	(%)	N	n	(%)	
WEIGHT LOSS										
Female	54	1	(1.9)	54	1	(1.9)	108	2	(1.9)	1.00
Male	55	1	(1.8)	56	0		111	1	(0.9)	.495
Total	109	2	(1.8)	110	1	(0.9)	219	3	(1.4)	.622
ACUTE BRAIN SYNDROME										
Female	54	0		54	0		108	0		
Male	55	1	(1.8)	56	0		111	1	(0.9)	.495
Total	109	1	(0.9)	110	0		219	1	(0.5)	.498

RMP.B1YP.JCLLIB2(AES6JEAA)
RMP.B1YO.HCJEREP(AES6JEAA)
Gender: Patient Gender
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.49. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Gender
All Randomized Patients
Acute Treatment Phase (Study Periods III-IV)
B1Y-MC-HCJE (continued)

	Flx 20			Placebo			Total			p-Value*
Gender	N	n	(%)	N	n	(%)	N	n	(%)	
APATHY										
Female	54	0		54	0		108	0		
Male	55	1	(1.8)	56	0		111	1	(0.9)	.495
Total	109	1	(0.9)	110	0		219	1	(0.5)	.498
BRONCHITIS										
Female	54	1	(1.9)	54	0		108	1	(0.9)	1.00
Male	55	0		56	0		111	0		
Total	109	1	(0.9)	110	0		219	1	(0.5)	.498

RMP.B1YP.JCLLIB2(AES6JEAA)
RMP.B1YO.HCJEREP(AES6JEAA)
Gender: Patient Gender
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.49. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Gender
All Randomized Patients
Acute Treatment Phase (Study Periods III-IV)
B1Y-MC-HCJE (continued)

	Flx 20			Placebo			Total			p-Value*
Gender	N	n	(%)	N	n	(%)	N	n	(%)	
BUCCOGLOSSAL SYNDROME										
Female	54	1	(1.9)	54	0		108	1	(0.9)	1.00
Male	55	0		56	0		111	0		
Total	109	1	(0.9)	110	0		219	1	(0.5)	.498
CONTACT DERMATITIS										
Female	54	0		54	0		108	0		
Male	55	1	(1.8)	56	0		111	1	(0.9)	.495
Total	109	1	(0.9)	110	0		219	1	(0.5)	.498

RMP.B1YP.JCLLIB2(AES6JEAA)
RMP.B1YO.HCJEREP(AES6JEAA)
Gender: Patient Gender
* Frequencies are analyzed using a Fisher’s Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.49. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Gender
All Randomized Patients
Acute Treatment Phase (Study Periods III-IV)
B1Y-MC-HCJE (continued)

	Flx 20			Placebo			Total			p-Value*
Gender	N	n	(%)	N	n	(%)	N	n	(%)	
DELUSIONS										
Female	54	0		54	0		108	0		
Male	55	1	(1.8)	56	0		111	1	(0.9)	.495
Total	109	1	(0.9)	110	0		219	1	(0.5)	.498
DYSPHAGIA										
Female	54	1	(1.9)	54	1	(1.9)	108	2	(1.9)	1.00
Male	55	0		56	0		111	0		
Total	109	1	(0.9)	110	1	(0.9)	219	2	(0.9)	1.00

RMP.B1YP.JCLLIB2(AES6JEAA)
RMP.B1YO.HCJEREP(AES6JEAA)
Gender: Patient Gender
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.49. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Gender
All Randomized Patients
Acute Treatment Phase (Study Periods III-IV)
B1Y-MC-HCJE (continued)

	Flx 20			Placebo			Total			p-Value*
Gender	N	n	(%)	N	n	(%)	N	n	(%)	
DYSPNEA										
Female	54	1	(1.9)	54	0		108	1	(0.9)	1.00
Male	55	0		56	0		111	0		
Total	109	1	(0.9)	110	0		219	1	(0.5)	.498
EAR DISORDER										
Female	54	1	(1.9)	54	0		108	1	(0.9)	1.00
Male	55	0		56	1	(1.8)	111	1	(0.9)	1.00
Total	109	1	(0.9)	110	1	(0.9)	219	2	(0.9)	1.00

RMP.B1YP.JCLLIB2(AES6JEAA)
RMP.B1YO.HCJEREP(AES6JEAA)
Gender: Patient Gender
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.49. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Gender
All Randomized Patients
Acute Treatment Phase (Study Periods III-IV)
B1Y-MC-HCJE (continued)

	Flx 20			Placebo			Total			p-Value*
Gender	N	n	(%)	N	n	(%)	N	n	(%)	
EMOTIONAL LABILITY										
Female	54	0		54	0		108	0		
Male	55	1	(1.8)	56	0		111	1	(0.9)	.495
Total	109	1	(0.9)	110	0		219	1	(0.5)	.498
ENDOMETRIAL HYPERPLASIA										
Female	54	1	(1.9)	54	0		108	1	(0.9)	1.00
Male	55	0		56	0		111	0		
Total	109	1	(0.9)	110	0		219	1	(0.5)	.498

RMP.B1YP.JCLLIB2(AES6JEAA)
RMP.B1YO.HCJEREP(AES6JEAA)
Gender: Patient Gender
* Frequencies are analyzed using a Fisher’s Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.49. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Gender
All Randomized Patients
Acute Treatment Phase (Study Periods III-IV)
B1Y-MC-HCJE (continued)

	Flx 20			Placebo			Total			p-Value*
Gender	N	n	(%)	N	n	(%)	N	n	(%)	
EUPHORIA										
Female	54	1	(1.9)	54	0		108	1	(0.9)	1.00
Male	55	0		56	0		111	0		
Total	109	1	(0.9)	110	0		219	1	(0.5)	.498
EYE PAIN										
Female	54	0		54	0		108	0		
Male	55	1	(1.8)	56	0		111	1	(0.9)	.495
Total	109	1	(0.9)	110	0		219	1	(0.5)	.498

RMP.B1YP.JCLLIB2(AES6JEAA)
RMP.B1YO.HCJEREP(AES6JEAA)
Gender: Patient Gender
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.49. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Gender
All Randomized Patients
Acute Treatment Phase (Study Periods III-IV)
B1Y-MC-HCJE (continued)

	Flx 20			Placebo			Total			p-Value*
Gender	N	n	(%)	N	n	(%)	N	n	(%)	
FECAL INCONTINENCE										
Female	54	0		54	0		108	0		
Male	55	1	(1.8)	56	0		111	1	(0.9)	.495
Total	109	1	(0.9)	110	0		219	1	(0.5)	.498
FLATULENCE										
Female	54	0		54	0		108	0		
Male	55	1	(1.8)	56	0		111	1	(0.9)	.495
Total	109	1	(0.9)	110	0		219	1	(0.5)	.498

RMP.B1YP.JCLLIB2(AES6JEAA)
RMP.B1YO.HCJEREP(AES6JEAA)
Gender: Patient Gender
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.49. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Gender
All Randomized Patients
Acute Treatment Phase (Study Periods III-IV)
B1Y-MC-HCJE (continued)

	Flx 20			Placebo			Total			p-Value*
Gender	N	n	(%)	N	n	(%)	N	n	(%)	
FUNGAL DERMATITIS										
Female	54	0		54	1	(1.9)	108	1	(0.9)	1.00
Male	55	1	(1.8)	56	0		111	1	(0.9)	.495
Total	109	1	(0.9)	110	1	(0.9)	219	2	(0.9)	1.00
HALLUCINATIONS										
Female	54	0		54	0		108	0		
Male	55	1	(1.8)	56	0		111	1	(0.9)	.495
Total	109	1	(0.9)	110	0		219	1	(0.5)	.498

RMP.B1YP.JCLLIB2(AES6JEAA)
RMP.B1YO.HCJEREP(AES6JEAA)
Gender: Patient Gender
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.49. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Gender
All Randomized Patients
Acute Treatment Phase (Study Periods III-IV)
B1Y-MC-HCJE (continued)

	Flx 20			Placebo			Total			p-Value*
Gender	N	n	(%)	N	n	(%)	N	n	(%)	
HEPATITIS NONSPECIFIC										
Female	54	0		54	0		108	0		
Male	55	1	(1.8)	56	0		111	1	(0.9)	.495
Total	109	1	(0.9)	110	0		219	1	(0.5)	.498
HEPATOMEGALY										
Female	54	0		54	0		108	0		
Male	55	1	(1.8)	56	0		111	1	(0.9)	.495
Total	109	1	(0.9)	110	0		219	1	(0.5)	.498

RMP.B1YP.JCLLIB2(AES6JEAA)
RMP.B1YO.HCJEREP(AES6JEAA)
Gender: Patient Gender
* Frequencies are analyzed using a Fisher’s Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.49. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Gender
All Randomized Patients
Acute Treatment Phase (Study Periods III-IV)
B1Y-MC-HCJE (continued)

	Flx 20			Placebo			Total			p-Value*
Gender	N	n	(%)	N	n	(%)	N	n	(%)	
HERPES SIMPLEX										
Female	54	1	(1.9)	54	0		108	1	(0.9)	1.00
Male	55	0		56	0		111	0		
Total	109	1	(0.9)	110	0		219	1	(0.5)	.498
HYPERTONIA										
Female	54	1	(1.9)	54	1	(1.9)	108	2	(1.9)	1.00
Male	55	0		56	0		111	0		
Total	109	1	(0.9)	110	1	(0.9)	219	2	(0.9)	1.00

RMP.B1YP.JCLLIB2(AES6JEAA)
RMP.B1YO.HCJEREP(AES6JEAA)
Gender: Patient Gender
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.49. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Gender
All Randomized Patients
Acute Treatment Phase (Study Periods III-IV)
B1Y-MC-HCJE (continued)

	Flx 20			Placebo			Total			p-Value*
Gender	N	n	(%)	N	n	(%)	N	n	(%)	
HYPOTENSION										
Female	54	0		54	0		108	0		
Male	55	1	(1.8)	56	0		111	1	(0.9)	.495
Total	109	1	(0.9)	110	0		219	1	(0.5)	.498
JOINT DISORDER										
Female	54	0		54	0		108	0		
Male	55	1	(1.8)	56	0		111	1	(0.9)	.495
Total	109	1	(0.9)	110	0		219	1	(0.5)	.498

RMP.B1YP.JCLLIB2(AES6JEAA)
RMP.B1YO.HCJEREP(AES6JEAA)
Gender: Patient Gender
* Frequencies are analyzed using a Fisher’s Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.49. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Gender
All Randomized Patients
Acute Treatment Phase (Study Periods III-IV)
B1Y-MC-HCJE (continued

	Flx 20			Placebo			Total			p-Value*
Gender	N	n	(%)	N	n	(%)	N	n	(%)	
LEG CRAMPS										
Female	54	0		54	0		108	0		
Male	55	1	(1.8)	56	1	(1.8)	111	2	(1.8)	1.00
Total	109	1	(0.9)	110	1	(0.9)	219	2	(0.9)	1.00
LUNG DISORDER										
Female	54	0		54	0		108	0		
Male	55	1	(1.8)	56	0		111	1	(0.9)	.495
Total	109	1	(0.9)	110	0		219	1	(0.5)	.498

RMP.B1YP.JCLLIB2(AES6JEAA)
RMP.B1YO.HCJEREP(AES6JEAA)
Gender: Patient Gender
* Frequencies are analyzed using a Fisher’s Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.49. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Gender
All Randomized Patients
Acute Treatment Phase (Study Periods III-IV)
B1Y-MC-HCJE (continued)

	Flx 20			Placebo			Total			p-Value*
Gender	N	n	(%)	N	n	(%)	N	n	(%)	
MACULOPAPULAR RASH										
Female	54	0		54	0		108	0		
Male	55	1	(1.8)	56	1	(1.8)	111	2	(1.8)	1.00
Total	109	1	(0.9)	110	1	(0.9)	219	2	(0.9)	1.00
MANIC REACTION										
Female	54	0		54	0		108	0		
Male	55	1	(1.8)	56	0		111	1	(0.9)	.495
Total	109	1	(0.9)	110	0		219	1	(0.5)	.498

RMP.B1YP.JCLLIB2(AES6JEAA)
RMP.B1YO.HCJEREP(AES6JEAA)
Gender: Patient Gender
* Frequencies are analyzed using a Fisher’s Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.49. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Gender
All Randomized Patients
Acute Treatment Phase (Study Periods III-IV)
B1Y-MC-HCJE (continued)

	Flx 20			Placebo			Total			p-Value*
Gender	N	n	(%)	N	n	(%)	N	n	(%)	
MIGRAINE										
Female	54	1	(1.9)	54	1	(1.9)	108	2	(1.9)	1.00
Male	55	0		56	0		111	0		
Total	109	1	(0.9)	110	1	(0.9)	219	2	(0.9)	1.00
MYALGIA										
Female	54	0		54	3	(5.6)	108	3	(2.8)	.243
Male	55	1	(1.8)	56	2	(3.6)	111	3	(2.7)	1.00
Total	109	1	(0.9)	110	5	(4.5)	219	6	(2.7)	.212

RMP.B1YP.JCLLIB2(AES6JEAA)
RMP.B1YO.HCJEREP(AES6JEAA)
Gender: Patient Gender
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.49. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Gender
All Randomized Patients
Acute Treatment Phase (Study Periods III-IV)
B1Y-MC-HCJE (continued)

	Flx 20			Placebo			Total			p-Value*
Gender	N	n	(%)	N	n	(%)	N	n	(%)	
NEUROSIS										
Female	54	1	(1.9)	54	0		108	1	(0.9)	1.00
Male	55	0		56	0		111	0		
Total	109	1	(0.9)	110	0		219	1	(0.5)	.498
OVERDOSE										
Female	54	0		54	0		108	0		
Male	55	1	(1.8)	56	0		111	1	(0.9)	.495
Total	109	1	(0.9)	110	0		219	1	(0.5)	.498

RMP.B1YP.JCLLIB2(AES6JEAA)
RMP.B1YO.HCJEREP(AES6JEAA)
Gender: Patient Gender
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.49. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Gender
All Randomized Patients
Acute Treatment Phase (Study Periods III-IV)
B1Y-MC-HCJE (continued)

	Flx 20			Placebo			Total			p-Value*
Gender	N	n	(%)	N	n	(%)	N	n	(%)	
PALPITATION										
Female	54	1	(1.9)	54	1	(1.9)	108	2	(1.9)	1.00
Male	55	0		56	0		111	0		
Total	109	1	(0.9)	110	1	(0.9)	219	2	(0.9)	1.00
PNEUMONIA										
Female	54	0		54	0		108	0		
Male	55	1	(1.8)	56	0		111	1	(0.9)	.495
Total	109	1	(0.9)	110	0		219	1	(0.5)	.498

RMP.B1YP.JCLLIB2(AES6JEAA)
RMP.B1YO.HCJEREP(AES6JEAA)
Gender: Patient Gender
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.49. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Gender
All Randomized Patients
Acute Treatment Phase (Study Periods III-IV)
B1Y-MC-HCJE (continued)

	Flx 20			Placebo			Total			p-Value*
Gender	N	n	(%)	N	n	(%)	N	n	(%)	
SURGICAL PROCEDURE										
Female	54	0		54	1	(1.9)	108	1	(0.9)	1.00
Male	55	1	(1.8)	56	0		111	1	(0.9)	.495
Total	109	1	(0.9)	110	1	(0.9)	219	2	(0.9)	1.00
SWEATING										
Female	54	0		54	0		108	0		
Male	55	1	(1.8)	56	0		111	1	(0.9)	.495
Total	109	1	(0.9)	110	0		219	1	(0.5)	.498

RMP.B1YP.JCLLIB2(AES6JEAA)
RMP.B1YO.HCJEREP(AES6JEAA)
Gender: Patient Gender
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.49. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Gender
All Randomized Patients
Acute Treatment Phase (Study Periods III-IV)
B1Y-MC-HCJE (continued)

	Flx 20			Placebo			Total			p-Value*
Gender	N	n	(%)	N	n	(%)	N	n	(%)	
SYNCOPE										
Female	54	0		54	0		108	0		
Male	55	1	(1.8)	56	0		111	1	(0.9)	.495
Total	109	1	(0.9)	110	0		219	1	(0.5)	.498
TACHYCARDIA										
Female	54	0		54	0		108	0		
Male	55	1	(1.8)	56	0		111	1	(0.9)	.495
Total	109	1	(0.9)	110	0		219	1	(0.5)	.498

RMP.B1YP.JCLLIB2(AES6JEAA)
RMP.B1YO.HCJEREP(AES6JEAA)
Gender: Patient Gender
* Frequencies are analyzed using a Fisher’s Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.49. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Gender
All Randomized Patients
Acute Treatment Phase (Study Periods III-IV)
B1Y-MC-HCJE (continued)

	Flx 20			Placebo			Total			p-Value*
Gender	N	n	(%)	N	n	(%)	N	n	(%)	
TINNITUS										
Female	54	1	(1.9)	54	0		108	1	(0.9)	1.00
Male	55	0		56	0		111	0		
Total	109	1	(0.9)	110	0		219	1	(0.5)	.498
TOOTH DISORDER										
Female	54	1	(1.9)	54	0		108	1	(0.9)	1.00
Male	55	0		56	0		111	0		
Total	109	1	(0.9)	110	0		219	1	(0.5)	.498

RMP.B1YP.JCLLIB2(AES6JEAA)
RMP.B1YO.HCJEREP(AES6JEAA)
Gender: Patient Gender
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.49. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Gender
All Randomized Patients
Acute Treatment Phase (Study Periods III-IV)
B1Y-MC-HCJE (continued)

	Flx 20			Placebo			Total			p-Value*
Gender	N	n	(%)	N	n	(%)	N	n	(%)	
URINARY FREQUENCY										
Female	54	1	(1.9)	54	1	(1.9)	108	2	(1.9)	1.00
Male	55	0		56	1	(1.8)	111	1	(0.9)	1.00
Total	109	1	(0.9)	110	2	(1.8)	219	3	(1.4)	1.00
URINARY TRACT INFECTION										
Female	54	0		54	1	(1.9)	108	1	(0.9)	1.00
Male	55	1	(1.8)	56	0		111	1	(0.9)	.495
Total	109	1	(0.9)	110	1	(0.9)	219	2	(0.9)	1.00

RMP.B1YP.JCLLIB2(AES6JEAA)
RMP.B1YO.HCJEREP(AES6JEAA)
Gender: Patient Gender
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.49. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Gender
All Randomized Patients
Acute Treatment Phase (Study Periods III-IV)
B1Y-MC-HCJE (continued)

	Flx 20			Placebo			Total			p-Value*
Gender	N	n	(%)	N	n	(%)	N	n	(%)	
VASODILATATION										
Female	54	1	(1.9)	54	0		108	1	(0.9)	1.00
Male	55	0		56	0		111	0		
Total	109	1	(0.9)	110	0		219	1	(0.5)	.498
YAWN										
Female	54	0		54	0		108	0		
Male	55	1	(1.8)	56	0		111	1	(0.9)	.495
Total	109	1	(0.9)	110	0		219	1	(0.5)	.498

RMP.B1YP.JCLLIB2(AES6JEAA)
RMP.B1YO.HCJEREP(AES6JEAA)
Gender: Patient Gender
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.49. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Gender
All Randomized Patients
Acute Treatment Phase (Study Periods III-IV)
B1Y-MC-HCJE (continued)

	Flx 20			Placebo			Total			p-Value*
Gender	N	n	(%)	N	n	(%)	N	n	(%)	
ABDOMINAL SYNDROME ACUTE										
Female	54	0		54	0		108	0		
Male	55	0		56	1	(1.8)	111	1	(0.9)	1.00
Total	109	0		110	1	(0.9)	219	1	(0.5)	1.00
ACNE										
Female	54	0		54	1	(1.9)	108	1	(0.9)	1.00
Male	55	0		56	0		111	0		
Total	109	0		110	1	(0.9)	219	1	(0.5)	1.00

RMP.B1YP.JCLLIB2(AES6JEAA)
RMP.B1YO.HCJEREP(AES6JEAA)
Gender: Patient Gender
* Frequencies are analyzed using a Fisher’s Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.49. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Gender
All Randomized Patients
Acute Treatment Phase (Study Periods III-IV)
B1Y-MC-HCJE (continued)

	Flx 20			Placebo			Total			p-Value*
Gender	N	n	(%)	N	n	(%)	N	n	(%)	
ALOPECIA										
Female	54	0		54	1	(1.9)	108	1	(0.9)	1.00
Male	55	0		56	0		111	0		
Total	109	0		110	1	(0.9)	219	1	(0.5)	1.00
AMNESIA										
Female	54	0		54	1	(1.9)	108	1	(0.9)	1.00
Male	55	0		56	0		111	0		
Total	109	0		110	1	(0.9)	219	1	(0.5)	1.00

RMP.B1YP.JCLLIB2(AES6JEAA)
RMP.B1YO.HCJEREP(AES6JEAA)
Gender: Patient Gender
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.49. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Gender
All Randomized Patients
Acute Treatment Phase (Study Periods III-IV)
B1Y-MC-HCJE (continued)

	Flx 20			Placebo			Total			p-Value*
Gender	N	n	(%)	N	n	(%)	N	n	(%)	
APHTHOUS STOMATITIS										
Female	54	0		54	1	(1.9)	108	1	(0.9)	1.00
Male	55	0		56	0		111	0		
Total	109	0		110	1	(0.9)	219	1	(0.5)	1.00
ARTHRALGIA										
Female	54	0		54	0		108	0		
Male	55	0		56	1	(1.8)	111	1	(0.9)	1.00
Total	109	0		110	1	(0.9)	219	1	(0.5)	1.00

RMP.B1YP.JCLLIB2(AES6JEAA)
RMP.B1YO.HCJEREP(AES6JEAA)
Gender: Patient Gender
* Frequencies are analyzed using a Fisher’s Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.49. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Gender
All Randomized Patients
Acute Treatment Phase (Study Periods III-IV)
B1Y-MC-HCJE (continued)

	Flx 20			Placebo			Total			p-Value*
Gender	N	n	(%)	N	n	(%)	N	n	(%)	
BRADYCARDIA										
Female	54	0		54	1	(1.9)	108	1	(0.9)	1.00
Male	55	0		56	0		111	0		
Total	109	0		110	1	(0.9)	219	1	(0.5)	1.00
CYSTITIS										
Female	54	0		54	1	(1.9)	108	1	(0.9)	1.00
Male	55	0		56	0		111	0		
Total	109	0		110	1	(0.9)	219	1	(0.5)	1.00

RMP.B1YP.JCLLIB2(AES6JEAA)
RMP.B1YO.HCJEREP(AES6JEAA)
Gender: Patient Gender
* Frequencies are analyzed using a Fisher’s Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.49. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Gender
All Randomized Patients
Acute Treatment Phase (Study Periods III-IV)
B1Y-MC-HCJE (continued)

	Flx 20			Placebo			Total			p-Value*
Gender	N	n	(%)	N	n	(%)	N	n	(%)	
DEHYDRATION										
Female	54	0		54	1	(1.9)	108	1	(0.9)	1.00
Male	55	0		56	1	(1.8)	111	1	(0.9)	1.00
Total	109	0		110	2	(1.8)	219	2	(0.9)	.498
DYSURIA										
Female	54	0		54	1	(1.9)	108	1	(0.9)	1.00
Male	55	0		56	0		111	0		
Total	109	0		110	1	(0.9)	219	1	(0.5)	1.00

RMP.B1YP.JCLLIB2(AES6JEAA)
RMP.B1YO.HCJEREP(AES6JEAA)
Gender: Patient Gender
* Frequencies are analyzed using a Fisher’s Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.49. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Gender
All Randomized Patients
Acute Treatment Phase (Study Periods III-IV)
B1Y-MC-HCJE (continued)

	Flx 20			Placebo			Total			p-Value*
Gender	N	n	(%)	N	n	(%)	N	n	(%)	
FACE EDEMA										
Female	54	0		54	1	(1.9)	108	1	(0.9)	1.00
Male	55	0		56	0		111	0		
Total	109	0		110	1	(0.9)	219	1	(0.5)	1.00
GASTROINTESTINAL DISORDER										
Female	54	0		54	1	(1.9)	108	1	(0.9)	1.00
Male	55	0		56	0		111	0		
Total	109	0		110	1	(0.9)	219	1	(0.5)	1.00

RMP.B1YP.JCLLIB2(AES6JEAA)
RMP.B1YO.HCJEREP(AES6JEAA)
Gender: Patient Gender
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.49. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Gender
All Randomized Patients
Acute Treatment Phase (Study Periods III-IV)
B1Y-MC-HCJE (continued)

	Flx 20			Placebo			Total			p-Value*
Gender	N	n	(%)	N	n	(%)	N	n	(%)	
HYPESTHESIA										
Female	54	0		54	1	(1.9)	108	1	(0.9)	1.00
Male	55	0		56	0		111	0		
Total	109	0		110	1	(0.9)	219	1	(0.5)	1.00
HYPOVENTILATION										
Female	54	0		54	0		108	0		
Male	55	0		56	1	(1.8)	111	1	(0.9)	1.00
Total	109	0		110	1	(0.9)	219	1	(0.5)	1.00

RMP.B1YP.JCLLIB2(AES6JEAA)
RMP.B1YO.HCJEREP(AES6JEAA)
Gender: Patient Gender
* Frequencies are analyzed using a Fisher’s Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.49. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Gender
All Randomized Patients
Acute Treatment Phase (Study Periods III-IV)
B1Y-MC-HCJE (continued)

	Flx 20			Placebo			Total			p-Value*
Gender	N	n	(%)	N	n	(%)	N	n	(%)	
INCREASED APPETITE										
Female	54	0		54	1	(1.9)	108	1	(0.9)	1.00
Male	55	0		56	2	(3.6)	111	2	(1.8)	.495
Total	109	0		110	3	(2.7)	219	3	(1.4)	.247
INTENTIONAL INJURY										
Female	54	0		54	0		108	0		
Male	55	0		56	1	(1.8)	111	1	(0.9)	1.00
Total	109	0		110	1	(0.9)	219	1	(0.5)	1.00

RMP.B1YP.JCLLIB2(AES6JEAA)
RMP.B1YO.HCJEREP(AES6JEAA)
Gender: Patient Gender
* Frequencies are analyzed using a Fisher’s Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.49. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Gender
All Randomized Patients
Acute Treatment Phase (Study Periods III-IV)
B1Y-MC-HCJE (continued)

	Flx 20			Placebo			Total			p-Value*
Gender	N	n	(%)	N	n	(%)	N	n	(%)	
LARYNGITIS										
Female	54	0		54	1	(1.9)	108	1	(0.9)	1.00
Male	55	0		56	0		111	0		
Total	109	0		110	1	(0.9)	219	1	(0.5)	1.00
LEUKORRHEA										
Female	54	0		54	1	(1.9)	108	1	(0.9)	1.00
Male	55	0		56	0		111	0		
Total	109	0		110	1	(0.9)	219	1	(0.5)	1.00

RMP.B1YP.JCLLIB2(AES6JEAA)
RMP.B1YO.HCJEREP(AES6JEAA)
Gender: Patient Gender
* Frequencies are analyzed using a Fisher’s Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.49. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Gender
All Randomized Patients
Acute Treatment Phase (Study Periods III-IV)
B1Y-MC-HCJE (continued)

	Flx 20			Placebo			Total			p-Value*
Gender	N	n	(%)	N	n	(%)	N	n	(%)	
METRORRHAGIA										
Female	54	0		54	1	(1.9)	108	1	(0.9)	1.00
Male	55	0		56	0		111	0		
Total	109	0		110	1	(0.9)	219	1	(0.5)	1.00
MOUTH ULCERATION										
Female	54	0		54	0		108	0		
Male	55	0		56	1	(1.8)	111	1	(0.9)	1.00
Total	109	0		110	1	(0.9)	219	1	(0.5)	1.00

RMP.B1YP.JCLLIB2(AES6JEAA)
RMP.B1YO.HCJEREP(AES6JEAA)
Gender: Patient Gender
* Frequencies are analyzed using a Fisher’s Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.49. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Gender
All Randomized Patients
Acute Treatment Phase (Study Periods III-IV)
B1Y-MC-HCJE (continued)

	Flx 20			Placebo			Total			p-Value*
Gender	N	n	(%)	N	n	(%)	N	n	(%)	
SKIN DISCOLORATION										
Female	54	0		54	1	(1.9)	108	1	(0.9)	1.00
Male	55	0		56	0		111	0		
Total	109	0		110	1	(0.9)	219	1	(0.5)	1.00
SKIN ULCER										
Female	54	0		54	1	(1.9)	108	1	(0.9)	1.00
Male	55	0		56	0		111	0		
Total	109	0		110	1	(0.9)	219	1	(0.5)	1.00

RMP.B1YP.JCLLIB2(AES6JEAA)
RMP.B1YO.HCJEREP(AES6JEAA)
Gender: Patient Gender
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.49. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Gender
All Randomized Patients
Acute Treatment Phase (Study Periods III-IV)
B1Y-MC-HCJE (continued)

	Flx 20			Placebo			Total			p-Value*
Gender	N	n	(%)	N	n	(%)	N	n	(%)	
SUBCUTANEOUS NODULE										
Female	54	0		54	0		108	0		
Male	55	0		56	1	(1.8)	111	1	(0.9)	1.00
Total	109	0		110	1	(0.9)	219	1	(0.5)	1.00
THINKING ABNORMAL										
Female	54	0		54	1	(1.9)	108	1	(0.9)	1.00
Male	55	0		56	0		111	0		
Total	109	0		110	1	(0.9)	219	1	(0.5)	1.00

RMP.B1YP.JCLLIB2(AES6JEAA)
RMP.B1YO.HCJEREP(AES6JEAA)
Gender: Patient Gender
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.49. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Gender
All Randomized Patients
Acute Treatment Phase (Study Periods III-IV)
B1Y-MC-HCJE (concluded)

	Flx 20			Placebo			Total			p-Value*
Gender	N	n	(%)	N	n	(%)	N	n	(%)	
UNEXPECTED BENEFIT										
Female	54	0		54	1	(1.9)	108	1	(0.9)	1.00
Male	55	0		56	0		111	0		
Total	109	0		110	1	(0.9)	219	1	(0.5)	1.00
WEIGHT GAIN										
Female	54	0		54	1	(1.9)	108	1	(0.9)	1.00
Male	55	0		56	0		111	0		
Total	109	0		110	1	(0.9)	219	1	(0.5)	1.00

RMP.B1YP.JCLLIB2(AES6JEAA)
RMP.B1YO.HCJEREP(AES6JEAA)
Gender: Patient Gender
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.50 presents the incidence of treatment-emergent solicited adverse events from the Side-Effects Checklist analyzed by gender subgroups during the acute treatment phase.

The Breslow-Day test did not detect a statistically significant difference in odds ratios across the gender subgroups for any treatment-emergent solicited adverse event. The Breslow-Day test detected a trend towards significance (p=.053) for muscle cramps and the between treatment group comparison for males showed a trend towards significance (p=.054), but not for females (p=.671). Placebo-treated males reported muscle cramps more often (36%) than fluoxetine-treated males (18%).

Table 14.50. Treatment-Emergent Solicited Adverse Events
Side Effects Checklist Subgroup Analysis by Gender
Significant (p<.05) Difference in Odds Ratio
All Randomized Patients
Acute Treatment Phase (Study Periods III-IV)
B1Y-MC-HCJE

SECL Event - Have you had trouble with:	GENDER	Flx 20 N	Flx 20 n	Flx 20 (%)	Placebo N	Placebo n	Placebo (%)	p-Values: Homogeneity of Odds Ratio p-Value*	p-Values: Between Group Comparison p-Value**
01. EATING	Female	54	20	(37.0)	54	20	(37.0)	.527	1.00
	Male	55	11	(20.0)	56	15	(26.8)		.502
02. DRINKING	Female	54	10	(18.5)	54	10	(18.5)	.197	1.00
	Male	55	4	(7.3)	56	10	(17.9)		.151
03. DRY MOUTH AND LIPS	Female	54	20	(37.0)	54	18	(33.3)	.147	.840
	Male	55	12	(21.8)	56	20	(35.7)		.143
04. WETNESS IN MOUTH	Female	54	5	(9.3)	54	13	(24.1)	.261	.069
	Male	55	5	(9.1)	56	6	(10.7)		1.00
05. CONSTIPATION	Female	54	5	(9.3)	54	4	(7.4)	.490	1.00
	Male	55	4	(7.3)	56	6	(10.7)		.742
06. DIARRHEA	Female	54	12	(22.2)	54	10	(18.5)	.908	.812
	Male	55	10	(18.2)	56	9	(16.1)		.806
07. STOMACHACHES	Female	54	20	(37.0)	54	19	(35.2)	.290	1.00
	Male	55	17	(30.9)	56	24	(42.9)		.239

* The homogeneity of odds ratio p-Value is derived from the Breslow-Day test.
**The between group comparison within strata p-Value is from the Fisher's Exact Test.
Treatment-Emergent Solicited = was present at baseline and worsened as defined by increase in score on the side-effects checklist or new occurrence after baseline.
RMP.B1YP.SASPGM(CUSJESG1)
RMP.B1YO.HCJEREP(CUSTJEMM)

Table 14.50. Treatment-Emergent Solicited Adverse Events
Side Effects Checklist Subgroup Analysis by Gender
Significant (p<.05) Difference in Odds Ratio
All Randomized Patients
Acute Treatment Phase (Study Periods III-IV)
B1Y-MC-HCJE (continued)

SECL Event - Have you had trouble with:	GENDER	Flx 20 N	Flx 20 n	Flx 20 (%)	Placebo N	Placebo n	Placebo (%)	p-Values: Homogeneity of Odds Ratio p-Value*	p-Values: Between Group Comparison p-Value**
08. MUSCLE CRAMPS	Female	54	17	(31.5)	54	14	(25.9)	.053	.671
	Male	55	10	(18.2)	56	20	(35.7)		.054
09. BEING SICK TO YOUR STOMACH	Female	54	20	(37.0)	54	16	(29.6)	.804	.541
	Male	55	19	(34.5)	56	17	(30.4)		.688
10. WETTING THE BED	Female	54	1	(1.9)	54	2	(3.7)	.843	1.00
	Male	55	2	(3.6)	56	3	(5.4)		1.00
11. URINATING	Female	54	6	(11.1)	54	10	(18.5)	.188	.417
	Male	55	4	(7.3)	56	2	(3.6)		.438
12. ITCHY OR SCRATCHY SKIN	Female	54	17	(31.5)	54	16	(29.6)	.275	1.00
	Male	55	10	(18.2)	56	16	(28.6)		.263
13. RASHES	Female	54	12	(22.2)	54	10	(18.5)	.336	.812
	Male	55	5	(9.1)	56	8	(14.3)		.557
14. COLD OR SNIFFLES	Female	54	21	(38.9)	54	30	(55.6)	.205	.123
	Male	55	20	(36.4)	56	20	(35.7)		1.00

* The homogeneity of odds ratio p-Value is derived from the Breslow-Day test.
**The between group comparison within strata p-Value is from the Fisher’s Exact Test.
Treatment-Emergent Solicited = was present at baseline and worsened as defined by increase in score on the side-effects checklist or new occurrence after baseline.
RMP.B1YP.SASPGM(CUSJESG1)
RMP.B1YO.HCJEREP(CUSTJEMM)

Table 14.50. Treatment-Emergent Solicited Adverse Events
Side Effects Checklist Subgroup Analysis by Gender
Significant (p<.05) Difference in Odds Ratio
All Randomized Patients
Acute Treatment Phase (Study Periods III-IV)
B1Y-MC-HCJE (continued)

SECL Event - Have you had trouble with:	GENDER	Flx 20 N	Flx 20 n	Flx 20 (%)	Placebo N	Placebo n	Placebo (%)	p-Values: Homogeneity of Odds Ratio p-Value*	p-Values: Between Group Comparison p-Value**
15. HEADACHE	Female	54	27	(50.0)	54	18	(33.3)	.182	.118
	Male	55	22	(40.0)	56	23	(41.1)		1.00
16. DIZZINESS	Female	54	21	(38.9)	54	14	(25.9)	.854	.217
	Male	55	13	(23.6)	56	9	(16.1)		.350
17. PLAYING SPORTS	Female	54	6	(11.1)	54	10	(18.5)	.316	.417
	Male	55	11	(20.0)	56	10	(17.9)		.812
18. SHAKINESS	Female	54	11	(20.4)	54	13	(24.1)	.727	.817
	Male	55	10	(18.2)	56	10	(17.9)		1.00
19. PRONOUNCING WORDS	Female	54	6	(11.1)	54	13	(24.1)	.988	.128
	Male	55	7	(12.7)	56	15	(26.8)		.095
20. DOING THINGS WITH YOUR HANDS	Female	54	7	(13.0)	54	8	(14.8)	.492	1.00
	Male	55	6	(10.9)	56	11	(19.6)		.292
21. SITTING STILL	Female	54	13	(24.1)	54	16	(29.6)	.521	.665
	Male	55	17	(30.9)	56	26	(46.4)		.120

* The homogeneity of odds ratio p-Value is derived from the Breslow-Day test.
**The between group comparison within strata p-Value is from the Fisher’s Exact Test.
Treatment-Emergent Solicited = was present at baseline and worsened as defined by increase in score on the side-effects checklist or new occurrence after baseline.
RMP.B1YP.SASPGM(CUSJESG1)
RMP.B1YO.HCJEREP(CUSTJEMM)

Table 14.50. Treatment-Emergent Solicited Adverse Events
Side Effects Checklist Subgroup Analysis by Gender
Significant (p<.05) Difference in Odds Ratio
All Randomized Patients
Acute Treatment Phase (Study Periods III-IV)
B1Y-MC-HCJE (continued)

SECL Event - Have you had trouble with:	GENDER	Flx 20 N	Flx 20 n	Flx 20 (%)	Placebo N	Placebo n	Placebo (%)	p-Values: Homogeneity of Odds Ratio p-Value*	p-Values: Between Group Comparison p-Value**
22. TIREDNESS	Female	54	26	(48.1)	54	24	(44.4)	.956	.847
	Male	55	24	(43.6)	56	22	(39.3)		.702
23. FEELING SLEEPY	Female	54	29	(53.7)	54	25	(46.3)	.726	.564
	Male	55	23	(41.8)	56	22	(39.3)		.848
24. SLEEPING	Female	54	21	(38.9)	54	20	(37.0)	.295	1.00
	Male	55	18	(32.7)	56	25	(44.6)		.244
25. BAD DREAMS	Female	54	15	(27.8)	54	17	(31.5)	.502	.833
	Male	55	12	(21.8)	56	10	(17.9)		.641
26. GETTING ALONG WITH PARENTS	Female	54	22	(40.7)	54	21	(38.9)	.623	1.00
	Male	55	21	(38.2)	56	24	(42.9)		.700
27. GETTING ALONG WITH KIDS	Female	54	13	(24.1)	54	14	(25.9)	.538	1.00
	Male	55	20	(36.4)	56	17	(30.4)		.550
28. CRYING	Female	54	20	(37.0)	54	23	(42.6)	.370	.694
	Male	55	19	(34.5)	56	16	(28.6)		.544

* The homogeneity of odds ratio p-Value is derived from the Breslow-Day test.
**The between group comparison within strata p-Value is from the Fisher’s Exact Test.
Treatment-Emergent Solicited = was present at baseline and worsened as defined by increase in score on the side-effects checklist or new occurrence after baseline.
RMP.B1YP.SASPGM(CUSJESG1)
RMP.B1YO.HCJEREP(CUSTJEMM)

Table 14.50. Treatment-Emergent Solicited Adverse Events
Side Effects Checklist Subgroup Analysis by Gender
Significant (p<.05) Difference in Odds Ratio
All Randomized Patients
Acute Treatment Phase (Study Periods III-IV)
B1Y-MC-HCJE (concluded)

SECL Event - Have you had trouble with:	GENDER	Flx 20 N	Flx 20 n	Flx 20 (%)	Placebo N	Placebo n	Placebo (%)	p-Values: Homogeneity of Odds Ratio p-Value*	p-Values: Between Group Comparison p-Value**
29. GETTING MAD	Female	54	21	(38.9)	54	23	(42.6)	.721	.845
	Male	55	19	(34.5)	56	24	(42.9)		.437
30. NOT BEING HAPPY	Female	54	22	(40.7)	54	15	(27.8)	.269	.224
	Male	55	18	(32.7)	56	19	(33.9)		1.00
31. BEING SAD	Female	54	19	(35.2)	54	17	(31.5)	.453	.838
	Male	55	22	(40.0)	56	15	(26.8)		.162
32. PAYING ATTENTION	Female	54	21	(38.9)	54	15	(27.8)	.990	.307
	Male	55	22	(40.0)	56	16	(28.6)		.234

* The homogeneity of odds ratio p-Value is derived from the Breslow-Day test.
**The between group comparison within strata p-Value is from the Fisher's Exact Test.
Treatment-Emergent Solicited = was present at baseline and worsened as defined by increase in score on the side-effects checklist or new occurrence after baseline.
RMP.B1YP.SASPGM(CUSJESG1)
RMP.B1YO.HCJEREP(CUSTJEMM)

14.3.2.1.3. By Family History of Depression

Table 14.51 presents the incidence of treatment-emergent non-solicited adverse events examined by family history of depression subgroups for the acute treatment phase.

There was a statistically significant difference between treatment groups in the number of patients with a negative family history of depression reporting treatment-emergent non-solicited adverse events (p=.014). Overall, more fluoxetine-treated patients with a negative family history (90%) reported at least one treatment-emergent non-solicited adverse event than placebo-treated patients with a negative family history (67%). Despite the overall difference in reporting frequencies, there were no statistically significant differences between treatment groups for either subgroup based on family history of depression for any individual treatment-emergent non-solicited adverse event.

Table 14.51. Treatment-Emergent Non-Solicited Adverse Events Subgroup Analysis by Family History of Depression All Randomized Patients Acute Treatment Phase (Study Periods III-IV) B1Y-MC-HCJE

FAMHIST (Visit: 1)	Flx 20 N	Flx 20 n (%)	Placebo N	Placebo n (%)	Total N	Total n (%)	p-Value*
PATIENTS WITH >= 1 TESS							
No	41	37 (90.2)	39	26 (66.7)	80	63 (78.8)	.014
Yes	61	52 (85.2)	60	48 (80.0)	121	100 (82.6)	.481
Total	102	89 (87.3)	99	74 (74.7)	201	163 (81.1)	.030
PATIENTS WITH NO TESS							
No	41	4 (9.8)	39	13 (33.3)	80	17 (21.3)	.014
Yes	61	9 (14.8)	60	12 (20.0)	121	21 (17.4)	.481
Total	102	13 (12.7)	99	25 (25.3)	201	38 (18.9)	.030

RMP.B1YP.JCLLIB2(AES6JEAE)
RMP.B1YO.HCJEREP(AES6JEAE)
FAMHIST: FAM HISTORY = Family History of Depression (Visit: 1)
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
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Table 14.51. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Family History of Depression
All Randomized Patients
Acute Treatment Phase (Study Periods III-IV)
B1Y-MC-HCJE (continued)

FAMHIST (Visit: 1)	Flx 20 N	Flx 20 n (%)	Placebo N	Placebo n (%)	Total N	Total n (%)	p-Value*
HEADACHE							
No	41	14 (34.1)	39	7 (17.9)	80	21 (26.3)	.130
Yes	61	17 (27.9)	60	11 (18.3)	121	28 (23.1)	.282
Total	102	31 (30.4)	99	18 (18.2)	201	49 (24.4)	.050
RHINITIS							
No	41	9 (22.0)	39	4 (10.3)	80	13 (16.3)	.227
Yes	61	15 (24.6)	60	15 (25.0)	121	30 (24.8)	1.00
Total	102	24 (23.5)	99	19 (19.2)	201	43 (21.4)	.494

RMP.B1YP.JCLLIB2(AES6JEAE)
RMP.B1YO.HCJEREP(AES6JEAE)
FAMHIST: FAM HISTORY = Family History of Depression (Visit: 1)
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.51. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Family History of Depression
All Randomized Patients
Acute Treatment Phase (Study Periods III-IV)
B1Y-MC-HCJE (continued)

FAMHIST (Visit: 1)	Flx 20 N	Flx 20 n (%)	Placebo N	Placebo n (%)	Total N	Total n (%)	p-Value*
ABDOMINAL PAIN							
No	41	7 (17.1)	39	6 (15.4)	80	13 (16.3)	1.00
Yes	61	9 (14.8)	60	9 (15.0)	121	18 (14.9)	1.00
Total	102	16 (15.7)	99	15 (15.2)	201	31 (15.4)	1.00
PHARYNGITIS							
No	41	6 (14.6)	39	2 (5.1)	80	8 (10.0)	.265
Yes	61	10 (16.4)	60	5 (8.3)	121	15 (12.4)	.270
Total	102	16 (15.7)	99	7 (7.1)	201	23 (11.4)	.075

RMP.B1YP.JCLLIB2(AES6JEAE)
RMP.B1YO.HCJEREP(AES6JEAE)
FAMHIST: FAM HISTORY = Family History of Depression (Visit: 1)
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.51. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Family History of Depression
All Randomized Patients
Acute Treatment Phase (Study Periods III-IV)
B1Y-MC-HCJE (continued)

FAMHIST (Visit: 1)	Flx 20 N	Flx 20 n (%)	Placebo N	Placebo n (%)	Total N	Total n (%)	p-Value*
ACCIDENTAL INJURY							
No	41	3 (7.3)	39	0	80	3 (3.8)	.241
Yes	61	8 (13.1)	60	8 (13.3)	121	16 (13.2)	1.00
Total	102	11 (10.8)	99	8 (8.1)	201	19 (9.5)	.632
DIARRHEA							
No	41	7 (17.1)	39	6 (15.4)	80	13 (16.3)	1.00
Yes	61	3 (4.9)	60	4 (6.7)	121	7 (5.8)	.717
Total	102	10 (9.8)	99	10 (10.1)	201	20 (10.0)	1.00

RMP.B1YP.JCLLIB2(AES6JEAE)
RMP.B1YO.HCJEREP(AES6JEAE)
FAMHIST: FAM HISTORY = Family History of Depression (Visit: 1)
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.51. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Family History of Depression
All Randomized Patients
Acute Treatment Phase (Study Periods III-IV)
B1Y-MC-HCJE (continued)

FAMHIST (Visit: 1)	Flx 20 N	Flx 20 n (%)	Placebo N	Placebo n (%)	Total N	Total n (%)	p-Value*
DIZZINESS							
No	41	4 (9.8)	39	3 (7.7)	80	7 (8.8)	1.00
Yes	61	6 (9.8)	60	1 (1.7)	121	7 (5.8)	.114
Total	102	10 (9.8)	99	4 (4.0)	201	14 (7.0)	.165
RASH							
No	41	5 (12.2)	39	2 (5.1)	80	7 (8.8)	.433
Yes	61	5 (8.2)	60	2 (3.3)	121	7 (5.8)	.439
Total	102	10 (9.8)	99	4 (4.0)	201	14 (7.0)	.165

RMP.B1YP.JCLLIB2(AES6JEAE)
RMP.B1YO.HCJEREP(AES6JEAE)
FAMHIST: FAM HISTORY = Family History of Depression (Visit: 1)
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.51. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Family History of Depression
All Randomized Patients
Acute Treatment Phase (Study Periods III-IV)
B1Y-MC-HCJE (continued)

FAMHIST (Visit: 1)	Flx 20 N	Flx 20 n (%)	Placebo N	Placebo n (%)	Total N	Total n (%)	p-Value*
ANOREXIA							
No	41	4 (9.8)	39	3 (7.7)	80	7 (8.8)	1.00
Yes	61	5 (8.2)	60	2 (3.3)	121	7 (5.8)	.439
Total	102	9 (8.8)	99	5 (5.1)	201	14 (7.0)	.408
COUGH INCREASED							
No	41	5 (12.2)	39	1 (2.6)	80	6 (7.5)	.202
Yes	61	4 (6.6)	60	5 (8.3)	121	9 (7.4)	.743
Total	102	9 (8.8)	99	6 (6.1)	201	15 (7.5)	.594

RMP.B1YP.JCLLIB2(AES6JEAE)
RMP.B1YO.HCJEREP(AES6JEAE)
FAMHIST: FAM HISTORY = Family History of Depression (Visit: 1)
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.51. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Family History of Depression
All Randomized Patients
Acute Treatment Phase (Study Periods III-IV)
B1Y-MC-HCJE (continued)

FAMHIST (Visit: 1)	Flx 20 N	Flx 20 n	Flx 20 (%)	Placebo N	Placebo n	Placebo (%)	Total N	Total n	Total (%)	p-Value*
NERVOUSNESS										
No	41	4	(9.8)	39	1	(2.6)	80	5	(6.3)	.360
Yes	61	5	(8.2)	60	4	(6.7)	121	9	(7.4)	1.00
Total	102	9	(8.8)	99	5	(5.1)	201	14	(7.0)	.408
ASTHENIA										
No	41	3	(7.3)	39	1	(2.6)	80	4	(5.0)	.616
Yes	61	5	(8.2)	60	4	(6.7)	121	9	(7.4)	1.00
Total	102	8	(7.8)	99	5	(5.1)	201	13	(6.5)	.569

RMP.B1YP.JCLLIB2(AES6JEAE)
RMP.B1YO.HCJEREP(AES6JEAE)
FAMHIST: FAM HISTORY = Family History of Depression (Visit: 1)
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.51. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Family History of Depression
All Randomized Patients
Acute Treatment Phase (Study Periods III-IV)
B1Y-MC-HCJE (continued)

FAMHIST (Visit: 1)	Flx 20 N	Flx 20 n (%)	Placebo N	Placebo n (%)	Total N	Total n (%)	p-Value*
NAUSEA							
No	41	6 (14.6)	39	5 (12.8)	80	11 (13.8)	1.00
Yes	61	2 (3.3)	60	3 (5.0)	121	5 (4.1)	.680
Total	102	8 (7.8)	99	8 (8.1)	201	16 (8.0)	1.00
PAIN							
No	41	4 (9.8)	39	3 (7.7)	80	7 (8.8)	1.00
Yes	61	4 (6.6)	60	5 (8.3)	121	9 (7.4)	.743
Total	102	8 (7.8)	99	8 (8.1)	201	16 (8.0)	1.00

RMP.B1YP.JCLLIB2(AES6JEAE)
RMP.B1YO.HCJEREP(AES6JEAE)
FAMHIST: FAM HISTORY = Family History of Depression (Visit: 1)
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.51. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Family History of Depression
All Randomized Patients
Acute Treatment Phase (Study Periods III-IV)
B1Y-MC-HCJE (continued)

FAMHIST (Visit: 1)	Flx 20 N	Flx 20 n (%)	Placebo N	Placebo n (%)	Total N	Total n (%)	p-Value*
VOMITING							
No	41	2 (4.9)	39	4 (10.3)	80	6 (7.5)	.426
Yes	61	6 (9.8)	60	3 (5.0)	121	9 (7.4)	.491
Total	102	8 (7.8)	99	7 (7.1)	201	15 (7.5)	1.00
FEVER							
No	41	4 (9.8)	39	1 (2.6)	80	5 (6.3)	.360
Yes	61	3 (4.9)	60	3 (5.0)	121	6 (5.0)	1.00
Total	102	7 (6.9)	99	4 (4.0)	201	11 (5.5)	.538

RMP.B1YP.JCLLIB2(AES6JEAE)
RMP.B1YO.HCJEREP(AES6JEAE)
FAMHIST: FAM HISTORY = Family History of Depression (Visit: 1)
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.51. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Family History of Depression
All Randomized Patients
Acute Treatment Phase (Study Periods III-IV)
B1Y-MC-HCJE (continued)

FAMHIST (Visit: 1)	Flx 20 N	Flx 20 n	Flx 20 (%)	Placebo N	Placebo n	Placebo (%)	Total N	Total n	Total (%)	p-Value*
ABNORMAL DREAMS										
No	41	1	(2.4)	39	2	(5.1)	80	3	(3.8)	.611
Yes	61	5	(8.2)	60	1	(1.7)	121	6	(5.0)	.207
Total	102	6	(5.9)	99	3	(3.0)	201	9	(4.5)	.498
EPISTAXIS										
No	41	2	(4.9)	39	0		80	2	(2.5)	.494
Yes	61	3	(4.9)	60	1	(1.7)	121	4	(3.3)	.619
Total	102	5	(4.9)	99	1	(1.0)	201	6	(3.0)	.212

RMP.B1YP.JCLLIB2(AES6JEAE)
RMP.B1YO.HCJEREP(AES6JEAE)
FAMHIST: FAM HISTORY = Family History of Depression (Visit: 1)
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.51. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Family History of Depression
All Randomized Patients
Acute Treatment Phase (Study Periods III-IV)
B1Y-MC-HCJE (continued)

FAMHIST (Visit: 1)	Flx 20 N	Flx 20 n	Flx 20 (%)	Placebo N	Placebo n	Placebo (%)	Total N	Total n	Total (%)	p-Value*
DYSMENORRHEA										
No	41	4	(9.8)	39	1	(2.6)	80	5	(6.3)	.360
Yes	61	0		60	1	(1.7)	121	1	(0.8)	.496
Total	102	4	(3.9)	99	2	(2.0)	201	6	(3.0)	.683
EAR PAIN										
No	41	2	(4.9)	39	0		80	2	(2.5)	.494
Yes	61	2	(3.3)	60	1	(1.7)	121	3	(2.5)	1.00
Total	102	4	(3.9)	99	1	(1.0)	201	5	(2.5)	.369

RMP.B1YP.JCLLIB2(AES6JEAE)
RMP.B1YO.HCJEREP(AES6JEAE)
FAMHIST: FAM HISTORY = Family History of Depression (Visit: 1)
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.51. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Family History of Depression
All Randomized Patients
Acute Treatment Phase (Study Periods III-IV)
B1Y-MC-HCJE (continued)

FAMHIST (Visit: 1)	Flx 20 N	Flx 20 n	Flx 20 (%)	Placebo N	Placebo n	Placebo (%)	Total N	Total n	Total (%)	p-Value*
FLU SYNDROME										
No	41	1	(2.4)	39	0		80	1	(1.3)	1.00
Yes	61	3	(4.9)	60	3	(5.0)	121	6	(5.0)	1.00
Total	102	4	(3.9)	99	3	(3.0)	201	7	(3.5)	1.00
INSOMNIA										
No	41	4	(9.8)	39	1	(2.6)	80	5	(6.3)	.360
Yes	61	0		60	4	(6.7)	121	4	(3.3)	.057
Total	102	4	(3.9)	99	5	(5.1)	201	9	(4.5)	.745

RMP.B1YP.JCLLIB2(AES6JEAE)
RMP.B1YO.HCJEREP(AES6JEAE)
FAMHIST: FAM HISTORY = Family History of Depression (Visit: 1)
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.51. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Family History of Depression
All Randomized Patients
Acute Treatment Phase (Study Periods III-IV)
B1Y-MC-HCJE (continued)

FAMHIST (Visit: 1)	Flx 20 N	Flx 20 n	Flx 20 (%)	Placebo N	Placebo n	Placebo (%)	Total N	Total n	Total (%)	p-Value*
PRURITUS										
No	41	1	(2.4)	39	1	(2.6)	80	2	(2.5)	1.00
Yes	61	3	(4.9)	60	4	(6.7)	121	7	(5.8)	.717
Total	102	4	(3.9)	99	5	(5.1)	201	9	(4.5)	.745
AGITATION										
No	41	2	(4.9)	39	0		80	2	(2.5)	.494
Yes	61	1	(1.6)	60	0		121	1	(0.8)	1.00
Total	102	3	(2.9)	99	0		201	3	(1.5)	.246

RMP.B1YP.JCLLIB2(AES6JEAE)
RMP.B1YO.HCJEREP(AES6JEAE)
FAMHIST: FAM HISTORY = Family History of Depression (Visit: 1)
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.51. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Family History of Depression
All Randomized Patients
Acute Treatment Phase (Study Periods III-IV)
B1Y-MC-HCJE (continued)

FAMHIST (Visit: 1)	Flx 20 N	Flx 20 n	Flx 20 (%)	Placebo N	Placebo n	Placebo (%)	Total N	Total n	Total (%)	p-Value*
CHEST PAIN										
No	41	1	(2.4)	39	0		80	1	(1.3)	1.00
Yes	61	2	(3.3)	60	2	(3.3)	121	4	(3.3)	1.00
Total	102	3	(2.9)	99	2	(2.0)	201	5	(2.5)	1.00
CONSTIPATION										
No	41	2	(4.9)	39	0		80	2	(2.5)	.494
Yes	61	1	(1.6)	60	2	(3.3)	121	3	(2.5)	.619
Total	102	3	(2.9)	99	2	(2.0)	201	5	(2.5)	1.00

RMP.B1YP.JCLLIB2(AES6JEAE)
RMP.B1YO.HCJEREP(AES6JEAE)
FAMHIST: FAM HISTORY = Family History of Depression (Visit: 1)
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.51. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Family History of Depression
All Randomized Patients
Acute Treatment Phase (Study Periods III-IV)
B1Y-MC-HCJE (continued)

FAMHIST (Visit: 1)	Flx 20 N	Flx 20 n (%)	Placebo N	Placebo n (%)	Total N	Total n (%)	p-Value*
DRY MOUTH							
No	41	2 (4.9)	39	4 (10.3)	80	6 (7.5)	.426
Yes	61	1 (1.6)	60	1 (1.7)	121	2 (1.7)	1.00
Total	102	3 (2.9)	99	5 (5.1)	201	8 (4.0)	.494
DYSPEPSIA							
No	41	2 (4.9)	39	1 (2.6)	80	3 (3.8)	1.00
Yes	61	1 (1.6)	60	3 (5.0)	121	4 (3.3)	.365
Total	102	3 (2.9)	99	4 (4.0)	201	7 (3.5)	.718

RMP.B1YP.JCLLIB2(AES6JEAE)
RMP.B1YO.HCJEREP(AES6JEAE)
FAMHIST: FAM HISTORY = Family History of Depression (Visit: 1)
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.51. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Family History of Depression
All Randomized Patients
Acute Treatment Phase (Study Periods III-IV)
B1Y-MC-HCJE (continued)

FAMHIST (Visit: 1)	Flx 20 N	Flx 20 n (%)	Placebo N	Placebo n (%)	Total N	Total n (%)	p-Value*
ECCHYMOSIS							
No	41	1 (2.4)	39	0	80	1 (1.3)	1.00
Yes	61	2 (3.3)	60	1 (1.7)	121	3 (2.5)	1.00
Total	102	3 (2.9)	99	1 (1.0)	201	4 (2.0)	.621
NECK PAIN							
No	41	1 (2.4)	39	0	80	1 (1.3)	1.00
Yes	61	2 (3.3)	60	0	121	2 (1.7)	.496
Total	102	3 (2.9)	99	0	201	3 (1.5)	.246

RMP.B1YP.JCLLIB2(AES6JEAE)
RMP.B1YO.HCJEREP(AES6JEAE)
FAMHIST: FAM HISTORY = Family History of Depression (Visit: 1)
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.51. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Family History of Depression
All Randomized Patients
Acute Treatment Phase (Study Periods III-IV)
B1Y-MC-HCJE (continued)

FAMHIST (Visit: 1)	Flx 20 N	Flx 20 n	Flx 20 (%)	Placebo N	Placebo n	Placebo (%)	Total N	Total n	Total (%)	p-Value*
SINUSITIS										
No	41	0		39	1	(2.6)	80	1	(1.3)	.488
Yes	61	3	(4.9)	60	1	(1.7)	121	4	(3.3)	.619
Total	102	3	(2.9)	99	2	(2.0)	201	5	(2.5)	1.00
SOMNOLENCE										
No	41	0		39	0		80	0		
Yes	61	3	(4.9)	60	3	(5.0)	121	6	(5.0)	1.00
Total	102	3	(2.9)	99	3	(3.0)	201	6	(3.0)	1.00

RMP.B1YP.JCLLIB2(AES6JEAE)
RMP.B1YO.HCJEREP(AES6JEAE)
FAMHIST: FAM HISTORY = Family History of Depression (Visit: 1)
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.51. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Family History of Depression
All Randomized Patients
Acute Treatment Phase (Study Periods III-IV)
B1Y-MC-HCJE (continued)

FAMHIST (Visit: 1)	Flx 20 N	Flx 20 n (%)	Placebo N	Placebo n (%)	Total N	Total n (%)	p-Value*
TREMOR							
No	41	2 (4.9)	39	0	80	2 (2.5)	.494
Yes	61	1 (1.6)	60	0	121	1 (0.8)	1.00
Total	102	3 (2.9)	99	0	201	3 (1.5)	.246
AKATHISIA							
No	41	2 (4.9)	39	0	80	2 (2.5)	.494
Yes	61	0	60	0	121	0	
Total	102	2 (2.0)	99	0	201	2 (1.0)	.498

RMP.B1YP.JCLLIB2(AES6JEAE)
RMP.B1YO.HCJEREP(AES6JEAE)
FAMHIST: FAM HISTORY = Family History of Depression (Visit: 1)
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.51. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Family History of Depression
All Randomized Patients
Acute Treatment Phase (Study Periods III-IV)
B1Y-MC-HCJE (continued)

FAMHIST (Visit: 1)	Flx 20 N	Flx 20 n	Flx 20 (%)	Placebo N	Placebo n	Placebo (%)	Total N	Total n	Total (%)	p-Value*
ALLERGIC REACTION										
No	41	0		39	0		80	0		
Yes	61	2	(3.3)	60	2	(3.3)	121	4	(3.3)	1.00
Total	102	2	(2.0)	99	2	(2.0)	201	4	(2.0)	1.00
ANXIETY										
No	41	1	(2.4)	39	0		80	1	(1.3)	1.00
Yes	61	1	(1.6)	60	0		121	1	(0.8)	1.00
Total	102	2	(2.0)	99	0		201	2	(1.0)	.498

RMP.B1YP.JCLLIB2(AES6JEAE)
RMP.B1YO.HCJEREP(AES6JEAE)
FAMHIST: FAM HISTORY = Family History of Depression (Visit: 1)
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.51. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Family History of Depression
All Randomized Patients
Acute Treatment Phase (Study Periods III-IV)
B1Y-MC-HCJE (continued)

FAMHIST (Visit: 1)	Flx 20 N	Flx 20 n (%)	Placebo N	Placebo n (%)	Total N	Total n (%)	p-Value*
ASTHMA							
No	41	1 (2.4)	39	0	80	1 (1.3)	1.00
Yes	61	1 (1.6)	60	0	121	1 (0.8)	1.00
Total	102	2 (2.0)	99	0	201	2 (1.0)	.498
BACK PAIN							
No	41	1 (2.4)	39	2 (5.1)	80	3 (3.8)	.611
Yes	61	1 (1.6)	60	1 (1.7)	121	2 (1.7)	1.00
Total	102	2 (2.0)	99	3 (3.0)	201	5 (2.5)	.680

RMP.B1YP.JCLLIB2(AES6JEAE)
RMP.B1YO.HCJEREP(AES6JEAE)
FAMHIST: FAM HISTORY = Family History of Depression (Visit: 1)
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.51. Treatment-Emergent Non-Solicited Adverse Events Subgroup Analysis by Family History of Depression All Randomized Patients Acute Treatment Phase (Study Periods III-IV) B1Y-MC-HCJE (continued)

FAMHIST (Visit: 1)	Flx 20 N	Flx 20 n (%)	Placebo N	Placebo n (%)	Total N	Total n (%)	p-Value*
CHILLS							
No	41	1 (2.4)	39	0	80	1 (1.3)	1.00
Yes	61	1 (1.6)	60	0	121	1 (0.8)	1.00
Total	102	2 (2.0)	99	0	201	2 (1.0)	.498
DEPRESSION							
No	41	0	39	0	80	0	
Yes	61	2 (3.3)	60	1 (1.7)	121	3 (2.5)	1.00
Total	102	2 (2.0)	99	1 (1.0)	201	3 (1.5)	1.00

RMP.B1YP.JCLLIB2(AES6JEAE)
RMP.B1YO.HCJEREP(AES6JEAE)
FAMHIST: FAM HISTORY = Family History of Depression (Visit: 1)
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.51. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Family History of Depression
All Randomized Patients
Acute Treatment Phase (Study Periods III-IV)
B1Y-MC-HCJE (continued)

FAMHIST (Visit: 1)	Flx 20 N	Flx 20 n	Flx 20 (%)	Placebo N	Placebo n	Placebo (%)	Total N	Total n	Total (%)	p-Value*
DRY SKIN										
No	41	0		39	0		80	0		
Yes	61	2	(3.3)	60	0		121	2	(1.7)	.496
Total	102	2	(2.0)	99	0		201	2	(1.0)	.498
EYE DISORDER										
No	41	0		39	0		80	0		
Yes	61	2	(3.3)	60	0		121	2	(1.7)	.496
Total	102	2	(2.0)	99	0		201	2	(1.0)	.498

RMP.B1YP.JCLLIB2(AES6JEAE)
RMP.B1YO.HCJEREP(AES6JEAE)
FAMHIST: FAM HISTORY = Family History of Depression (Visit: 1)
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.51. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Family History of Depression
All Randomized Patients
Acute Treatment Phase (Study Periods III-IV)
B1Y-MC-HCJE (continued)

FAMHIST (Visit: 1)	Flx 20 N	Flx 20 n (%)	Placebo N	Placebo n (%)	Total N	Total n (%)	p-Value*
GASTROENTERITIS							
No	41	1 (2.4)	39	0	80	1 (1.3)	1.00
Yes	61	1 (1.6)	60	0	121	1 (0.8)	1.00
Total	102	2 (2.0)	99	0	201	2 (1.0)	.498
HOSTILITY							
No	41	1 (2.4)	39	2 (5.1)	80	3 (3.8)	.611
Yes	61	1 (1.6)	60	3 (5.0)	121	4 (3.3)	.365
Total	102	2 (2.0)	99	5 (5.1)	201	7 (3.5)	.274

RMP.B1YP.JCLLIB2(AES6JEAE)
RMP.B1YO.HCJEREP(AES6JEAE)
FAMHIST: FAM HISTORY = Family History of Depression (Visit: 1)
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.51. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Family History of Depression
All Randomized Patients
Acute Treatment Phase (Study Periods III-IV)
B1Y-MC-HCJE (continued)

FAMHIST (Visit: 1)	Flx 20 N	Flx 20 n	Flx 20 (%)	Placebo N	Placebo n	Placebo (%)	Total N	Total n	Total (%)	p-Value*
HYPERKINESIA										
No	41	0		39	0		80	0		
Yes	61	2	(3.3)	60	0		121	2	(1.7)	.496
Total	102	2	(2.0)	99	0		201	2	(1.0)	.498
INFECTION										
No	41	1	(2.4)	39	0		80	1	(1.3)	1.00
Yes	61	1	(1.6)	60	1	(1.7)	121	2	(1.7)	1.00
Total	102	2	(2.0)	99	1	(1.0)	201	3	(1.5)	1.00

RMP.B1YP.JCLLIB2(AES6JEAE)
RMP.B1YO.HCJEREP(AES6JEAE)
FAMHIST: FAM HISTORY = Family History of Depression (Visit: 1)
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.51. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Family History of Depression
All Randomized Patients
Acute Treatment Phase (Study Periods III-IV)
B1Y-MC-HCJE (continued)

FAMHIST (Visit: 1)	Flx 20 N	Flx 20 n	Flx 20 (%)	Placebo N	Placebo n	Placebo (%)	Total N	Total n	Total (%)	p-Value*
OTITIS EXTERNA										
No	41	1	(2.4)	39	1	(2.6)	80	2	(2.5)	1.00
Yes	61	1	(1.6)	60	0		121	1	(0.8)	1.00
Total	102	2	(2.0)	99	1	(1.0)	201	3	(1.5)	1.00
PERSONALITY DISORDER										
No	41	2	(4.9)	39	1	(2.6)	80	3	(3.8)	1.00
Yes	61	0		60	0		121	0		
Total	102	2	(2.0)	99	1	(1.0)	201	3	(1.5)	1.00

RMP.B1YP.JCLLIB2(AES6JEAE)
RMP.B1YO.HCJEREP(AES6JEAE)
FAMHIST: FAM HISTORY = Family History of Depression (Visit: 1)
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.51. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Family History of Depression
All Randomized Patients
Acute Treatment Phase (Study Periods III-IV)
B1Y-MC-HCJE (continued)

FAMHIST (Visit: 1)	Flx 20 N	Flx 20 n (%)	Placebo N	Placebo n (%)	Total N	Total n (%)	p-Value*
PHOTOSENSITIVITY REACTION							
No	41	1 (2.4)	39	0	80	1 (1.3)	1.00
Yes	61	1 (1.6)	60	0	121	1 (0.8)	1.00
Total	102	2 (2.0)	99	0	201	2 (1.0)	.498
SLEEP DISORDER							
No	41	1 (2.4)	39	0	80	1 (1.3)	1.00
Yes	61	1 (1.6)	60	0	121	1 (0.8)	1.00
Total	102	2 (2.0)	99	0	201	2 (1.0)	.498

RMP.B1YP.JCLLIB2(AES6JEAE)
RMP.B1YO.HCJEREP(AES6JEAE)
FAMHIST: FAM HISTORY = Family History of Depression (Visit: 1)
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.51. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Family History of Depression
All Randomized Patients
Acute Treatment Phase (Study Periods III-IV)
B1Y-MC-HCJE (continued)

FAMHIST (Visit: 1)	Flx 20 N	Flx 20 n	Flx 20 (%)	Placebo N	Placebo n	Placebo (%)	Total N	Total n	Total (%)	p-Value*
SPEECH DISORDER										
No	41	1	(2.4)	39	1	(2.6)	80	2	(2.5)	1.00
Yes	61	1	(1.6)	60	0		121	1	(0.8)	1.00
Total	102	2	(2.0)	99	1	(1.0)	201	3	(1.5)	1.00
THIRST										
No	41	2	(4.9)	39	1	(2.6)	80	3	(3.8)	1.00
Yes	61	0		60	1	(1.7)	121	1	(0.8)	.496
Total	102	2	(2.0)	99	2	(2.0)	201	4	(2.0)	1.00

RMP.B1YP.JCLLIB2(AES6JEAE)
RMP.B1YO.HCJEREP(AES6JEAE)
FAMHIST: FAM HISTORY = Family History of Depression (Visit: 1)
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.51. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Family History of Depression
All Randomized Patients
Acute Treatment Phase (Study Periods III-IV)
B1Y-MC-HCJE (continued)

FAMHIST (Visit: 1)	Flx 20 N	Flx 20 n	Flx 20 (%)	Placebo N	Placebo n	Placebo (%)	Total N	Total n	Total (%)	p-Value*
ACUTE BRAIN SYNDROME										
No	41	0		39	0		80	0		
Yes	61	1	(1.6)	60	0		121	1	(0.8)	1.00
Total	102	1	(1.0)	99	0		201	1	(0.5)	1.00
BRONCHITIS										
No	41	1	(2.4)	39	0		80	1	(1.3)	1.00
Yes	61	0		60	0		121	0		
Total	102	1	(1.0)	99	0		201	1	(0.5)	1.00

RMP.B1YP.JCLLIB2(AES6JEAE)
RMP.B1YO.HCJEREP(AES6JEAE)
FAMHIST: FAM HISTORY = Family History of Depression (Visit: 1)
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.51. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Family History of Depression
All Randomized Patients
Acute Treatment Phase (Study Periods III-IV)
B1Y-MC-HCJE (continued)

FAMHIST (Visit: 1)	Flx 20 N	Flx 20 n	Flx 20 (%)	Placebo N	Placebo n	Placebo (%)	Total N	Total n	Total (%)	p-Value*
BUCCOGLOSSAL SYNDROME										
No	41	0		39	0		80	0		
Yes	61	1	(1.6)	60	0		121	1	(0.8)	1.00
Total	102	1	(1.0)	99	0		201	1	(0.5)	1.00
CONTACT DERMATITIS										
No	41	1	(2.4)	39	0		80	1	(1.3)	1.00
Yes	61	0		60	0		121	0		
Total	102	1	(1.0)	99	0		201	1	(0.5)	1.00

RMP.B1YP.JCLLIB2(AES6JEAE)
RMP.B1YO.HCJEREP(AES6JEAE)
FAMHIST: FAM HISTORY = Family History of Depression (Visit: 1)
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.51. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Family History of Depression
All Randomized Patients
Acute Treatment Phase (Study Periods III-IV)
B1Y-MC-HCJE (continued)

FAMHIST (Visit: 1)	Flx 20 N	Flx 20 n (%)	Placebo N	Placebo n (%)	Total N	Total n (%)	p-Value*
DELUSIONS							
No	41	1 (2.4)	39	0	80	1 (1.3)	1.00
Yes	61	0	60	0	121	0	
Total	102	1 (1.0)	99	0	201	1 (0.5)	1.00
DYSPHAGIA							
No	41	0	39	0	80	0	
Yes	61	1 (1.6)	60	1 (1.7)	121	2 (1.7)	1.00
Total	102	1 (1.0)	99	1 (1.0)	201	2 (1.0)	1.00

RMP.B1YP.JCLLIB2(AES6JEAE)
RMP.B1YO.HCJEREP(AES6JEAE)
FAMHIST: FAM HISTORY = Family History of Depression (Visit: 1)
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.51. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Family History of Depression
All Randomized Patients
Acute Treatment Phase (Study Periods III-IV)
B1Y-MC-HCJE (continued)

FAMHIST (Visit: 1)	Flx 20 N	Flx 20 n	Flx 20 (%)	Placebo N	Placebo n	Placebo (%)	Total N	Total n	Total (%)	p-Value*
DYSPNEA										
No	41	0		39	0		80	0		
Yes	61	1	(1.6)	60	0		121	1	(0.8)	1.00
Total	102	1	(1.0)	99	0		201	1	(0.5)	1.00
EAR DISORDER										
No	41	0		39	0		80	0		
Yes	61	1	(1.6)	60	0		121	1	(0.8)	1.00
Total	102	1	(1.0)	99	0		201	1	(0.5)	1.00

RMP.B1YP.JCLLIB2(AES6JEAE)
RMP.B1YO.HCJEREP(AES6JEAE)
FAMHIST: FAM HISTORY = Family History of Depression (Visit: 1)
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.51. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Family History of Depression
All Randomized Patients
Acute Treatment Phase (Study Periods III-IV)
B1Y-MC-HCJE (continued)

FAMHIST (Visit: 1)	Flx 20 N	Flx 20 n (%)	Placebo N	Placebo n (%)	Total N	Total n (%)	p-Value*
EMOTIONAL LABILITY							
No	41	1 (2.4)	39	0	80	1 (1.3)	1.00
Yes	61	0	60	0	121	0	
Total	102	1 (1.0)	99	0	201	1 (0.5)	1.00
ENDOMETRIAL HYPERPLASIA							
No	41	1 (2.4)	39	0	80	1 (1.3)	1.00
Yes	61	0	60	0	121	0	
Total	102	1 (1.0)	99	0	201	1 (0.5)	1.00

RMP.B1YP.JCLLIB2(AES6JEAE)
RMP.B1YO.HCJEREP(AES6JEAE)
FAMHIST: FAM HISTORY = Family History of Depression (Visit: 1)
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.51. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Family History of Depression
All Randomized Patients
Acute Treatment Phase (Study Periods III-IV)
B1Y-MC-HCJE (continued)

FAMHIST (Visit: 1)	Flx 20 N	Flx 20 n	Flx 20 (%)	Placebo N	Placebo n	Placebo (%)	Total N	Total n	Total (%)	p-Value*
EUPHORIA										
No	41	0		39	0		80	0		
Yes	61	1	(1.6)	60	0		121	1	(0.8)	1.00
Total	102	1	(1.0)	99	0		201	1	(0.5)	1.00
FLATULENCE										
No	41	1	(2.4)	39	0		80	1	(1.3)	1.00
Yes	61	0		60	0		121	0		
Total	102	1	(1.0)	99	0		201	1	(0.5)	1.00

RMP.B1YP.JCLLIB2(AES6JEAE)
RMP.B1YO.HCJEREP(AES6JEAE)
FAMHIST: FAM HISTORY = Family History of Depression (Visit: 1)
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.51. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Family History of Depression
All Randomized Patients
Acute Treatment Phase (Study Periods III-IV)
B1Y-MC-HCJE (continued)

FAMHIST (Visit: 1)	Flx 20 N	Flx 20 n	Flx 20 (%)	Placebo N	Placebo n	Placebo (%)	Total N	Total n	Total (%)	p-Value*
FUNGAL DERMATITIS										
No	41	0		39	1	(2.6)	80	1	(1.3)	.488
Yes	61	1	(1.6)	60	0		121	1	(0.8)	1.00
Total	102	1	(1.0)	99	1	(1.0)	201	2	(1.0)	1.00
HALLUCINATIONS										
No	41	1	(2.4)	39	0		80	1	(1.3)	1.00
Yes	61	0		60	0		121	0		
Total	102	1	(1.0)	99	0		201	1	(0.5)	1.00

RMP.B1YP.JCLLIB2(AES6JEAE)
RMP.B1YO.HCJEREP(AES6JEAE)
FAMHIST: FAM HISTORY = Family History of Depression (Visit: 1)
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.51. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Family History of Depression
All Randomized Patients
Acute Treatment Phase (Study Periods III-IV)
B1Y-MC-HCJE (continued)

FAMHIST (Visit: 1)	Flx 20 N	Flx 20 n (%)	Placebo N	Placebo n (%)	Total N	Total n (%)	p-Value*
HEPATITIS NONSPECIFIC							
No	41	1 (2.4)	39	0	80	1 (1.3)	1.00
Yes	61	0	60	0	121	0	
Total	102	1 (1.0)	99	0	201	1 (0.5)	1.00
HEPATOMEGALY							
No	41	1 (2.4)	39	0	80	1 (1.3)	1.00
Yes	61	0	60	0	121	0	
Total	102	1 (1.0)	99	0	201	1 (0.5)	1.00

RMP.B1YP.JCLLIB2(AES6JEAE)
RMP.B1YO.HCJEREP(AES6JEAE)
FAMHIST: FAM HISTORY = Family History of Depression (Visit: 1)
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.51. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Family History of Depression
All Randomized Patients
Acute Treatment Phase (Study Periods III-IV)
B1Y-MC-HCJE (continued)

FAMHIST (Visit: 1)	Flx 20 N	Flx 20 n	Flx 20 (%)	Placebo N	Placebo n	Placebo (%)	Total N	Total n	Total (%)	p-Value*
HERPES SIMPLEX										
No	41	1	(2.4)	39	0		80	1	(1.3)	1.00
Yes	61	0		60	0		121	0		
Total	102	1	(1.0)	99	0		201	1	(0.5)	1.00
HYPERTONIA										
No	41	0		39	1	(2.6)	80	1	(1.3)	.488
Yes	61	1	(1.6)	60	0		121	1	(0.8)	1.00
Total	102	1	(1.0)	99	1	(1.0)	201	2	(1.0)	1.00

RMP.B1YP.JCLLIB2(AES6JEAE)
RMP.B1YO.HCJEREP(AES6JEAE)
FAMHIST: FAM HISTORY = Family History of Depression (Visit: 1)
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.51. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Family History of Depression
All Randomized Patients
Acute Treatment Phase (Study Periods III-IV)
B1Y-MC-HCJE (continued)

FAMHIST (Visit: 1)	Flx 20 N	Flx 20 n (%)	Placebo N	Placebo n (%)	Total N	Total n (%)	p-Value*
HYPOTENSION							
No	41	1 (2.4)	39	0	80	1 (1.3)	1.00
Yes	61	0	60	0	121	0	
Total	102	1 (1.0)	99	0	201	1 (0.5)	1.00
JOINT DISORDER							
No	41	0	39	0	80	0	
Yes	61	1 (1.6)	60	0	121	1 (0.8)	1.00
Total	102	1 (1.0)	99	0	201	1 (0.5)	1.00

RMP.B1YP.JCLLIB2(AES6JEAE)
RMP.B1YO.HCJEREP(AES6JEAE)
FAMHIST: FAM HISTORY = Family History of Depression (Visit: 1)
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.51. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Family History of Depression
All Randomized Patients
Acute Treatment Phase (Study Periods III-IV)
B1Y-MC-HCJE (continued)

FAMHIST (Visit: 1)	Flx 20 N	Flx 20 n	Flx 20 (%)	Placebo N	Placebo n	Placebo (%)	Total N	Total n	Total (%)	p-Value*
LEG CRAMPS										
No	41	0		39	1	(2.6)	80	1	(1.3)	.488
Yes	61	1	(1.6)	60	0		121	1	(0.8)	1.00
Total	102	1	(1.0)	99	1	(1.0)	201	2	(1.0)	1.00
LUNG DISORDER										
No	41	0		39	0		80	0		
Yes	61	1	(1.6)	60	0		121	1	(0.8)	1.00
Total	102	1	(1.0)	99	0		201	1	(0.5)	1.00

RMP.B1YP.JCLLIB2(AES6JEAE)
RMP.B1YO.HCJEREP(AES6JEAE)
FAMHIST: FAM HISTORY = Family History of Depression (Visit: 1)
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.51. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Family History of Depression
All Randomized Patients
Acute Treatment Phase (Study Periods III-IV)
B1Y-MC-HCJE (continued)

FAMHIST (Visit: 1)	Flx 20 N	Flx 20 n (%)	Placebo N	Placebo n (%)	Total N	Total n (%)	p-Value*
MANIC REACTION							
No	41	1 (2.4)	39	0	80	1 (1.3)	1.00
Yes	61	0	60	0	121	0	
Total	102	1 (1.0)	99	0	201	1 (0.5)	1.00
MIGRAINE							
No	41	1 (2.4)	39	0	80	1 (1.3)	1.00
Yes	61	0	60	1 (1.7)	121	1 (0.8)	.496
Total	102	1 (1.0)	99	1 (1.0)	201	2 (1.0)	1.00

RMP.B1YP.JCLLIB2(AES6JEAE)
RMP.B1YO.HCJEREP(AES6JEAE)
FAMHIST: FAM HISTORY = Family History of Depression (Visit: 1)
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.51. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Family History of Depression
All Randomized Patients
Acute Treatment Phase (Study Periods III-IV)
B1Y-MC-HCJE (continued)

FAMHIST (Visit: 1)	Flx 20 N	Flx 20 n	Flx 20 (%)	Placebo N	Placebo n	Placebo (%)	Total N	Total n	Total (%)	p-Value*
MYALGIA										
No	41	1	(2.4)	39	0		80	1	(1.3)	1.00
Yes	61	0		60	3	(5.0)	121	3	(2.5)	.119
Total	102	1	(1.0)	99	3	(3.0)	201	4	(2.0)	.364
NEUROSIS										
No	41	0		39	0		80	0		
Yes	61	1	(1.6)	60	0		121	1	(0.8)	1.00
Total	102	1	(1.0)	99	0		201	1	(0.5)	1.00

RMP.B1YP.JCLLIB2(AES6JEAE)
RMP.B1YO.HCJEREP(AES6JEAE)
FAMHIST: FAM HISTORY = Family History of Depression (Visit: 1)
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.51. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Family History of Depression
All Randomized Patients
Acute Treatment Phase (Study Periods III-IV)
B1Y-MC-HCJE (continued)

FAMHIST (Visit: 1)	Flx 20 N	Flx 20 n	Flx 20 (%)	Placebo N	Placebo n	Placebo (%)	Total N	Total n	Total (%)	p-Value*
OVERDOSE										
No	41	0		39	0		80	0		
Yes	61	1	(1.6)	60	0		121	1	(0.8)	1.00
Total	102	1	(1.0)	99	0		201	1	(0.5)	1.00
PALPITATION										
No	41	0		39	0		80	0		
Yes	61	1	(1.6)	60	1	(1.7)	121	2	(1.7)	1.00
Total	102	1	(1.0)	99	1	(1.0)	201	2	(1.0)	1.00

RMP.B1YP.JCLLIB2(AES6JEAE)
RMP.B1YO.HCJEREP(AES6JEAE)
FAMHIST: FAM HISTORY = Family History of Depression (Visit: 1)
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.51. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Family History of Depression
All Randomized Patients
Acute Treatment Phase (Study Periods III-IV)
B1Y-MC-HCJE (continued)

FAMHIST (Visit: 1)	Flx 20 N	Flx 20 n (%)	Placebo N	Placebo n (%)	Total N	Total n (%)	p-Value*
PNEUMONIA							
No	41	1 (2.4)	39	0	80	1 (1.3)	1.00
Yes	61	0	60	0	121	0	
Total	102	1 (1.0)	99	0	201	1 (0.5)	1.00
SURGICAL PROCEDURE							
No	41	1 (2.4)	39	0	80	1 (1.3)	1.00
Yes	61	0	60	1 (1.7)	121	1 (0.8)	.496
Total	102	1 (1.0)	99	1 (1.0)	201	2 (1.0)	1.00

RMP.B1YP.JCLLIB2(AES6JEAE)
RMP.B1YO.HCJEREP(AES6JEAE)
FAMHIST: FAM HISTORY = Family History of Depression (Visit: 1)
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.51. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Family History of Depression
All Randomized Patients
Acute Treatment Phase (Study Periods III-IV)
B1Y-MC-HCJE (continued)

FAMHIST (Visit: 1)	Flx 20 N	Flx 20 n (%)	Placebo N	Placebo n (%)	Total N	Total n (%)	p-Value*
SWEATING							
No	41	1 (2.4)	39	0	80	1 (1.3)	1.00
Yes	61	0	60	0	121	0	
Total	102	1 (1.0)	99	0	201	1 (0.5)	1.00
SYNCOPE							
No	41	0	39	0	80	0	
Yes	61	1 (1.6)	60	0	121	1 (0.8)	1.00
Total	102	1 (1.0)	99	0	201	1 (0.5)	1.00

RMP.B1YP.JCLLIB2(AES6JEAE)
RMP.B1YO.HCJEREP(AES6JEAE)
FAMHIST: FAM HISTORY = Family History of Depression (Visit: 1)
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.51. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Family History of Depression
All Randomized Patients
Acute Treatment Phase (Study Periods III-IV)
B1Y-MC-HCJE (continued)

FAMHIST (Visit: 1)	Flx 20 N	Flx 20 n (%)	Placebo N	Placebo n (%)	Total N	Total n (%)	p-Value*
TACHYCARDIA							
No	41	1 (2.4)	39	0	80	1 (1.3)	1.00
Yes	61	0	60	0	121	0	
Total	102	1 (1.0)	99	0	201	1 (0.5)	1.00
TINNITUS							
No	41	1 (2.4)	39	0	80	1 (1.3)	1.00
Yes	61	0	60	0	121	0	
Total	102	1 (1.0)	99	0	201	1 (0.5)	1.00

RMP.B1YP.JCLLIB2(AES6JEAE)
RMP.B1YO.HCJEREP(AES6JEAE)
FAMHIST: FAM HISTORY = Family History of Depression (Visit: 1)
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.51. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Family History of Depression
All Randomized Patients
Acute Treatment Phase (Study Periods III-IV)
B1Y-MC-HCJE (continued)

FAMHIST (Visit: 1)	Flx 20 N	Flx 20 n	Flx 20 (%)	Placebo N	Placebo n	Placebo (%)	Total N	Total n	Total (%)	p-Value*
TOOTH DISORDER										
No	41	0		39	0		80	0		
Yes	61	1	(1.6)	60	0		121	1	(0.8)	1.00
Total	102	1	(1.0)	99	0		201	1	(0.5)	1.00
URINARY FREQUENCY										
No	41	0		39	0		80	0		
Yes	61	1	(1.6)	60	0		121	1	(0.8)	1.00
Total	102	1	(1.0)	99	0		201	1	(0.5)	1.00

RMP.B1YP.JCLLIB2(AES6JEAE)
RMP.B1YO.HCJEREP(AES6JEAE)
FAMHIST: FAM HISTORY = Family History of Depression (Visit: 1)
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.51. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Family History of Depression
All Randomized Patients
Acute Treatment Phase (Study Periods III-IV)
B1Y-MC-HCJE (continued)

FAMHIST (Visit: 1)	Flx 20 N	Flx 20 n	Flx 20 (%)	Placebo N	Placebo n	Placebo (%)	Total N	Total n	Total (%)	p-Value*
URINARY TRACT INFECTION										
No	41	0		39	0		80	0		
Yes	61	1	(1.6)	60	1	(1.7)	121	2	(1.7)	1.00
Total	102	1	(1.0)	99	1	(1.0)	201	2	(1.0)	1.00
VASODILATATION										
No	41	0		39	0		80	0		
Yes	61	1	(1.6)	60	0		121	1	(0.8)	1.00
Total	102	1	(1.0)	99	0		201	1	(0.5)	1.00

RMP.B1YP.JCLLIB2(AES6JEAE)
RMP.B1YO.HCJEREP(AES6JEAE)
FAMHIST: FAM HISTORY = Family History of Depression (Visit: 1)
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.51. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Family History of Depression
All Randomized Patients
Acute Treatment Phase (Study Periods III-IV)
B1Y-MC-HCJE (continued)

FAMHIST (Visit: 1)	Flx 20 N	Flx 20 n	Flx 20 (%)	Placebo N	Placebo n	Placebo (%)	Total N	Total n	Total (%)	p-Value*
WEIGHT LOSS										
No	41	1	(2.4)	39	1	(2.6)	80	2	(2.5)	1.00
Yes	61	0		60	0		121	0		
Total	102	1	(1.0)	99	1	(1.0)	201	2	(1.0)	1.00
YAWN										
No	41	0		39	0		80	0		
Yes	61	1	(1.6)	60	0		121	1	(0.8)	1.00
Total	102	1	(1.0)	99	0		201	1	(0.5)	1.00

RMP.B1YP.JCLLIB2(AES6JEAE)
RMP.B1YO.HCJEREP(AES6JEAE)
FAMHIST: FAM HISTORY = Family History of Depression (Visit: 1)
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.51. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Family History of Depression
All Randomized Patients
Acute Treatment Phase (Study Periods III-IV)
B1Y-MC-HCJE (continued)

FAMHIST (Visit: 1)	Flx 20 N	Flx 20 n (%)	Placebo N	Placebo n (%)	Total N	Total n (%)	p-Value*
ABDOMINAL SYNDROME ACUTE							
No	41	0	39	1 (2.6)	80	1 (1.3)	.488
Yes	61	0	60	0	121	0	
Total	102	0	99	1 (1.0)	201	1 (0.5)	.493
ACNE							
No	41	0	39	0	80	0	
Yes	61	0	60	1 (1.7)	121	1 (0.8)	.496
Total	102	0	99	1 (1.0)	201	1 (0.5)	.493

RMP.B1YP.JCLLIB2(AES6JEAE)
RMP.B1YO.HCJEREP(AES6JEAE)
FAMHIST: FAM HISTORY = Family History of Depression (Visit: 1)
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.51. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Family History of Depression
All Randomized Patients
Acute Treatment Phase (Study Periods III-IV)
B1Y-MC-HCJE (continued)

FAMHIST (Visit: 1)	Flx 20 N	Flx 20 n (%)	Placebo N	Placebo n (%)	Total N	Total n (%)	p-Value*
ALOPECIA							
No	41	0	39	0	80	0	
Yes	61	0	60	1 (1.7)	121	1 (0.8)	.496
Total	102	0	99	1 (1.0)	201	1 (0.5)	.493
ARTHRALGIA							
No	41	0	39	1 (2.6)	80	1 (1.3)	.488
Yes	61	0	60	0	121	0	
Total	102	0	99	1 (1.0)	201	1 (0.5)	.493

RMP.B1YP.JCLLIB2(AES6JEAE)
RMP.B1YO.HCJEREP(AES6JEAE)
FAMHIST: FAM HISTORY = Family History of Depression (Visit: 1)
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.51. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Family History of Depression
All Randomized Patients
Acute Treatment Phase (Study Periods III-IV)
B1Y-MC-HCJE (continued)

FAMHIST (Visit: 1)	Flx 20 N	Flx 20 n (%)	Placebo N	Placebo n (%)	Total N	Total n (%)	p-Value*
CYSTITIS							
No	41	0	39	1 (2.6)	80	1 (1.3)	.488
Yes	61	0	60	0	121	0	
Total	102	0	99	1 (1.0)	201	1 (0.5)	.493
DEHYDRATION							
No	41	0	39	0	80	0	
Yes	61	0	60	1 (1.7)	121	1 (0.8)	.496
Total	102	0	99	1 (1.0)	201	1 (0.5)	.493

RMP.B1YP.JCLLIB2(AES6JEAE)
RMP.B1YO.HCJEREP(AES6JEAE)
FAMHIST: FAM HISTORY = Family History of Depression (Visit: 1)
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.51. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Family History of Depression
All Randomized Patients
Acute Treatment Phase (Study Periods III-IV)
B1Y-MC-HCJE (continued)

FAMHIST (Visit: 1)	Flx 20 N	Flx 20 n (%)	Placebo N	Placebo n (%)	Total N	Total n (%)	p-Value*
FACE EDEMA							
No	41	0	39	0	80	0	
Yes	61	0	60	1 (1.7)	121	1 (0.8)	.496
Total	102	0	99	1 (1.0)	201	1 (0.5)	.493
GASTROINTESTINAL DISORDER							
No	41	0	39	0	80	0	
Yes	61	0	60	1 (1.7)	121	1 (0.8)	.496
Total	102	0	99	1 (1.0)	201	1 (0.5)	.493

RMP.B1YP.JCLLIB2(AES6JEAE)
RMP.B1YO.HCJEREP(AES6JEAE)
FAMHIST: FAM HISTORY = Family History of Depression (Visit: 1)
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.51. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Family History of Depression
All Randomized Patients
Acute Treatment Phase (Study Periods III-IV)
B1Y-MC-HCJE (continued)

FAMHIST (Visit: 1)	Flx 20 N	Flx 20 n (%)	Placebo N	Placebo n (%)	Total N	Total n (%)	p-Value*
HYPESTHESIA							
No	41	0	39	1 (2.6)	80	1 (1.3)	.488
Yes	61	0	60	0	121	0	
Total	102	0	99	1 (1.0)	201	1 (0.5)	.493
HYPOVENTILATION							
No	41	0	39	1 (2.6)	80	1 (1.3)	.488
Yes	61	0	60	0	121	0	
Total	102	0	99	1 (1.0)	201	1 (0.5)	.493

RMP.B1YP.JCLLIB2(AES6JEAE)
RMP.B1YO.HCJEREP(AES6JEAE)
FAMHIST: FAM HISTORY = Family History of Depression (Visit: 1)
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.51. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Family History of Depression
All Randomized Patients
Acute Treatment Phase (Study Periods III-IV)
B1Y-MC-HCJE (continued)

FAMHIST (Visit: 1)	Flx 20 N	Flx 20 n	Flx 20 (%)	Placebo N	Placebo n	Placebo (%)	Total N	Total n	Total (%)	p-Value*
INCREASED APPETITE										
No	41	0		39	0		80	0		
Yes	61	0		60	2	(3.3)	121	2	(1.7)	.244
Total	102	0		99	2	(2.0)	201	2	(1.0)	.241
INTENTIONAL INJURY										
No	41	0		39	0		80	0		
Yes	61	0		60	1	(1.7)	121	1	(0.8)	.496
Total	102	0		99	1	(1.0)	201	1	(0.5)	.493

RMP.B1YP.JCLLIB2(AES6JEAE)
RMP.B1YO.HCJEREP(AES6JEAE)
FAMHIST: FAM HISTORY = Family History of Depression (Visit: 1)
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.51. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Family History of Depression
All Randomized Patients
Acute Treatment Phase (Study Periods III-IV)
B1Y-MC-HCJE (continued)

FAMHIST (Visit: 1)	Flx 20 N	Flx 20 n (%)	Placebo N	Placebo n (%)	Total N	Total n (%)	p-Value*
LARYNGITIS							
No	41	0	39	0	80	0	
Yes	61	0	60	1 (1.7)	121	1 (0.8)	.496
Total	102	0	99	1 (1.0)	201	1 (0.5)	.493
MACULOPAPULAR RASH							
No	41	0	39	0	80	0	
Yes	61	0	60	1 (1.7)	121	1 (0.8)	.496
Total	102	0	99	1 (1.0)	201	1 (0.5)	.493

RMP.B1YP.JCLLIB2(AES6JEAE)
RMP.B1YO.HCJEREP(AES6JEAE)
FAMHIST: FAM HISTORY = Family History of Depression (Visit: 1)
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.51. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Family History of Depression
All Randomized Patients
Acute Treatment Phase (Study Periods III-IV)
B1Y-MC-HCJE (continued)

FAMHIST (Visit: 1)	Flx 20 N	Flx 20 n (%)	Placebo N	Placebo n (%)	Total N	Total n (%)	p-Value*
METRORRHAGIA							
No	41	0	39	0	80	0	
Yes	61	0	60	1 (1.7)	121	1 (0.8)	.496
Total	102	0	99	1 (1.0)	201	1 (0.5)	.493
MOUTH ULCERATION							
No	41	0	39	0	80	0	
Yes	61	0	60	1 (1.7)	121	1 (0.8)	.496
Total	102	0	99	1 (1.0)	201	1 (0.5)	.493

RMP.B1YP.JCLLIB2(AES6JEAE)
RMP.B1YO.HCJEREP(AES6JEAE)
FAMHIST: FAM HISTORY = Family History of Depression (Visit: 1)
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.51. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Family History of Depression
All Randomized Patients
Acute Treatment Phase (Study Periods III-IV)
B1Y-MC-HCJE (continued)

FAMHIST (Visit: 1)	Flx 20 N	Flx 20 n (%)	Placebo N	Placebo n (%)	Total N	Total n (%)	p-Value*
SUBCUTANEOUS NODULE							
No	41	0	39	0	80	0	
Yes	61	0	60	1 (1.7)	121	1 (0.8)	.496
Total	102	0	99	1 (1.0)	201	1 (0.5)	.493
THINKING ABNORMAL							
No	41	0	39	1 (2.6)	80	1 (1.3)	.488
Yes	61	0	60	0	121	0	
Total	102	0	99	1 (1.0)	201	1 (0.5)	.493

RMP.B1YP.JCLLIB2(AES6JEAE)
RMP.B1YO.HCJEREP(AES6JEAE)
FAMHIST: FAM HISTORY = Family History of Depression (Visit: 1)
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.51. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Family History of Depression
All Randomized Patients
Acute Treatment Phase (Study Periods III-IV)
B1Y-MC-HCJE (concluded)

FAMHIST (Visit: 1)	Flx 20 N	Flx 20 n (%)	Placebo N	Placebo n (%)	Total N	Total n (%)	p-Value*
UNEXPECTED BENEFIT							
No	41	0	39	0	80	0	
Yes	61	0	60	1 (1.7)	121	1 (0.8)	.496
Total	102	0	99	1 (1.0)	201	1 (0.5)	.493
WEIGHT GAIN							
No	41	0	39	0	80	0	
Yes	61	0	60	1 (1.7)	121	1 (0.8)	.496
Total	102	0	99	1 (1.0)	201	1 (0.5)	.493

RMP.B1YP.JCLLIB2(AES6JEAE)
RMP.B1YO.HCJEREP(AES6JEAE)
FAMHIST: FAM HISTORY = Family History of Depression (Visit: 1)
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.52 presents the incidence of treatment-emergent solicited adverse events from the Side-Effects Checklist analyzed by family history of depression subgroups for the acute treatment phase.

The Breslow-Day test detected a trend towards a significant difference in odds ratios across gender for trouble urinating (p=.092) and playing sports (p=.060). There was not a statistically significant difference detected between treatments for either depression subgroup.

Table 14.52. Treatment-Emergent Solicited Adverse Events
Side Effects Checklist Subgroup Analysis by Family History of Depression
Significant (p<.05) Difference in Odds Ratio
All Randomized Patients
Acute Treatment Phase (Study Periods III-IV)
B1Y-MC-HCJE

SECL Event - Have you had trouble with:	DEPRESSION	Flx 20 N	Flx 20 n	Flx 20 (%)	Placebo N	Placebo n	Placebo (%)	p-Values: Homogeneity of Odds Ratio p-Value*	p-Values: Between Group Comparison p-Value**
01. EATING	No	41	9	(22.0)	39	11	(28.2)	.715	.609
	Yes	61	20	(32.8)	60	21	(35.0)		.849
02. DRINKING	No	41	7	(17.1)	39	4	(10.3)	.105	.520
	Yes	61	7	(11.5)	60	13	(21.7)		.149
03. DRY MOUTH AND LIPS	No	41	9	(22.0)	39	13	(33.3)	.529	.319
	Yes	61	19	(31.1)	60	21	(35.0)		.702
04. WETNESS IN MOUTH	No	41	3	(7.3)	39	6	(15.4)	.845	.306
	Yes	61	7	(11.5)	60	12	(20.0)		.221
05. CONSTIPATION	No	41	3	(7.3)	39	2	(5.1)	.509	1.00
	Yes	61	6	(9.8)	60	8	(13.3)		.583
06. DIARRHEA	No	41	8	(19.5)	39	6	(15.4)	.801	.771
	Yes	61	11	(18.0)	60	10	(16.7)		1.00
07. STOMACHACHES	No	41	11	(26.8)	39	15	(38.5)	.712	.341
	Yes	61	21	(34.4)	60	25	(41.7)		.457

* The homogeneity of odds ratio p-Value is derived from the Breslow-Day test.
**The between group comparison within strata p-Value is from the Fisher's Exact Test.
Treatment-Emergent Solicited = was present at baseline and worsened as defined by increase in score on the side-effects checklist or new occurrence after baseline.
RMP.B1YP.SASPGM(CUSJESG2)
RMP.B1YO.HCJEREP(CUSTJEMN)

Table 14.52. Treatment-Emergent Solicited Adverse Events
Side Effects Checklist Subgroup Analysis by Family History of Depression
Significant (p<.05) Difference in Odds Ratio
All Randomized Patients
Acute Treatment Phase (Study Periods III-IV)
B1Y-MC-HCJE (continued)

SECL Event - Have you had trouble with:	DEPRESSION	Flx 20 N	Flx 20 n	Flx 20 (%)	Placebo N	Placebo n	Placebo (%)	p-Values: Homogeneity of Odds Ratio p-Value*	p-Values: Between Group Comparison p-Value**
08. MUSCLE CRAMPS	No	41	7	(17.1)	39	10	(25.6)	.539	.418
	Yes	61	19	(31.1)	60	20	(33.3)		.847
09. BEING SICK TO YOUR STOMACH	No	41	13	(31.7)	39	13	(33.3)	.345	1.00
	Yes	61	23	(37.7)	60	16	(26.7)		.244
10. WETTING THE BED	No	41	0		39	1	(2.6)	.263	.488
	Yes	61	3	(4.9)	60	2	(3.3)		1.00
11. URINATING	No	41	2	(4.9)	39	4	(10.3)	.092	.426
	Yes	61	8	(13.1)	60	3	(5.0)		.205
12. ITCHY OR SCRATCHY SKIN	No	41	7	(17.1)	39	8	(20.5)	.797	.779
	Yes	61	17	(27.9)	60	22	(36.7)		.335
13. RASHES	No	41	5	(12.2)	39	6	(15.4)	.548	.753
	Yes	61	11	(18.0)	60	9	(15.0)		.807
14. COLD OR SNIFFLES	No	41	14	(34.1)	39	16	(41.0)	.915	.645
	Yes	61	25	(41.0)	60	28	(46.7)		.585

* The homogeneity of odds ratio p-Value is derived from the Breslow-Day test.
**The between group comparison within strata p-Value is from the Fisher’s Exact Test.
Treatment-Emergent Solicited = was present at baseline and worsened as defined by increase in score on the side-effects checklist or new occurrence after baseline.
RMP.B1YP.SASPGM(CUSJESG2)
RMP.B1YO.HCJEREP(CUSTJEMN)

Table 14.52. Treatment-Emergent Solicited Adverse Events
Side Effects Checklist Subgroup Analysis by Family History of Depression
Significant (p<.05) Difference in Odds Ratio
All Randomized Patients
Acute Treatment Phase (Study Periods III-IV)
B1Y-MC-HCJE (continued)

SECL Event - Have you had trouble with:	DEPRESSION	Flx 20 N	Flx 20 n	Flx 20 (%)	Placebo N	Placebo n	Placebo (%)	p-Values: Homogeneity of Odds Ratio p-Value*	p-Values: Between Group Comparison p-Value**
15. HEADACHE	No	41	15	(36.6)	39	14	(35.9)	.355	1.00
	Yes	61	31	(50.8)	60	22	(36.7)		.144
16. DIZZINESS	No	41	10	(24.4)	39	10	(25.6)	.236	1.00
	Yes	61	22	(36.1)	60	13	(21.7)		.109
17. PLAYING SPORTS	No	41	9	(22.0)	39	4	(10.3)	.060	.227
	Yes	61	8	(13.1)	60	13	(21.7)		.239
18. SHAKINESS	No	41	6	(14.6)	39	7	(17.9)	.767	.767
	Yes	61	13	(21.3)	60	13	(21.7)		1.00
19. PRONOUNCING WORDS	No	41	3	(7.3)	39	8	(20.5)	.674	.111
	Yes	61	9	(14.8)	60	17	(28.3)		.080
20. DOING THINGS WITH YOUR HANDS	No	41	4	(9.8)	39	5	(12.8)	.956	.734
	Yes	61	9	(14.8)	60	11	(18.3)		.632
21. SITTING STILL	No	41	10	(24.4)	39	16	(41.0)	.626	.153
	Yes	61	18	(29.5)	60	24	(40.0)		.255

* The homogeneity of odds ratio p-Value is derived from the Breslow-Day test.
**The between group comparison within strata p-Value is from the Fisher's Exact Test.
Treatment-Emergent Solicited = was present at baseline and worsened as defined by increase in score on the side-effects checklist or new occurrence after baseline.
RMP.B1YP.SASPGM(CUSJESG2)
RMP.B1YO.HCJEREP(CUSTJEMN)

Table 14.52. Treatment-Emergent Solicited Adverse Events
Side Effects Checklist Subgroup Analysis by Family History of Depression
Significant (p<.05) Difference in Odds Ratio
All Randomized Patients
Acute Treatment Phase (Study Periods III-IV)
B1Y-MC-HCJE (continued)

SECL Event - Have you had trouble with:	DEPRESSION	Flx 20 N	Flx 20 n	Flx 20 (%)	Placebo N	Placebo n	Placebo (%)	p-Values: Homogeneity of Odds Ratio p-Value*	p-Values: Between Group Comparison p-Value**
22. TIREDNESS	No	41	15	(36.6)	39	18	(46.2)	.154	.496
	Yes	61	31	(50.8)	60	24	(40.0)		.275
23. FEELING SLEEPY	No	41	15	(36.6)	39	17	(43.6)	.215	.649
	Yes	61	33	(54.1)	60	26	(43.3)		.277
24. SLEEPING	No	41	15	(36.6)	39	13	(33.3)	.387	.817
	Yes	61	21	(34.4)	60	26	(43.3)		.354
25. BAD DREAMS	No	41	9	(22.0)	39	7	(17.9)	.694	.782
	Yes	61	16	(26.2)	60	16	(26.7)		1.00
26. GETTING ALONG WITH PARENTS	No	41	13	(31.7)	39	13	(33.3)	.765	1.00
	Yes	61	27	(44.3)	60	25	(41.7)		.855
27. GETTING ALONG WITH KIDS	No	41	14	(34.1)	39	9	(23.1)	.373	.328
	Yes	61	18	(29.5)	60	18	(30.0)		1.00
28. CRYING	No	41	14	(34.1)	39	12	(30.8)	.857	.814
	Yes	61	23	(37.7)	60	22	(36.7)		1.00

* The homogeneity of odds ratio p-Value is derived from the Breslow-Day test.
**The between group comparison within strata p-Value is from the Fisher’s Exact Test.
Treatment-Emergent Solicited = was present at baseline and worsened as defined by increase in score on the side-effects checklist or new occurrence after baseline.
RMP.B1YP.SASPGM(CUSJESG2)
RMP.B1YO.HCJEREP(CUSTJEMN)

Table 14.52. Treatment-Emergent Solicited Adverse Events
Side Effects Checklist Subgroup Analysis by Family History of Depression
Significant (p<.05) Difference in Odds Ratio
All Randomized Patients
Acute Treatment Phase (Study Periods III-IV)
B1Y-MC-HCJE (concluded)

SECL Event - Have you had trouble with:	DEPRESSION	Flx 20 N	Flx 20 n	Flx 20 (%)	Placebo N	Placebo n	Placebo (%)	p-Values: Homogeneity of Odds Ratio p-Value*	p-Values: Between Group Comparison p-Value**
29. GETTING MAD	No	41	14	(34.1)	39	13	(33.3)	.500	1.00
	Yes	61	23	(37.7)	60	28	(46.7)		.360
30. NOT BEING HAPPY	No	41	13	(31.7)	39	10	(25.6)	.951	.625
	Yes	61	24	(39.3)	60	19	(31.7)		.449
31. BEING SAD	No	41	15	(36.6)	39	12	(30.8)	.425	.641
	Yes	61	24	(39.3)	60	14	(23.3)		.078
32. PAYING ATTENTION	No	41	16	(39.0)	39	8	(20.5)	.439	.090
	Yes	61	24	(39.3)	60	18	(30.0)		.341

* The homogeneity of odds ratio p-Value is derived from the Breslow-Day test.
**The between group comparison within strata p-Value is from the Fisher's Exact Test.
Treatment-Emergent Solicited = was present at baseline and worsened as defined by increase in score on the side-effects checklist or new occurrence after baseline.
RMP.B1YP.SASPGM(CUSJESG2)
RMP.B1YO.HCJEREP(CUSTJEMN)

14.3.2.2. Subchronic Treatment Phase (Study Periods III-V)

14.3.2.2.1. By Age

Table 14.53 presents the incidence of treatment-emergent non-solicited adverse events examined by age subgroups for the subchronic treatment phase.

There was a statistically significant difference between treatment groups in the number of children reporting treatment-emergent non-solicited adverse events (p=.034); however, no difference was detected for adolescents (p=.147). Overall, more fluoxetine-treated children (93%) reported at least one treatment-emergent non-solicited adverse event than placebo-treated children (79%). Despite the overall difference in reporting frequencies, there were no statistically significant differences between age subgroups for any individual treatment-emergent non-solicited adverse event.

Table 14.53. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Age Category
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE

AGE	Flx N	Flx n (%)	Placebo N	Placebo n (%)	Total N	Total n (%)	p-Value*
PATIENTS WITH >= 1 TESS							
8 - < 13	61	57 (93.4)	61	48 (78.7)	122	105 (86.1)	.034
13 - < 18	48	44 (91.7)	49	39 (79.6)	97	83 (85.6)	.147
Total	109	101 (92.7)	110	87 (79.1)	219	188 (85.8)	.006
PATIENTS WITH NO TESS							
8 - < 13	61	4 (6.6)	61	13 (21.3)	122	17 (13.9)	.034
13 - < 18	48	4 (8.3)	49	10 (20.4)	97	14 (14.4)	.147
Total	109	8 (7.3)	110	23 (20.9)	219	31 (14.2)	.006

RMP.B1YP.JCLLIB2(AES6JEAD)
RMP.B1YO.HCJEREP(AES6JEAD)
AGE: Patient Age
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
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Table 14.53. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Age Category
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE (continued)

AGE	Flx N	Flx n (%)	Placebo N	Placebo n (%)	Total N	Total n (%)	p-Value*
HEADACHE							
8 - < 13	61	19 (31.1)	61	10 (16.4)	122	29 (23.8)	.088
13 - < 18	48	18 (37.5)	49	11 (22.4)	97	29 (29.9)	.124
Total	109	37 (33.9)	110	21 (19.1)	219	58 (26.5)	.014
RHINITIS							
8 - < 13	61	18 (29.5)	61	17 (27.9)	122	35 (28.7)	1.00
13 - < 18	48	16 (33.3)	49	12 (24.5)	97	28 (28.9)	.376
Total	109	34 (31.2)	110	29 (26.4)	219	63 (28.8)	.458

RMP.B1YP.JCLLIB2(AES6JEAD)
RMP.B1YO.HCJEREP(AES6JEAD)
AGE: Patient Age
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
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Table 14.53. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Age Category
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE (continued)

	Flx		Placebo		Total		p-Value*
AGE	N	n (%)	N	n (%)	N	n (%)	
ABDOMINAL PAIN							
8 - < 13	61	13 (21.3)	61	14 (23.0)	122	27 (22.1)	1.00
13 - < 18	48	9 (18.8)	49	8 (16.3)	97	17 (17.5)	.795
Total	109	22 (20.2)	110	22 (20.0)	219	44 (20.1)	1.00
PHARYNGITIS							
8 - < 13	61	12 (19.7)	61	8 (13.1)	122	20 (16.4)	.464
13 - < 18	48	9 (18.8)	49	6 (12.2)	97	15 (15.5)	.413
Total	109	21 (19.3)	110	14 (12.7)	219	35 (16.0)	.202

RMP.B1YP.JCLLIB2(AES6JEAD)
RMP.B1YO.HCJEREP(AES6JEAD)
AGE: Patient Age
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
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Table 14.53. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Age Category
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE (continued)

AGE	Flx N	Flx n (%)	Placebo N	Placebo n (%)	Total N	Total n (%)	p-Value*
ACCIDENTAL INJURY							
8 - < 13	61	12 (19.7)	61	6 (9.8)	122	18 (14.8)	.201
13 - < 18	48	7 (14.6)	49	4 (8.2)	97	11 (11.3)	.356
Total	109	19 (17.4)	110	10 (9.1)	219	29 (13.2)	.076
COUGH INCREASED							
8 - < 13	61	13 (21.3)	61	5 (8.2)	122	18 (14.8)	.072
13 - < 18	48	3 (6.3)	49	4 (8.2)	97	7 (7.2)	1.00
Total	109	16 (14.7)	110	9 (8.2)	219	25 (11.4)	.143

RMP.B1YP.JCLLIB2(AES6JEAD)
RMP.B1YO.HCJEREP(AES6JEAD)
AGE: Patient Age
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
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Table 14.53. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Age Category
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE (continued)

AGE	Flx N	Flx n (%)	Placebo N	Placebo n (%)	Total N	Total n (%)	p-Value*
DIARRHEA							
8 - < 13	61	10 (16.4)	61	9 (14.8)	122	19 (15.6)	1.00
13 - < 18	48	4 (8.3)	49	4 (8.2)	97	8 (8.2)	1.00
Total	109	14 (12.8)	110	13 (11.8)	219	27 (12.3)	.840
RASH							
8 - < 13	61	9 (14.8)	61	9 (14.8)	122	18 (14.8)	1.00
13 - < 18	48	4 (8.3)	49	1 (2.0)	97	5 (5.2)	.204
Total	109	13 (11.9)	110	10 (9.1)	219	23 (10.5)	.517

RMP.B1YP.JCLLIB2(AES6JEAD)
RMP.B1YO.HCJEREP(AES6JEAD)
AGE: Patient Age
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
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Table 14.53. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Age Category
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE (continued)

	Flx		Placebo		Total		p-Value*
AGE	N	n (%)	N	n (%)	N	n (%)	
DIZZINESS							
8 - < 13	61	8 (13.1)	61	5 (8.2)	122	13 (10.7)	.559
13 - < 18	48	3 (6.3)	49	3 (6.1)	97	6 (6.2)	1.00
Total	109	11 (10.1)	110	8 (7.3)	219	19 (8.7)	.483
NERVOUSNESS							
8 - < 13	61	8 (13.1)	61	3 (4.9)	122	11 (9.0)	.205
13 - < 18	48	3 (6.3)	49	3 (6.1)	97	6 (6.2)	1.00
Total	109	11 (10.1)	110	6 (5.5)	219	17 (7.8)	.218

RMP.B1YP.JCLLIB2(AES6JEAD)
RMP.B1YO.HCJEREP(AES6JEAD)
AGE: Patient Age
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
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Table 14.53. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Age Category
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE (continued)

	Flx		Placebo		Total		p-Value*
AGE	N	n (%)	N	n (%)	N	n (%)	
VOMITING							
8 - < 13	61	10 (16.4)	61	7 (11.5)	122	17 (13.9)	.602
13 - < 18	48	1 (2.1)	49	5 (10.2)	97	6 (6.2)	.204
Total	109	11 (10.1)	110	12 (10.9)	219	23 (10.5)	1.00
ANOREXIA							
8 - < 13	61	7 (11.5)	61	5 (8.2)	122	12 (9.8)	.762
13 - < 18	48	3 (6.3)	49	4 (8.2)	97	7 (7.2)	1.00
Total	109	10 (9.2)	110	9 (8.2)	219	19 (8.7)	.815

RMP.B1YP.JCLLIB2(AES6JEAD)
RMP.B1YO.HCJEREP(AES6JEAD)
AGE: Patient Age
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.53. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Age Category
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE (continued)

	Flx			Placebo			Total			p-Value*
AGE	N	n	(%)	N	n	(%)	N	n	(%)	
ASTHENIA										
8 - < 13	61	6	(9.8)	61	5	(8.2)	122	11	(9.0)	1.00
13 - < 18	48	4	(8.3)	49	2	(4.1)	97	6	(6.2)	.436
Total	109	10	(9.2)	110	7	(6.4)	219	17	(7.8)	.462
FEVER										
8 - < 13	61	7	(11.5)	61	6	(9.8)	122	13	(10.7)	1.00
13 - < 18	48	3	(6.3)	49	2	(4.1)	97	5	(5.2)	.678
Total	109	10	(9.2)	110	8	(7.3)	219	18	(8.2)	.632

RMP.B1YP.JCLLIB2(AES6JEAD)
RMP.B1YO.HCJEREP(AES6JEAD)
AGE: Patient Age
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.53. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Age Category
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE (continued)

	Flx			Placebo			Total			p-Value*
AGE	N	n	(%)	N	n	(%)	N	n	(%)	
PAIN										
8 - < 13	61	6	(9.8)	61	5	(8.2)	122	11	(9.0)	1.00
13 - < 18	48	4	(8.3)	49	7	(14.3)	97	11	(11.3)	.524
Total	109	10	(9.2)	110	12	(10.9)	219	22	(10.0)	.823
NAUSEA										
8 - < 13	61	6	(9.8)	61	6	(9.8)	122	12	(9.8)	1.00
13 - < 18	48	3	(6.3)	49	5	(10.2)	97	8	(8.2)	.715
Total	109	9	(8.3)	110	11	(10.0)	219	20	(9.1)	.815

RMP.B1YP.JCLLIB2(AES6JEAD)
RMP.B1YO.HCJEREP(AES6JEAD)
AGE: Patient Age
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.53. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Age Category
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE (continued)

		Flx		Placebo			Total			p-Value*
AGE	N	n	(%)	N	n	(%)	N	n	(%)	
ABNORMAL DREAMS										
8 - < 13	61	3	(4.9)	61	1	(1.6)	122	4	(3.3)	.619
13 - < 18	48	4	(8.3)	49	2	(4.1)	97	6	(6.2)	.436
Total	109	7	(6.4)	110	3	(2.7)	219	10	(4.6)	.215
BACK PAIN										
8 - < 13	61	4	(6.6)	61	1	(1.6)	122	5	(4.1)	.365
13 - < 18	48	2	(4.2)	49	4	(8.2)	97	6	(6.2)	.678
Total	109	6	(5.5)	110	5	(4.5)	219	11	(5.0)	.768

RMP.B1YP.JCLLIB2(AES6JEAD)
RMP.B1YO.HCJEREP(AES6JEAD)
AGE: Patient Age
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.53. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Age Category
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE (continued)

	Flx			Placebo			Total			p-Value*
AGE	N	n	(%)	N	n	(%)	N	n	(%)	
DRY MOUTH										
8 - < 13	61	3	(4.9)	61	3	(4.9)	122	6	(4.9)	1.00
13 - < 18	48	3	(6.3)	49	3	(6.1)	97	6	(6.2)	1.00
Total	109	6	(5.5)	110	6	(5.5)	219	12	(5.5)	1.00
EAR PAIN										
8 - < 13	61	5	(8.2)	61	3	(4.9)	122	8	(6.6)	.717
13 - < 18	48	1	(2.1)	49	0		97	1	(1.0)	.495
Total	109	6	(5.5)	110	3	(2.7)	219	9	(4.1)	.332

RMP.B1YP.JCLLIB2(AES6JEAD)
RMP.B1YO.HCJEREP(AES6JEAD)
AGE: Patient Age
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.53. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Age Category
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE (continued)

	Flx			Placebo			Total			p-Value*
AGE	N	n	(%)	N	n	(%)	N	n	(%)	
INSOMNIA										
8 - < 13	61	5	(8.2)	61	4	(6.6)	122	9	(7.4)	1.00
13 - < 18	48	1	(2.1)	49	1	(2.0)	97	2	(2.1)	1.00
Total	109	6	(5.5)	110	5	(4.5)	219	11	(5.0)	.768
PRURITUS										
8 - < 13	61	5	(8.2)	61	3	(4.9)	122	8	(6.6)	.717
13 - < 18	48	1	(2.1)	49	3	(6.1)	97	4	(4.1)	.617
Total	109	6	(5.5)	110	6	(5.5)	219	12	(5.5)	1.00

RMP.B1YP.JCLLIB2(AES6JEAD)
RMP.B1YO.HCJEREP(AES6JEAD)
AGE: Patient Age
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.53. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Age Category
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE (continued)

	Flx			Placebo			Total			p-Value*
AGE	N	n	(%)	N	n	(%)	N	n	(%)	
EPISTAXIS										
8 - < 13	61	4	(6.6)	61	2	(3.3)	122	6	(4.9)	.680
13 - < 18	48	1	(2.1)	49	0		97	1	(1.0)	.495
Total	109	5	(4.6)	110	2	(1.8)	219	7	(3.2)	.280
HOSTILITY										
8 - < 13	61	5	(8.2)	61	3	(4.9)	122	8	(6.6)	.717
13 - < 18	48	0		49	2	(4.1)	97	2	(2.1)	.495
Total	109	5	(4.6)	110	5	(4.5)	219	10	(4.6)	1.00

RMP.B1YP.JCLLIB2(AES6JEAD)
RMP.B1YO.HCJEREP(AES6JEAD)
AGE: Patient Age
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.53. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Age Category
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE (continued)

	Flx			Placebo			Total			p-Value*
AGE	N	n	(%)	N	n	(%)	N	n	(%)	
INFECTION										
8 - < 13	61	4	(6.6)	61	4	(6.6)	122	8	(6.6)	1.00
13 - < 18	48	1	(2.1)	49	1	(2.0)	97	2	(2.1)	1.00
Total	109	5	(4.6)	110	5	(4.5)	219	10	(4.6)	1.00
PERSONALITY DISORDER										
8 - < 13	61	4	(6.6)	61	2	(3.3)	122	6	(4.9)	.680
13 - < 18	48	1	(2.1)	49	0		97	1	(1.0)	.495
Total	109	5	(4.6)	110	2	(1.8)	219	7	(3.2)	.280

RMP.B1YP.JCLLIB2(AES6JEAD)
RMP.B1YO.HCJEREP(AES6JEAD)
AGE: Patient Age
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.53. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Age Category
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE (continued)

	Flx			Placebo			Total			p-Value*
AGE	N	n	(%)	N	n	(%)	N	n	(%)	
SOMNOLENCE										
8 - < 13	61	2	(3.3)	61	1	(1.6)	122	3	(2.5)	1.00
13 - < 18	48	3	(6.3)	49	3	(6.1)	97	6	(6.2)	1.00
Total	109	5	(4.6)	110	4	(3.6)	219	9	(4.1)	.748
AGITATION										
8 - < 13	61	4	(6.6)	61	0		122	4	(3.3)	.119
13 - < 18	48	0		49	0		97	0		
Total	109	4	(3.7)	110	0		219	4	(1.8)	.060

RMP.B1YP.JCLLIB2(AES6JEAD)
RMP.B1YO.HCJEREP(AES6JEAD)
AGE: Patient Age
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
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Table 14.53. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Age Category
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE (continued)

	Flx			Placebo			Total			p-Value*
AGE	N	n	(%)	N	n	(%)	N	n	(%)	
ALLERGIC REACTION										
8 - < 13	61	3	(4.9)	61	1	(1.6)	122	4	(3.3)	.619
13 - < 18	48	1	(2.1)	49	1	(2.0)	97	2	(2.1)	1.00
Total	109	4	(3.7)	110	2	(1.8)	219	6	(2.7)	.446
DYSMENORRHEA										
8 - < 13	61	1	(1.6)	61	1	(1.6)	122	2	(1.6)	1.00
13 - < 18	48	3	(6.3)	49	3	(6.1)	97	6	(6.2)	1.00
Total	109	4	(3.7)	110	4	(3.6)	219	8	(3.7)	1.00

RMP.B1YP.JCLLIB2(AES6JEAD)
RMP.B1YO.HCJEREP(AES6JEAD)
AGE: Patient Age
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.53. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Age Category
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE (continued)

	Flx			Placebo			Total			p-Value*
AGE	N	n	(%)	N	n	(%)	N	n	(%)	
DYSPEPSIA										
8 - < 13	61	3	(4.9)	61	2	(3.3)	122	5	(4.1)	1.00
13 - < 18	48	1	(2.1)	49	3	(6.1)	97	4	(4.1)	.617
Total	109	4	(3.7)	110	5	(4.5)	219	9	(4.1)	1.00
ECCHYMOSIS										
8 - < 13	61	2	(3.3)	61	2	(3.3)	122	4	(3.3)	1.00
13 - < 18	48	2	(4.2)	49	0		97	2	(2.1)	.242
Total	109	4	(3.7)	110	2	(1.8)	219	6	(2.7)	.446

RMP.B1YP.JCLLIB2(AES6JEAD)
RMP.B1YO.HCJEREP(AES6JEAD)
AGE: Patient Age
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.53. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Age Category
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE (continued)

	Flx			Placebo			Total			p-Value*
AGE	N	n	(%)	N	n	(%)	N	n	(%)	
FLU SYNDROME										
8 - < 13	61	2	(3.3)	61	2	(3.3)	122	4	(3.3)	1.00
13 - < 18	48	2	(4.2)	49	1	(2.0)	97	3	(3.1)	.617
Total	109	4	(3.7)	110	3	(2.7)	219	7	(3.2)	.721
HYPERKINESIA										
8 - < 13	61	3	(4.9)	61	1	(1.6)	122	4	(3.3)	.619
13 - < 18	48	1	(2.1)	49	0		97	1	(1.0)	.495
Total	109	4	(3.7)	110	1	(0.9)	219	5	(2.3)	.212

RMP.B1YP.JCLLIB2(AES6JEAD)
RMP.B1YO.HCJEREP(AES6JEAD)
AGE: Patient Age
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.53. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Age Category
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE (continued)

	Flx			Placebo			Total			p-Value*
AGE	N	n	(%)	N	n	(%)	N	n	(%)	
PHOTOSENSITIVITY REACTION										
8 - < 13	61	3	(4.9)	61	1	(1.6)	122	4	(3.3)	.619
13 - < 18	48	1	(2.1)	49	0		97	1	(1.0)	.495
Total	109	4	(3.7)	110	1	(0.9)	219	5	(2.3)	.212
SINUSITIS										
8 - < 13	61	3	(4.9)	61	1	(1.6)	122	4	(3.3)	.619
13 - < 18	48	1	(2.1)	49	1	(2.0)	97	2	(2.1)	1.00
Total	109	4	(3.7)	110	2	(1.8)	219	6	(2.7)	.446

RMP.B1YP.JCLLIB2(AES6JEAD)
RMP.B1YO.HCJEREP(AES6JEAD)
AGE: Patient Age
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.53. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Age Category
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE (continued)

	Flx			Placebo			Total			p-Value*
AGE	N	n	(%)	N	n	(%)	N	n	(%)	
AKATHISIA										
8 - < 13	61	2	(3.3)	61	0		122	2	(1.6)	.496
13 - < 18	48	1	(2.1)	49	0		97	1	(1.0)	.495
Total	109	3	(2.8)	110	0		219	3	(1.4)	.122
ASTHMA										
8 - < 13	61	2	(3.3)	61	0		122	2	(1.6)	.496
13 - < 18	48	1	(2.1)	49	0		97	1	(1.0)	.495
Total	109	3	(2.8)	110	0		219	3	(1.4)	.122

RMP.B1YP.JCLLIB2(AES6JEAD)
RMP.B1YO.HCJEREP(AES6JEAD)
AGE: Patient Age
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.53. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Age Category
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE (continued)

	Flx			Placebo			Total			p-Value*
AGE	N	n	(%)	N	n	(%)	N	n	(%)	
CHEST PAIN										
8 - < 13	61	1	(1.6)	61	1	(1.6)	122	2	(1.6)	1.00
13 - < 18	48	2	(4.2)	49	1	(2.0)	97	3	(3.1)	.617
Total	109	3	(2.8)	110	2	(1.8)	219	5	(2.3)	.683
CONSTIPATION										
8 - < 13	61	3	(4.9)	61	3	(4.9)	122	6	(4.9)	1.00
13 - < 18	48	0		49	3	(6.1)	97	3	(3.1)	.242
Total	109	3	(2.8)	110	6	(5.5)	219	9	(4.1)	.499

RMP.B1YP.JCLLIB2(AES6JEAD)
RMP.B1YO.HCJEREP(AES6JEAD)
AGE: Patient Age
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.53. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Age Category
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE (continued)

	Flx			Placebo			Total			p-Value*
AGE	N	n	(%)	N	n	(%)	N	n	(%)	
CONTACT DERMATITIS										
8 - < 13	61	3	(4.9)	61	0		122	3	(2.5)	.244
13 - < 18	48	0		49	0		97	0		
Total	109	3	(2.8)	110	0		219	3	(1.4)	.122
DEPRESSION										
8 - < 13	61	0		61	1	(1.6)	122	1	(0.8)	1.00
13 - < 18	48	3	(6.3)	49	1	(2.0)	97	4	(4.1)	.362
Total	109	3	(2.8)	110	2	(1.8)	219	5	(2.3)	.683

RMP.B1YP.JCLLIB2(AES6JEAD)
RMP.B1YO.HCJEREP(AES6JEAD)
AGE: Patient Age
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.53. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Age Category
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE (continued)

	Flx			Placebo			Total			p-Value*
AGE	N	n	(%)	N	n	(%)	N	n	(%)	
MYALGIA										
8 - < 13	61	3	(4.9)	61	3	(4.9)	122	6	(4.9)	1.00
13 - < 18	48	0		49	3	(6.1)	97	3	(3.1)	.242
Total	109	3	(2.8)	110	6	(5.5)	219	9	(4.1)	.499
NECK PAIN										
8 - < 13	61	3	(4.9)	61	0		122	3	(2.5)	.244
13 - < 18	48	0		49	1	(2.0)	97	1	(1.0)	1.00
Total	109	3	(2.8)	110	1	(0.9)	219	4	(1.8)	.369

RMP.B1YP.JCLLIB2(AES6JEAD)
RMP.B1YO.HCJEREP(AES6JEAD)
AGE: Patient Age
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.53. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Age Category
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE (continued)

	Flx			Placebo			Total			p-Value*
AGE	N	n	(%)	N	n	(%)	N	n	(%)	
SPEECH DISORDER										
8 - < 13	61	2	(3.3)	61	0		122	2	(1.6)	.496
13 - < 18	48	1	(2.1)	49	2	(4.1)	97	3	(3.1)	1.00
Total	109	3	(2.8)	110	2	(1.8)	219	5	(2.3)	.683
TREMOR										
8 - < 13	61	0		61	1	(1.6)	122	1	(0.8)	1.00
13 - < 18	48	3	(6.3)	49	0		97	3	(3.1)	.117
Total	109	3	(2.8)	110	1	(0.9)	219	4	(1.8)	.369

RMP.B1YP.JCLLIB2(AES6JEAD)
RMP.B1YO.HCJEREP(AES6JEAD)
AGE: Patient Age
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.53. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Age Category
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE (continued)

	Flx			Placebo			Total			p-Value*
AGE	N	n	(%)	N	n	(%)	N	n	(%)	
ACUTE BRAIN SYNDROME										
8 - < 13	61	0		61	0		122	0		
13 - < 18	48	2	(4.2)	49	0		97	2	(2.1)	.242
Total	109	2	(1.8)	110	0		219	2	(0.9)	.247
ANXIETY										
8 - < 13	61	2	(3.3)	61	0		122	2	(1.6)	.496
13 - < 18	48	0		49	0		97	0		
Total	109	2	(1.8)	110	0		219	2	(0.9)	.247

RMP.B1YP.JCLLIB2(AES6JEAD)
RMP.B1YO.HCJEREP(AES6JEAD)
AGE: Patient Age
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.53. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Age Category
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE (continued)

	Flx			Placebo			Total			p-Value*
AGE	N	n	(%)	N	n	(%)	N	n	(%)	
BRONCHITIS										
8 - < 13	61	2	(3.3)	61	1	(1.6)	122	3	(2.5)	1.00
13 - < 18	48	0		49	1	(2.0)	97	1	(1.0)	1.00
Total	109	2	(1.8)	110	2	(1.8)	219	4	(1.8)	1.00
CHILLS										
8 - < 13	61	1	(1.6)	61	1	(1.6)	122	2	(1.6)	1.00
13 - < 18	48	1	(2.1)	49	0		97	1	(1.0)	.495
Total	109	2	(1.8)	110	1	(0.9)	219	3	(1.4)	.622

RMP.B1YP.JCLLIB2(AES6JEAD)
RMP.B1YO.HCJEREP(AES6JEAD)
AGE: Patient Age
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.53. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Age Category
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE (continued)

	Flx			Placebo			Total			p-Value*
AGE	N	n	(%)	N	n	(%)	N	n	(%)	
DRY SKIN										
8 - < 13	61	2	(3.3)	61	3	(4.9)	122	5	(4.1)	1.00
13 - < 18	48	0		49	0		97	0		
Total	109	2	(1.8)	110	3	(2.7)	219	5	(2.3)	1.00
EAR DISORDER										
8 - < 13	61	2	(3.3)	61	1	(1.6)	122	3	(2.5)	1.00
13 - < 18	48	0		49	0		97	0		
Total	109	2	(1.8)	110	1	(0.9)	219	3	(1.4)	.622

RMP.B1YP.JCLLIB2(AES6JEAD)
RMP.B1YO.HCJEREP(AES6JEAD)
AGE: Patient Age
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.53. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Age Category
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE (continued)

	Flx			Placebo			Total			p-Value*
AGE	N	n	(%)	N	n	(%)	N	n	(%)	
EUPHORIA										
8 - < 13	61	2	(3.3)	61	0		122	2	(1.6)	.496
13 - < 18	48	0		49	0		97	0		
Total	109	2	(1.8)	110	0		219	2	(0.9)	.247
EYE DISORDER										
8 - < 13	61	2	(3.3)	61	0		122	2	(1.6)	.496
13 - < 18	48	0		49	0		97	0		
Total	109	2	(1.8)	110	0		219	2	(0.9)	.247

RMP.B1YP.JCLLIB2(AES6JEAD)
RMP.B1YO.HCJEREP(AES6JEAD)
AGE: Patient Age
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.53. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Age Category
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE (continued)

	Flx			Placebo			Total			p-Value*
AGE	N	n	(%)	N	n	(%)	N	n	(%)	
GASTROENTERITIS										
8 - < 13	61	1	(1.6)	61	0		122	1	(0.8)	1.00
13 - < 18	48	1	(2.1)	49	0		97	1	(1.0)	.495
Total	109	2	(1.8)	110	0		219	2	(0.9)	.247
INCREASED APPETITE										
8 - < 13	61	1	(1.6)	61	2	(3.3)	122	3	(2.5)	1.00
13 - < 18	48	1	(2.1)	49	1	(2.0)	97	2	(2.1)	1.00
Total	109	2	(1.8)	110	3	(2.7)	219	5	(2.3)	1.00

RMP.B1YP.JCLLIB2(AES6JEAD)
RMP.B1YO.HCJEREP(AES6JEAD)
AGE: Patient Age
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.53. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Age Category
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE (continued)

	Flx			Placebo			Total			p-Value*
AGE	N	n	(%)	N	n	(%)	N	n	(%)	
NECK RIGIDITY										
8 - < 13	61	1	(1.6)	61	1	(1.6)	122	2	(1.6)	1.00
13 - < 18	48	1	(2.1)	49	0		97	1	(1.0)	.495
Total	109	2	(1.8)	110	1	(0.9)	219	3	(1.4)	.622
OTITIS EXTERNA										
8 - < 13	61	1	(1.6)	61	1	(1.6)	122	2	(1.6)	1.00
13 - < 18	48	1	(2.1)	49	0		97	1	(1.0)	.495
Total	109	2	(1.8)	110	1	(0.9)	219	3	(1.4)	.622

RMP.B1YP.JCLLIB2(AES6JEAD)
RMP.B1YO.HCJEREP(AES6JEAD)
AGE: Patient Age
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.53. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Age Category
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE (continued)

	Flx			Placebo			Total			p-Value*
AGE	N	n	(%)	N	n	(%)	N	n	(%)	
SLEEP DISORDER										
8 - < 13	61	2	(3.3)	61	0		122	2	(1.6)	.496
13 - < 18	48	0		49	0		97	0		
Total	109	2	(1.8)	110	0		219	2	(0.9)	.247
SURGICAL PROCEDURE										
8 - < 13	61	0		61	1	(1.6)	122	1	(0.8)	1.00
13 - < 18	48	2	(4.2)	49	1	(2.0)	97	3	(3.1)	.617
Total	109	2	(1.8)	110	2	(1.8)	219	4	(1.8)	1.00

RMP.B1YP.JCLLIB2(AES6JEAD)
RMP.B1YO.HCJEREP(AES6JEAD)
AGE: Patient Age
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.53. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Age Category
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE (continued)

	Flx			Placebo			Total			p-Value*
AGE	N	n	(%)	N	n	(%)	N	n	(%)	
SWEATING										
8 - < 13	61	1	(1.6)	61	0		122	1	(0.8)	1.00
13 - < 18	48	1	(2.1)	49	0		97	1	(1.0)	.495
Total	109	2	(1.8)	110	0		219	2	(0.9)	.247
THINKING ABNORMAL										
8 - < 13	61	2	(3.3)	61	1	(1.6)	122	3	(2.5)	1.00
13 - < 18	48	0		49	0		97	0		
Total	109	2	(1.8)	110	1	(0.9)	219	3	(1.4)	.622

RMP.B1YP.JCLLIB2(AES6JEAD)
RMP.B1YO.HCJEREP(AES6JEAD)
AGE: Patient Age
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.53. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Age Category
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE (continued)

	Flx			Placebo			Total			p-Value*
AGE	N	n	(%)	N	n	(%)	N	n	(%)	
THIRST										
8 - < 13	61	2	(3.3)	61	2	(3.3)	122	4	(3.3)	1.00
13 - < 18	48	0		49	0		97	0		
Total	109	2	(1.8)	110	2	(1.8)	219	4	(1.8)	1.00
TOOTH DISORDER										
8 - < 13	61	1	(1.6)	61	0		122	1	(0.8)	1.00
13 - < 18	48	1	(2.1)	49	0		97	1	(1.0)	.495
Total	109	2	(1.8)	110	0		219	2	(0.9)	.247

RMP.B1YP.JCLLIB2(AES6JEAD)
RMP.B1YO.HCJEREP(AES6JEAD)
AGE: Patient Age
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.53. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Age Category
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE (continued)

	Flx			Placebo			Total			p-Value*
AGE	N	n	(%)	N	n	(%)	N	n	(%)	
WEIGHT LOSS										
8 - < 13	61	1	(1.6)	61	0		122	1	(0.8)	1.00
13 - < 18	48	1	(2.1)	49	1	(2.0)	97	2	(2.1)	1.00
Total	109	2	(1.8)	110	1	(0.9)	219	3	(1.4)	.622
YAWN										
8 - < 13	61	2	(3.3)	61	0		122	2	(1.6)	.496
13 - < 18	48	0		49	0		97	0		
Total	109	2	(1.8)	110	0		219	2	(0.9)	.247

RMP.B1YP.JCLLIB2(AES6JEAD)
RMP.B1YO.HCJEREP(AES6JEAD)
AGE: Patient Age
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.53. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Age Category
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE (continued)

	Flx			Placebo			Total			p-Value*
AGE	N	n	(%)	N	n	(%)	N	n	(%)	
AMBLYOPIA										
8 - < 13	61	1	(1.6)	61	0		122	1	(0.8)	1.00
13 - < 18	48	0		49	0		97	0		
Total	109	1	(0.9)	110	0		219	1	(0.5)	.498
AMNESIA										
8 - < 13	61	1	(1.6)	61	0		122	1	(0.8)	1.00
13 - < 18	48	0		49	1	(2.0)	97	1	(1.0)	1.00
Total	109	1	(0.9)	110	1	(0.9)	219	2	(0.9)	1.00

RMP.B1YP.JCLLIB2(AES6JEAD)
RMP.B1YO.HCJEREP(AES6JEAD)
AGE: Patient Age
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.53. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Age Category
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE (continued)

	Flx			Placebo			Total			p-Value*
AGE	N	n	(%)	N	n	(%)	N	n	(%)	
ANEMIA										
8 - < 13	61	0		61	0		122	0		
13 - < 18	48	1	(2.1)	49	0		97	1	(1.0)	.495
Total	109	1	(0.9)	110	0		219	1	(0.5)	.498
APATHY										
8 - < 13	61	0		61	0		122	0		
13 - < 18	48	1	(2.1)	49	0		97	1	(1.0)	.495
Total	109	1	(0.9)	110	0		219	1	(0.5)	.498

RMP.B1YP.JCLLIB2(AES6JEAD)
RMP.B1YO.HCJEREP(AES6JEAD)
AGE: Patient Age
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.53. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Age Category
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE (continued)

	Flx			Placebo			Total			p-Value*
AGE	N	n	(%)	N	n	(%)	N	n	(%)	
BRADYCARDIA										
8 - < 13	61	1	(1.6)	61	1	(1.6)	122	2	(1.6)	1.00
13 - < 18	48	0		49	0		97	0		
Total	109	1	(0.9)	110	1	(0.9)	219	2	(0.9)	1.00
BUCCOGLOSSAL SYNDROME										
8 - < 13	61	0		61	0		122	0		
13 - < 18	48	1	(2.1)	49	0		97	1	(1.0)	.495
Total	109	1	(0.9)	110	0		219	1	(0.5)	.498

RMP.B1YP.JCLLIB2(AES6JEAD)
RMP.B1YO.HCJEREP(AES6JEAD)
AGE: Patient Age
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.53. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Age Category
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE (continued)

	Flx			Placebo			Total			p-Value*
AGE	N	n	(%)	N	n	(%)	N	n	(%)	
CARDIOVASCULAR DISORDER										
8 - < 13	61	0		61	0		122	0		
13 - < 18	48	1	(2.1)	49	0		97	1	(1.0)	.495
Total	109	1	(0.9)	110	0		219	1	(0.5)	.498
DELUSIONS										
8 - < 13	61	1	(1.6)	61	0		122	1	(0.8)	1.00
13 - < 18	48	0		49	0		97	0		
Total	109	1	(0.9)	110	0		219	1	(0.5)	.498

RMP.B1YP.JCLLIB2(AES6JEAD)
RMP.B1YO.HCJEREP(AES6JEAD)
AGE: Patient Age
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.53. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Age Category
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE (continued)

	Flx			Placebo			Total			p-Value*
AGE	N	n	(%)	N	n	(%)	N	n	(%)	
DYSPHAGIA										
8 - < 13	61	1	(1.6)	61	0		122	1	(0.8)	1.00
13 - < 18	48	0		49	1	(2.0)	97	1	(1.0)	1.00
Total	109	1	(0.9)	110	1	(0.9)	219	2	(0.9)	1.00
DYSPNEA										
8 - < 13	61	1	(1.6)	61	0		122	1	(0.8)	1.00
13 - < 18	48	0		49	0		97	0		
Total	109	1	(0.9)	110	0		219	1	(0.5)	.498

RMP.B1YP.JCLLIB2(AES6JEAD)
RMP.B1YO.HCJEREP(AES6JEAD)
AGE: Patient Age
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.53. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Age Category
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE (continued)

	Flx			Placebo			Total			p-Value*
AGE	N	n	(%)	N	n	(%)	N	n	(%)	
EMOTIONAL LABILITY										
8 - < 13	61	1	(1.6)	61	0		122	1	(0.8)	1.00
13 - < 18	48	0		49	0		97	0		
Total	109	1	(0.9)	110	0		219	1	(0.5)	.498
ENDOCRINE DISORDER										
8 - < 13	61	0		61	0		122	0		
13 - < 18	48	1	(2.1)	49	0		97	1	(1.0)	.495
Total	109	1	(0.9)	110	0		219	1	(0.5)	.498

RMP.B1YP.JCLLIB2(AES6JEAD)
RMP.B1YO.HCJEREP(AES6JEAD)
AGE: Patient Age
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.53. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Age Category
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE (continued)

	Flx			Placebo			Total			p-Value*
AGE	N	n	(%)	N	n	(%)	N	n	(%)	
ENDOMETRIAL HYPERPLASIA										
8 - < 13	61	0		61	0		122	0		
13 - < 18	48	1	(2.1)	49	0		97	1	(1.0)	.495
Total	109	1	(0.9)	110	0		219	1	(0.5)	.498
EYE PAIN										
8 - < 13	61	1	(1.6)	61	0		122	1	(0.8)	1.00
13 - < 18	48	0		49	0		97	0		
Total	109	1	(0.9)	110	0		219	1	(0.5)	.498

RMP.B1YP.JCLLIB2(AES6JEAD)
RMP.B1YO.HCJEREP(AES6JEAD)
AGE: Patient Age
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.53. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Age Category
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE (continued)

	Flx			Placebo			Total			p-Value*
AGE	N	n	(%)	N	n	(%)	N	n	(%)	
FECAL INCONTINENCE										
8 - < 13	61	1	(1.6)	61	0		122	1	(0.8)	1.00
13 - < 18	48	0		49	0		97	0		
Total	109	1	(0.9)	110	0		219	1	(0.5)	.498
FLATULENCE										
8 - < 13	61	1	(1.6)	61	0		122	1	(0.8)	1.00
13 - < 18	48	0		49	0		97	0		
Total	109	1	(0.9)	110	0		219	1	(0.5)	.498

RMP.B1YP.JCLLIB2(AES6JEAD)
RMP.B1YO.HCJEREP(AES6JEAD)
AGE: Patient Age
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.53. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Age Category
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE (continued)

	Flx			Placebo			Total			p-Value*
AGE	N	n	(%)	N	n	(%)	N	n	(%)	
FUNGAL DERMATITIS										
8 - < 13	61	1	(1.6)	61	1	(1.6)	122	2	(1.6)	1.00
13 - < 18	48	0		49	0		97	0		
Total	109	1	(0.9)	110	1	(0.9)	219	2	(0.9)	1.00
GASTROINTESTINAL DISORDER										
8 - < 13	61	1	(1.6)	61	1	(1.6)	122	2	(1.6)	1.00
13 - < 18	48	0		49	0		97	0		
Total	109	1	(0.9)	110	1	(0.9)	219	2	(0.9)	1.00

RMP.B1YP.JCLLIB2(AES6JEAD)
RMP.B1YO.HCJEREP(AES6JEAD)
AGE: Patient Age
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.53. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Age Category
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE (continued)

	Flx			Placebo			Total			p-Value*
AGE	N	n	(%)	N	n	(%)	N	n	(%)	
HALLUCINATIONS										
8 - < 13	61	1	(1.6)	61	0		122	1	(0.8)	1.00
13 - < 18	48	0		49	0		97	0		
Total	109	1	(0.9)	110	0		219	1	(0.5)	.498
HEPATITIS NONSPECIFIC										
8 - < 13	61	1	(1.6)	61	0		122	1	(0.8)	1.00
13 - < 18	48	0		49	0		97	0		
Total	109	1	(0.9)	110	0		219	1	(0.5)	.498

RMP.B1YP.JCLLIB2(AES6JEAD)
RMP.B1YO.HCJEREP(AES6JEAD)
AGE: Patient Age
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.53. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Age Category
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE (continued)

	Flx			Placebo			Total			p-Value*
AGE	N	n	(%)	N	n	(%)	N	n	(%)	
HEPATOMEGALY										
8 - < 13	61	1	(1.6)	61	1	(1.6)	122	2	(1.6)	1.00
13 - < 18	48	0		49	0		97	0		
Total	109	1	(0.9)	110	1	(0.9)	219	2	(0.9)	1.00
HERPES SIMPLEX										
8 - < 13	61	0		61	0		122	0		
13 - < 18	48	1	(2.1)	49	0		97	1	(1.0)	.495
Total	109	1	(0.9)	110	0		219	1	(0.5)	.498

RMP.B1YP.JCLLIB2(AES6JEAD)
RMP.B1YO.HCJEREP(AES6JEAD)
AGE: Patient Age
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.53. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Age Category
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE (continued)

	Flx			Placebo			Total			p-Value*
AGE	N	n	(%)	N	n	(%)	N	n	(%)	
HYPERCHOLESTEREMIA										
8 - < 13	61	1	(1.6)	61	0		122	1	(0.8)	1.00
13 - < 18	48	0		49	0		97	0		
Total	109	1	(0.9)	110	0		219	1	(0.5)	.498
HYPERTONIA										
8 - < 13	61	1	(1.6)	61	1	(1.6)	122	2	(1.6)	1.00
13 - < 18	48	0		49	0		97	0		
Total	109	1	(0.9)	110	1	(0.9)	219	2	(0.9)	1.00

RMP.B1YP.JCLLIB2(AES6JEAD)
RMP.B1YO.HCJEREP(AES6JEAD)
AGE: Patient Age
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.53. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Age Category
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE (continued)

	Flx			Placebo			Total			p-Value*
AGE	N	n	(%)	N	n	(%)	N	n	(%)	
HYPOTENSION										
8 - < 13	61	0		61	0		122	0		
13 - < 18	48	1	(2.1)	49	0		97	1	(1.0)	.495
Total	109	1	(0.9)	110	0		219	1	(0.5)	.498
INCREASED SALIVATION										
8 - < 13	61	0		61	1	(1.6)	122	1	(0.8)	1.00
13 - < 18	48	1	(2.1)	49	0		97	1	(1.0)	.495
Total	109	1	(0.9)	110	1	(0.9)	219	2	(0.9)	1.00

RMP.B1YP.JCLLIB2(AES6JEAD)
RMP.B1YO.HCJEREP(AES6JEAD)
AGE: Patient Age
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.53. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Age Category
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE (continued)

	Flx			Placebo			Total			p-Value*
AGE	N	n	(%)	N	n	(%)	N	n	(%)	
INTENTIONAL INJURY										
8 - < 13	61	0		61	0		122	0		
13 - < 18	48	1	(2.1)	49	1	(2.0)	97	2	(2.1)	1.00
Total	109	1	(0.9)	110	1	(0.9)	219	2	(0.9)	1.00
JOINT DISORDER										
8 - < 13	61	1	(1.6)	61	0		122	1	(0.8)	1.00
13 - < 18	48	0		49	0		97	0		
Total	109	1	(0.9)	110	0		219	1	(0.5)	.498

RMP.B1YP.JCLLIB2(AES6JEAD)
RMP.B1YO.HCJEREP(AES6JEAD)
AGE: Patient Age
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.53. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Age Category
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE (continued)

	Flx			Placebo			Total			p-Value*
AGE	N	n	(%)	N	n	(%)	N	n	(%)	
LARYNGITIS										
8 - < 13	61	1	(1.6)	61	1	(1.6)	122	2	(1.6)	1.00
13 - < 18	48	0		49	0		97	0		
Total	109	1	(0.9)	110	1	(0.9)	219	2	(0.9)	1.00
LEG CRAMPS										
8 - < 13	61	1	(1.6)	61	1	(1.6)	122	2	(1.6)	1.00
13 - < 18	48	0		49	2	(4.1)	97	2	(2.1)	.495
Total	109	1	(0.9)	110	3	(2.7)	219	4	(1.8)	.622

RMP.B1YP.JCLLIB2(AES6JEAD)
RMP.B1YO.HCJEREP(AES6JEAD)
AGE: Patient Age
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.53. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Age Category
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE (continued)

	Flx			Placebo			Total			p-Value*
AGE	N	n	(%)	N	n	(%)	N	n	(%)	
LEUKOPENIA										
8 - < 13	61	0		61	0		122	0		
13 - < 18	48	1	(2.1)	49	0		97	1	(1.0)	.495
Total	109	1	(0.9)	110	0		219	1	(0.5)	.498
LUNG DISORDER										
8 - < 13	61	1	(1.6)	61	0		122	1	(0.8)	1.00
13 - < 18	48	0		49	0		97	0		
Total	109	1	(0.9)	110	0		219	1	(0.5)	.498

RMP.B1YP.JCLLIB2(AES6JEAD)
RMP.B1YO.HCJEREP(AES6JEAD)
AGE: Patient Age
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.53. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Age Category
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE (continued)

	Flx			Placebo			Total			p-Value*
AGE	N	n	(%)	N	n	(%)	N	n	(%)	
LYMPHADENOPATHY										
8 - < 13	61	0		61	1	(1.6)	122	1	(0.8)	1.00
13 - < 18	48	1	(2.1)	49	0		97	1	(1.0)	.495
Total	109	1	(0.9)	110	1	(0.9)	219	2	(0.9)	1.00
MACULOPAPULAR RASH										
8 - < 13	61	0		61	0		122	0		
13 - < 18	48	1	(2.1)	49	1	(2.0)	97	2	(2.1)	1.00
Total	109	1	(0.9)	110	1	(0.9)	219	2	(0.9)	1.00

RMP.B1YP.JCLLIB2(AES6JEAD)
RMP.B1YO.HCJEREP(AES6JEAD)
AGE: Patient Age
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.53. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Age Category
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE (continued)

	Flx			Placebo			Total			p-Value*
AGE	N	n	(%)	N	n	(%)	N	n	(%)	
MANIC REACTION										
8 - < 13	61	1	(1.6)	61	0		122	1	(0.8)	1.00
13 - < 18	48	0		49	0		97	0		
Total	109	1	(0.9)	110	0		219	1	(0.5)	.498
MIGRAINE										
8 - < 13	61	1	(1.6)	61	1	(1.6)	122	2	(1.6)	1.00
13 - < 18	48	0		49	0		97	0		
Total	109	1	(0.9)	110	1	(0.9)	219	2	(0.9)	1.00

RMP.B1YP.JCLLIB2(AES6JEAD)
RMP.B1YO.HCJEREP(AES6JEAD)
AGE: Patient Age
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.53. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Age Category
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE (continued)

	Flx			Placebo			Total			p-Value*
AGE	N	n	(%)	N	n	(%)	N	n	(%)	
NEUROSIS										
8 - < 13	61	1	(1.6)	61	0		122	1	(0.8)	1.00
13 - < 18	48	0		49	0		97	0		
Total	109	1	(0.9)	110	0		219	1	(0.5)	.498
OTITIS MEDIA										
8 - < 13	61	1	(1.6)	61	0		122	1	(0.8)	1.00
13 - < 18	48	0		49	0		97	0		
Total	109	1	(0.9)	110	0		219	1	(0.5)	.498

RMP.B1YP.JCLLIB2(AES6JEAD)
RMP.B1YO.HCJEREP(AES6JEAD)
AGE: Patient Age
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.53. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Age Category
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE (continued)

	Flx			Placebo			Total			p-Value*
AGE	N	n	(%)	N	n	(%)	N	n	(%)	
OVERDOSE										
8 - < 13	61	1	(1.6)	61	0		122	1	(0.8)	1.00
13 - < 18	48	0		49	1	(2.0)	97	1	(1.0)	1.00
Total	109	1	(0.9)	110	1	(0.9)	219	2	(0.9)	1.00
PALPITATION										
8 - < 13	61	0		61	0		122	0		
13 - < 18	48	1	(2.1)	49	1	(2.0)	97	2	(2.1)	1.00
Total	109	1	(0.9)	110	1	(0.9)	219	2	(0.9)	1.00

RMP.B1YP.JCLLIB2(AES6JEAD)
RMP.B1YO.HCJEREP(AES6JEAD)
AGE: Patient Age
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.53. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Age Category
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE (continued)

	Flx			Placebo			Total			p-Value*
AGE	N	n	(%)	N	n	(%)	N	n	(%)	
PNEUMONIA										
8 - < 13	61	1	(1.6)	61	0		122	1	(0.8)	1.00
13 - < 18	48	0		49	0		97	0		
Total	109	1	(0.9)	110	0		219	1	(0.5)	.498
RECTAL HEMORRHAGE										
8 - < 13	61	1	(1.6)	61	0		122	1	(0.8)	1.00
13 - < 18	48	0		49	0		97	0		
Total	109	1	(0.9)	110	0		219	1	(0.5)	.498

RMP.B1YP.JCLLIB2(AES6JEAD)
RMP.B1YO.HCJEREP(AES6JEAD)
AGE: Patient Age
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.53. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Age Category
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE (continued)

	Flx			Placebo			Total			p-Value*
AGE	N	n	(%)	N	n	(%)	N	n	(%)	
SINUS BRADYCARDIA										
8 - < 13	61	0		61	0		122	0		
13 - < 18	48	1	(2.1)	49	0		97	1	(1.0)	.495
Total	109	1	(0.9)	110	0		219	1	(0.5)	.498
SYNCOPE										
8 - < 13	61	0		61	0		122	0		
13 - < 18	48	1	(2.1)	49	0		97	1	(1.0)	.495
Total	109	1	(0.9)	110	0		219	1	(0.5)	.498

RMP.B1YP.JCLLIB2(AES6JEAD)
RMP.B1YO.HCJEREP(AES6JEAD)
AGE: Patient Age
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.53. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Age Category
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE (continued)

	Flx			Placebo			Total			p-Value*
AGE	N	n	(%)	N	n	(%)	N	n	(%)	
TACHYCARDIA										
8 - < 13	61	0		61	0		122	0		
13 - < 18	48	1	(2.1)	49	0		97	1	(1.0)	.495
Total	109	1	(0.9)	110	0		219	1	(0.5)	.498
THYROID DISORDER										
8 - < 13	61	0		61	0		122	0		
13 - < 18	48	1	(2.1)	49	0		97	1	(1.0)	.495
Total	109	1	(0.9)	110	0		219	1	(0.5)	.498

RMP.B1YP.JCLLIB2(AES6JEAD)
RMP.B1YO.HCJEREP(AES6JEAD)
AGE: Patient Age
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.53. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Age Category
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE (continued)

	Flx			Placebo			Total			p-Value*
AGE	N	n	(%)	N	n	(%)	N	n	(%)	
TINNITUS										
8 - < 13	61	0		61	0		122	0		
13 - < 18	48	1	(2.1)	49	0		97	1	(1.0)	.495
Total	109	1	(0.9)	110	0		219	1	(0.5)	.498
ULCERATIVE STOMATITIS										
8 - < 13	61	1	(1.6)	61	0		122	1	(0.8)	1.00
13 - < 18	48	0		49	0		97	0		
Total	109	1	(0.9)	110	0		219	1	(0.5)	.498

RMP.B1YP.JCLLIB2(AES6JEAD)
RMP.B1YO.HCJEREP(AES6JEAD)
AGE: Patient Age
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.53. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Age Category
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE (continued)

	Flx			Placebo			Total			p-Value*
AGE	N	n	(%)	N	n	(%)	N	n	(%)	
URINARY FREQUENCY										
8 - < 13	61	1	(1.6)	61	1	(1.6)	122	2	(1.6)	1.00
13 - < 18	48	0		49	1	(2.0)	97	1	(1.0)	1.00
Total	109	1	(0.9)	110	2	(1.8)	219	3	(1.4)	1.00
URINARY TRACT INFECTION										
8 - < 13	61	1	(1.6)	61	0		122	1	(0.8)	1.00
13 - < 18	48	0		49	1	(2.0)	97	1	(1.0)	1.00
Total	109	1	(0.9)	110	1	(0.9)	219	2	(0.9)	1.00

RMP.B1YP.JCLLIB2(AES6JEAD)
RMP.B1YO.HCJEREP(AES6JEAD)
AGE: Patient Age
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.53. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Age Category
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE (continued)

	Flx			Placebo			Total			p-Value*
AGE	N	n	(%)	N	n	(%)	N	n	(%)	
VASODILATATION										
8 - < 13	61	0		61	0		122	0		
13 - < 18	48	1	(2.1)	49	0		97	1	(1.0)	.495
Total	109	1	(0.9)	110	0		219	1	(0.5)	.498
VESICULOBULLOUS RASH										
8 - < 13	61	1	(1.6)	61	0		122	1	(0.8)	1.00
13 - < 18	48	0		49	0		97	0		
Total	109	1	(0.9)	110	0		219	1	(0.5)	.498

RMP.B1YP.JCLLIB2(AES6JEAD)
RMP.B1YO.HCJEREP(AES6JEAD)
AGE: Patient Age
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.53. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Age Category
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE (continued)

	Flx			Placebo			Total			p-Value*
AGE	N	n	(%)	N	n	(%)	N	n	(%)	
ABDOMINAL SYNDROME ACUTE										
8 - < 13	61	0		61	1	(1.6)	122	1	(0.8)	1.00
13 - < 18	48	0		49	0		97	0		
Total	109	0		110	1	(0.9)	219	1	(0.5)	1.00
ACNE										
8 - < 13	61	0		61	1	(1.6)	122	1	(0.8)	1.00
13 - < 18	48	0		49	0		97	0		
Total	109	0		110	1	(0.9)	219	1	(0.5)	1.00

RMP.B1YP.JCLLIB2(AES6JEAD)
RMP.B1YO.HCJEREP(AES6JEAD)
AGE: Patient Age
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.53. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Age Category
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE (continued)

	Flx			Placebo			Total			p-Value*
AGE	N	n	(%)	N	n	(%)	N	n	(%)	
ALOPECIA										
8 - < 13	61	0		61	0		122	0		
13 - < 18	48	0		49	1	(2.0)	97	1	(1.0)	1.00
Total	109	0		110	1	(0.9)	219	1	(0.5)	1.00
APHTHOUS STOMATITIS										
8 - < 13	61	0		61	1	(1.6)	122	1	(0.8)	1.00
13 - < 18	48	0		49	0		97	0		
Total	109	0		110	1	(0.9)	219	1	(0.5)	1.00

RMP.B1YP.JCLLIB2(AES6JEAD)
RMP.B1YO.HCJEREP(AES6JEAD)
AGE: Patient Age
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.53. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Age Category
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE (continued)

	Flx			Placebo			Total			p-Value*
AGE	N	n	(%)	N	n	(%)	N	n	(%)	
ARTHRALGIA										
8 - < 13	61	0		61	1	(1.6)	122	1	(0.8)	1.00
13 - < 18	48	0		49	0		97	0		
Total	109	0		110	1	(0.9)	219	1	(0.5)	1.00
BILIRUBINURIA										
8 - < 13	61	0		61	1	(1.6)	122	1	(0.8)	1.00
13 - < 18	48	0		49	0		97	0		
Total	109	0		110	1	(0.9)	219	1	(0.5)	1.00

RMP.B1YP.JCLLIB2(AES6JEAD)
RMP.B1YO.HCJEREP(AES6JEAD)
AGE: Patient Age
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.53. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Age Category
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE (continued)

	Flx			Placebo			Total			p-Value*
AGE	N	n	(%)	N	n	(%)	N	n	(%)	
CYSTITIS										
8 - < 13	61	0		61	0		122	0		
13 - < 18	48	0		49	1	(2.0)	97	1	(1.0)	1.00
Total	109	0		110	1	(0.9)	219	1	(0.5)	1.00
DEHYDRATION										
8 - < 13	61	0		61	2	(3.3)	122	2	(1.6)	.496
13 - < 18	48	0		49	0		97	0		
Total	109	0		110	2	(1.8)	219	2	(0.9)	.498

RMP.B1YP.JCLLIB2(AES6JEAD)
RMP.B1YO.HCJEREP(AES6JEAD)
AGE: Patient Age
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.53. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Age Category
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE (continued)

	Flx			Placebo			Total			p-Value*
AGE	N	n	(%)	N	n	(%)	N	n	(%)	
DYSURIA										
8 - < 13	61	0		61	1	(1.6)	122	1	(0.8)	1.00
13 - < 18	48	0		49	0		97	0		
Total	109	0		110	1	(0.9)	219	1	(0.5)	1.00
FACE EDEMA										
8 - < 13	61	0		61	0		122	0		
13 - < 18	48	0		49	1	(2.0)	97	1	(1.0)	1.00
Total	109	0		110	1	(0.9)	219	1	(0.5)	1.00

RMP.B1YP.JCLLIB2(AES6JEAD)
RMP.B1YO.HCJEREP(AES6JEAD)
AGE: Patient Age
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.53. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Age Category
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE (continued)

	Flx			Placebo			Total			p-Value*
AGE	N	n	(%)	N	n	(%)	N	n	(%)	
HYPESTHESIA										
8 - < 13	61	0		61	1	(1.6)	122	1	(0.8)	1.00
13 - < 18	48	0		49	0		97	0		
Total	109	0		110	1	(0.9)	219	1	(0.5)	1.00
HYPOVENTILATION										
8 - < 13	61	0		61	1	(1.6)	122	1	(0.8)	1.00
13 - < 18	48	0		49	0		97	0		
Total	109	0		110	1	(0.9)	219	1	(0.5)	1.00

RMP.B1YP.JCLLIB2(AES6JEAD)
RMP.B1YO.HCJEREP(AES6JEAD)
AGE: Patient Age
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.53. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Age Category
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE (continued)

	Flx			Placebo			Total			p-Value*
AGE	N	n	(%)	N	n	(%)	N	n	(%)	
LEUKORRHEA										
8 - < 13	61	0		61	1	(1.6)	122	1	(0.8)	1.00
13 - < 18	48	0		49	0		97	0		
Total	109	0		110	1	(0.9)	219	1	(0.5)	1.00
LYMPHOCYTOSIS										
8 - < 13	61	0		61	1	(1.6)	122	1	(0.8)	1.00
13 - < 18	48	0		49	0		97	0		
Total	109	0		110	1	(0.9)	219	1	(0.5)	1.00

RMP.B1YP.JCLLIB2(AES6JEAD)
RMP.B1YO.HCJEREP(AES6JEAD)
AGE: Patient Age
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.53. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Age Category
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE (continued)

	Flx			Placebo			Total			p-Value*
AGE	N	n	(%)	N	n	(%)	N	n	(%)	
MENORRHAGIA										
8 - < 13	61	0		61	1	(1.6)	122	1	(0.8)	1.00
13 - < 18	48	0		49	0		97	0		
Total	109	0		110	1	(0.9)	219	1	(0.5)	1.00
METRORRHAGIA										
8 - < 13	61	0		61	0		122	0		
13 - < 18	48	0		49	1	(2.0)	97	1	(1.0)	1.00
Total	109	0		110	1	(0.9)	219	1	(0.5)	1.00

RMP.B1YP.JCLLIB2(AES6JEAD)
RMP.B1YO.HCJEREP(AES6JEAD)
AGE: Patient Age
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.53. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Age Category
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE (continued)

	Flx			Placebo			Total			p-Value*
AGE	N	n	(%)	N	n	(%)	N	n	(%)	
MOUTH ULCERATION										
8 - < 13	61	0		61	1	(1.6)	122	1	(0.8)	1.00
13 - < 18	48	0		49	0		97	0		
Total	109	0		110	1	(0.9)	219	1	(0.5)	1.00
PUSTULAR RASH										
8 - < 13	61	0		61	1	(1.6)	122	1	(0.8)	1.00
13 - < 18	48	0		49	0		97	0		
Total	109	0		110	1	(0.9)	219	1	(0.5)	1.00

RMP.B1YP.JCLLIB2(AES6JEAD)
RMP.B1YO.HCJEREP(AES6JEAD)
AGE: Patient Age
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.53. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Age Category
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE (continued)

	Flx			Placebo			Total			p-Value*
AGE	N	n	(%)	N	n	(%)	N	n	(%)	
SKIN DISCOLORATION										
8 - < 13	61	0		61	1	(1.6)	122	1	(0.8)	1.00
13 - < 18	48	0		49	0		97	0		
Total	109	0		110	1	(0.9)	219	1	(0.5)	1.00
SKIN ULCER										
8 - < 13	61	0		61	1	(1.6)	122	1	(0.8)	1.00
13 - < 18	48	0		49	0		97	0		
Total	109	0		110	1	(0.9)	219	1	(0.5)	1.00

RMP.B1YP.JCLLIB2(AES6JEAD)
RMP.B1YO.HCJEREP(AES6JEAD)
AGE: Patient Age
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.53. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Age Category
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE (continued)

	Flx			Placebo			Total			p-Value*
AGE	N	n	(%)	N	n	(%)	N	n	(%)	
SPLENOMEGALY										
8 - < 13	61	0		61	1	(1.6)	122	1	(0.8)	1.00
13 - < 18	48	0		49	0		97	0		
Total	109	0		110	1	(0.9)	219	1	(0.5)	1.00
SUBCUTANEOUS NODULE										
8 - < 13	61	0		61	1	(1.6)	122	1	(0.8)	1.00
13 - < 18	48	0		49	0		97	0		
Total	109	0		110	1	(0.9)	219	1	(0.5)	1.00

RMP.B1YP.JCLLIB2(AES6JEAD)
RMP.B1YO.HCJEREP(AES6JEAD)
AGE: Patient Age
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.53. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Age Category
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE (continued)

	Flx			Placebo			Total			p-Value*
AGE	N	n	(%)	N	n	(%)	N	n	(%)	
UNEXPECTED BENEFIT										
8 - < 13	61	0		61	0		122	0		
13 - < 18	48	0		49	1	(2.0)	97	1	(1.0)	1.00
Total	109	0		110	1	(0.9)	219	1	(0.5)	1.00
VERTIGO										
8 - < 13	61	0		61	0		122	0		
13 - < 18	48	0		49	1	(2.0)	97	1	(1.0)	1.00
Total	109	0		110	1	(0.9)	219	1	(0.5)	1.00

RMP.B1YP.JCLLIB2(AES6JEAD)
RMP.B1YO.HCJEREP(AES6JEAD)
AGE: Patient Age
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.53. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Age Category
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE (concluded)

	Flx			Placebo			Total			p-Value*
AGE	N	n	(%)	N	n	(%)	N	n	(%)	
WEIGHT GAIN										
8 - < 13	61	0		61	1	(1.6)	122	1	(0.8)	1.00
13 - < 18	48	0		49	0		97	0		
Total	109	0		110	1	(0.9)	219	1	(0.5)	1.00

RMP.B1YP.JCLLIB2(AES6JEAD)
RMP.B1YO.HCJEREP(AES6JEAD)
AGE: Patient Age
* Frequencies are analyzed using a Fisher’s Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

{{Insert AES6JEAD here}}

Table 14.54 presents the incidence of treatment-emergent solicited adverse events from the Side-Effects Checklist analyzed by age subgroups for the subchronic treatment phase.

The Breslow-Day test did not detect a statistically significant difference in odds ratios across the age subgroups for any treatment-emergent solicited adverse event. There was a trend towards significance for the events trouble with eating (p=.058), trouble doing things with your hands (p=.063), being sick to your stomach (p=.092), and being sad (p=.064).

For the events being sick to your stomach and trouble with eating, the between-treatment group comparisons were not statistically significant for either age subgroup. The between-group comparison was statistically significant for adolescents (p=.022) for the event trouble doing things with your hands, with placebo-treated adolescents (25%) reporting the event more frequently than fluoxetine-treated adolescents (6%). The between-treatment group comparison was significant for children (p=.026) for the event being sad, with fluoxetine-treated children (51%) reporting the event more frequently than placebo-treated children (30%). The difference between treatment groups for adolescents was not statistically significant.

Table 14.54. Treatment-Emergent Solicited Adverse Events
Side Effects Checklist Subgroup Analysis by Age
Significant (p<.05) Difference in Odds Ratio
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE

SECL Event - Have you had trouble with:	AGE	Flx N	Flx n	Flx (%)	Placebo N	Placebo n	Placebo (%)	p-Values: Homogeneity of Odds Ratio p-Value*	p-Values: Between Group Comparison p-Value**
01. EATING	8 - <13	61	22	(36.1)	61	18	(29.5)	.058	.563
	13 - <=18	48	12	(25.0)	49	21	(42.9)		.087
02. DRINKING	8 - <13	61	11	(18.0)	61	14	(23.0)	.941	.654
	13 - <=18	48	5	(10.4)	49	7	(14.3)		.759
03. DRY MOUTH AND LIPS	8 - <13	61	16	(26.2)	61	20	(32.8)	.986	.552
	13 - <=18	48	18	(37.5)	49	22	(44.9)		.538
04. WETNESS IN MOUTH	8 - <13	61	6	(9.8)	61	15	(24.6)	.584	.053
	13 - <=18	48	5	(10.4)	49	9	(18.4)		.387
05. CONSTIPATION	8 - <13	61	7	(11.5)	61	8	(13.1)	.752	1.00
	13 - <=18	48	4	(8.3)	49	6	(12.2)		.740
06. DIARRHEA	8 - <13	61	19	(31.1)	61	15	(24.6)	.812	.545
	13 - <=18	48	9	(18.8)	49	8	(16.3)		.795
07. STOMACHACHES	8 - <13	61	30	(49.2)	61	27	(44.3)	.360	.717
	13 - <=18	48	18	(37.5)	49	22	(44.9)		.538

* The homogeneity of odds ratio p-Value is derived from the Breslow-Day test.
**The between group comparison within strata p-Value is from the Fisher's Exact Test.
Treatment-Emergent Solicited = was present at baseline and worsened as defined by increase in score on the side-effects checklist or new occurrence after baseline.
RMP.B1YP.SASPGM(CUSJESG1)
RMP.B1YO.HCJEREP(CUSTJEMP)

Table 14.54. Treatment-Emergent Solicited Adverse Events
Side Effects Checklist Subgroup Analysis by Age
Significant (p<.05) Difference in Odds Ratio
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE (continued)

SECL Event - Have you had trouble with:	AGE	Flx N	Flx n	Flx (%)	Placebo N	Placebo n	Placebo (%)	p-Values: Homogeneity of Odds Ratio p-Value*	p-Values: Between Group Comparison p-Value**
08. MUSCLE CRAMPS	8 - <13	61	19	(31.1)	61	22	(36.1)	.860	.702
	13 - <=18	48	16	(33.3)	49	20	(40.8)		.530
09. BEING SICK TO YOUR STOMACH	8 - <13	61	28	(45.9)	61	19	(31.1)	.092	.136
	13 - <=18	48	16	(33.3)	49	20	(40.8)		.530
10. WETTING THE BED	8 - <13	61	3	(4.9)	61	4	(6.6)	.414	1.00
	13 - <=18	48	0		49	1	(2.0)		1.00
11. URINATING	8 - <13	61	5	(8.2)	61	7	(11.5)	.830	.762
	13 - <=18	48	5	(10.4)	49	6	(12.2)		1.00
12. ITCHY OR SCRATCHY SKIN	8 - <13	61	18	(29.5)	61	19	(31.1)	.763	1.00
	13 - <=18	48	14	(29.2)	49	17	(34.7)		.664
13. RASHES	8 - <13	61	13	(21.3)	61	15	(24.6)	.407	.830
	13 - <=18	48	5	(10.4)	49	10	(20.4)		.261
14. COLD OR SNIFFLES	8 - <13	61	24	(39.3)	61	28	(45.9)	.673	.583
	13 - <=18	48	27	(56.3)	49	28	(57.1)		1.00

* The homogeneity of odds ratio p-Value is derived from the Breslow-Day test.
**The between group comparison within strata p-Value is from the Fisher’s Exact Test.
Treatment-Emergent Solicited = was present at baseline and worsened as defined by increase in score on the side-effects checklist or new occurrence after baseline.
RMP.B1YP.SASPGM(CUSJESG1)
RMP.B1YO.HCJEREP(CUSTJEMP)

Table 14.54. Treatment-Emergent Solicited Adverse Events
Side Effects Checklist Subgroup Analysis by Age
Significant (p<.05) Difference in Odds Ratio
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE (continued)

SECL Event - Have you had trouble with:	AGE	Flx N	Flx n	Flx (%)	Placebo N	Placebo n	Placebo (%)	p-Values: Homogeneity of Odds Ratio p-Value*	p-Values: Between Group Comparison p-Value**
15. HEADACHE	8 - <13	61	35	(57.4)	61	27	(44.3)	.911	.205
	13 - <=18	48	22	(45.8)	49	17	(34.7)		.304
16. DIZZINESS	8 - <13	61	20	(32.8)	61	16	(26.2)	.860	.552
	13 - <=18	48	18	(37.5)	49	16	(32.7)		.674
17. PLAYING SPORTS	8 - <13	61	12	(19.7)	61	10	(16.4)	.291	.814
	13 - <=18	48	7	(14.6)	49	11	(22.4)		.435
18. SHAKINESS	8 - <13	61	12	(19.7)	61	11	(18.0)	.970	1.00
	13 - <=18	48	14	(29.2)	49	13	(26.5)		.823
19. PRONOUNCING WORDS	8 - <13	61	12	(19.7)	61	18	(29.5)	.387	.293
	13 - <=18	48	6	(12.5)	49	15	(30.6)		.047
20. DOING THINGS WITH YOUR HANDS	8 - <13	61	12	(19.7)	61	13	(21.3)	.063	1.00
	13 - <=18	48	3	(6.3)	49	12	(24.5)		.022
21. SITTING STILL	8 - <13	61	21	(34.4)	61	23	(37.7)	.408	.851
	13 - <=18	48	13	(27.1)	49	20	(40.8)		.199

* The homogeneity of odds ratio p-Value is derived from the Breslow-Day test.
**The between group comparison within strata p-Value is from the Fisher's Exact Test.
Treatment-Emergent Solicited = was present at baseline and worsened as defined by increase in score on the side-effects checklist or new occurrence after baseline.
RMP.B1YP.SASPGM(CUSJESG1)
RMP.B1YO.HCJEREP(CUSTJEMP)

Table 14.54. Treatment-Emergent Solicited Adverse Events
Side Effects Checklist Subgroup Analysis by Age
Significant (p<.05) Difference in Odds Ratio
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE (continued)

SECL Event - Have you had trouble with:	AGE	Flx N	Flx n	Flx (%)	Placebo N	Placebo n	Placebo (%)	p-Values: Homogeneity of Odds Ratio p-Value*	p-Values: Between Group Comparison p-Value**
22. TIREDNESS	8 - <13	61	31	(50.8)	61	26	(42.6)	.819	.468
	13 - <=18	48	24	(50.0)	49	22	(44.9)		.686
23. FEELING SLEEPY	8 - <13	61	32	(52.5)	61	25	(41.0)	.439	.276
	13 - <=18	48	24	(50.0)	49	24	(49.0)		1.00
24. SLEEPING	8 - <13	61	25	(41.0)	61	27	(44.3)	.885	.855
	13 - <=18	48	20	(41.7)	49	23	(46.9)		.684
25. BAD DREAMS	8 - <13	61	14	(23.0)	61	18	(29.5)	.639	.537
	13 - <=18	48	16	(33.3)	49	17	(34.7)		1.00
26. GETTING ALONG WITH PARENTS	8 - <13	61	28	(45.9)	61	21	(34.4)	.163	.268
	13 - <=18	48	23	(47.9)	49	27	(55.1)		.545
27. GETTING ALONG WITH KIDS	8 - <13	61	20	(32.8)	61	18	(29.5)	.707	.845
	13 - <=18	48	14	(29.2)	49	15	(30.6)		1.00
28. CRYING	8 - <13	61	30	(49.2)	61	25	(41.0)	.393	.467
	13 - <=18	48	17	(35.4)	49	19	(38.8)		.834

* The homogeneity of odds ratio p-Value is derived from the Breslow-Day test.
**The between group comparison within strata p-Value is from the Fisher's Exact Test.
Treatment-Emergent Solicited = was present at baseline and worsened as defined by increase in score on the side-effects checklist or new occurrence after baseline.
RMP.B1YP.SASPGM(CUSJESG1)
RMP.B1YO.HCJEREP(CUSTJEMP)

Table 14.54. Treatment-Emergent Solicited Adverse Events
Side Effects Checklist Subgroup Analysis by Age
Significant (p<.05) Difference in Odds Ratio
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE (concluded)

SECL Event - Have you had trouble with:	AGE	Flx N	Flx n	Flx (%)	Placebo N	Placebo n	Placebo (%)	p-Values: Homogeneity of Odds Ratio p-Value*	p-Values: Between Group Comparison p-Value**
29. GETTING MAD	8 - <13	61	25	(41.0)	61	27	(44.3)	.769	.855
	13 - <=18	48	20	(41.7)	49	24	(49.0)		.543
30. NOT BEING HAPPY	8 - <13	61	26	(42.6)	61	24	(39.3)	.761	.854
	13 - <=18	48	18	(37.5)	49	15	(30.6)		.525
31. BEING SAD	8 - <13	61	31	(50.8)	61	18	(29.5)	.064	.026
	13 - <=18	48	16	(33.3)	49	18	(36.7)		.832
32. PAYING ATTENTION	8 - <13	61	24	(39.3)	61	20	(32.8)	.639	.572
	13 - <=18	48	23	(47.9)	49	17	(34.7)		.219

* The homogeneity of odds ratio p-Value is derived from the Breslow-Day test.
**The between group comparison within strata p-Value is from the Fisher's Exact Test.
Treatment-Emergent Solicited = was present at baseline and worsened as defined by increase in score on the side-effects checklist or new occurrence after baseline.
RMP.B1YP.SASPGM(CUSJESG1)
RMP.B1YO.HCJEREP(CUSTJEMP)

14.3.2.2.2. By Gender

Table 14.55 presents the incidence of treatment-emergent non-solicited adverse events analyzed by gender subgroups for the subchronic treatment phase.

There was a statistically significant difference between treatment groups in the number of females reporting treatment-emergent non-solicited adverse events (p=.004). Overall, more fluoxetine-treated females (96%) reported at least one treatment-emergent non-solicited adverse event than placebo-treated females (76%). There was a statistically significant difference in the reporting of headache in females (p=.036), with more fluoxetine-treated females (41%) reporting the event than placebo-treated females (20%).

Table 14.55. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Gender
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE

Gender	Flx N	Flx n (%)	Placebo N	Placebo n (%)	Total N	Total n (%)	p-Value*
PATIENTS WITH >= 1 TESS							
Female	54	52 (96.3)	54	41 (75.9)	108	93 (86.1)	.004
Male	55	49 (89.1)	56	46 (82.1)	111	95 (85.6)	.419
Total	109	101 (92.7)	110	87 (79.1)	219	188 (85.8)	.006
PATIENTS WITH NO TESS							
Female	54	2 (3.7)	54	13 (24.1)	108	15 (13.9)	.004
Male	55	6 (10.9)	56	10 (17.9)	111	16 (14.4)	.419
Total	109	8 (7.3)	110	23 (20.9)	219	31 (14.2)	.006

RMP.B1YP.JCLLIB2(AES6JEAB)
RMP.B1YO.HCJEREP(AES6JEAB)
Gender: Patient Gender
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.55. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Gender
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE (continued)

Gender	Flx N	Flx n (%)	Placebo N	Placebo n (%)	Total N	Total n (%)	p-Value*
HEADACHE							
Female	54	22 (40.7)	54	11 (20.4)	108	33 (30.6)	.036
Male	55	15 (27.3)	56	10 (17.9)	111	25 (22.5)	.263
Total	109	37 (33.9)	110	21 (19.1)	219	58 (26.5)	.014
RHINITIS							
Female	54	16 (29.6)	54	14 (25.9)	108	30 (27.8)	.830
Male	55	18 (32.7)	56	15 (26.8)	111	33 (29.7)	.538
Total	109	34 (31.2)	110	29 (26.4)	219	63 (28.8)	.458

RMP.B1YP.JCLLIB2(AES6JEAB)
RMP.B1YO.HCJEREP(AES6JEAB)
Gender: Patient Gender
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.55. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Gender
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE (continued)

Gender	Flx N	Flx n (%)	Placebo N	Placebo n (%)	Total N	Total n (%)	p-Value*
ABDOMINAL PAIN							
Female	54	14 (25.9)	54	11 (20.4)	108	25 (23.1)	.649
Male	55	8 (14.5)	56	11 (19.6)	111	19 (17.1)	.616
Total	109	22 (20.2)	110	22 (20.0)	219	44 (20.1)	1.00
PHARYNGITIS							
Female	54	13 (24.1)	54	11 (20.4)	108	24 (22.2)	.817
Male	55	8 (14.5)	56	3 (5.4)	111	11 (9.9)	.124
Total	109	21 (19.3)	110	14 (12.7)	219	35 (16.0)	.202

RMP.B1YP.JCLLIB2(AES6JEAB)
RMP.B1YO.HCJEREP(AES6JEAB)
Gender: Patient Gender
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.55. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Gender
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE (continued)

	Flx		Placebo		Total		p-Value*
Gender	N	n (%)	N	n (%)	N	n (%)	
ACCIDENTAL INJURY							
Female	54	8 (14.8)	54	5 (9.3)	108	13 (12.0)	.556
Male	55	11 (20.0)	56	5 (8.9)	111	16 (14.4)	.112
Total	109	19 (17.4)	110	10 (9.1)	219	29 (13.2)	.076
COUGH INCREASED							
Female	54	7 (13.0)	54	3 (5.6)	108	10 (9.3)	.320
Male	55	9 (16.4)	56	6 (10.7)	111	15 (13.5)	.419
Total	109	16 (14.7)	110	9 (8.2)	219	25 (11.4)	.143

RMP.B1YP.JCLLIB2(AES6JEAB)
RMP.B1YO.HCJEREP(AES6JEAB)
Gender: Patient Gender
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.55. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Gender
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE (continued)

Gender	Flx N	Flx n (%)	Placebo N	Placebo n (%)	Total N	Total n (%)	p-Value*
DIARRHEA							
Female	54	5 (9.3)	54	6 (11.1)	108	11 (10.2)	1.00
Male	55	9 (16.4)	56	7 (12.5)	111	16 (14.4)	.599
Total	109	14 (12.8)	110	13 (11.8)	219	27 (12.3)	.840
RASH							
Female	54	6 (11.1)	54	5 (9.3)	108	11 (10.2)	1.00
Male	55	7 (12.7)	56	5 (8.9)	111	12 (10.8)	.557
Total	109	13 (11.9)	110	10 (9.1)	219	23 (10.5)	.517

RMP.B1YP.JCLLIB2(AES6JEAB)
RMP.B1YO.HCJEREP(AES6JEAB)
Gender: Patient Gender
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.55. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Gender
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE (continued)

	Flx		Placebo		Total		p-Value*
Gender	N	n (%)	N	n (%)	N	n (%)	
DIZZINESS							
Female	54	5 (9.3)	54	6 (11.1)	108	11 (10.2)	1.00
Male	55	6 (10.9)	56	2 (3.6)	111	8 (7.2)	.162
Total	109	11 (10.1)	110	8 (7.3)	219	19 (8.7)	.483
NERVOUSNESS							
Female	54	4 (7.4)	54	3 (5.6)	108	7 (6.5)	1.00
Male	55	7 (12.7)	56	3 (5.4)	111	10 (9.0)	.203
Total	109	11 (10.1)	110	6 (5.5)	219	17 (7.8)	.218

RMP.B1YP.JCLLIB2(AES6JEAB)
RMP.B1YO.HCJEREP(AES6JEAB)
Gender: Patient Gender
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.55. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Gender
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE (continued)

	Flx		Placebo		Total		p-Value*
Gender	N	n (%)	N	n (%)	N	n (%)	
VOMITING							
Female	54	5 (9.3)	54	7 (13.0)	108	12 (11.1)	.761
Male	55	6 (10.9)	56	5 (8.9)	111	11 (9.9)	.761
Total	109	11 (10.1)	110	12 (10.9)	219	23 (10.5)	1.00
ANOREXIA							
Female	54	7 (13.0)	54	6 (11.1)	108	13 (12.0)	1.00
Male	55	3 (5.5)	56	3 (5.4)	111	6 (5.4)	1.00
Total	109	10 (9.2)	110	9 (8.2)	219	19 (8.7)	.815

RMP.B1YP.JCLLIB2(AES6JEAB)
RMP.B1YO.HCJEREP(AES6JEAB)
Gender: Patient Gender
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.55. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Gender
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE (continued)

	Flx		Placebo		Total		p-Value*
Gender	N	n (%)	N	n (%)	N	n (%)	
ASTHENIA							
Female	54	7 (13.0)	54	4 (7.4)	108	11 (10.2)	.526
Male	55	3 (5.5)	56	3 (5.4)	111	6 (5.4)	1.00
Total	109	10 (9.2)	110	7 (6.4)	219	17 (7.8)	.462
FEVER							
Female	54	6 (11.1)	54	6 (11.1)	108	12 (11.1)	1.00
Male	55	4 (7.3)	56	2 (3.6)	111	6 (5.4)	.438
Total	109	10 (9.2)	110	8 (7.3)	219	18 (8.2)	.632

RMP.B1YP.JCLLIB2(AES6JEAB)
RMP.B1YO.HCJEREP(AES6JEAB)
Gender: Patient Gender
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.55. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Gender
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE (continued)

	Flx		Placebo		Total		p-Value*
Gender	N	n (%)	N	n (%)	N	n (%)	
PAIN							
Female	54	5 (9.3)	54	5 (9.3)	108	10 (9.3)	1.00
Male	55	5 (9.1)	56	7 (12.5)	111	12 (10.8)	.761
Total	109	10 (9.2)	110	12 (10.9)	219	22 (10.0)	.823
NAUSEA							
Female	54	2 (3.7)	54	7 (13.0)	108	9 (8.3)	.161
Male	55	7 (12.7)	56	4 (7.1)	111	11 (9.9)	.360
Total	109	9 (8.3)	110	11 (10.0)	219	20 (9.1)	.815

RMP.B1YP.JCLLIB2(AES6JEAB)
RMP.B1YO.HCJEREP(AES6JEAB)
Gender: Patient Gender
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.55. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Gender
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE (continued)

	Flx			Placebo			Total			p-Value*
Gender	N	n	(%)	N	n	(%)	N	n	(%)	
ABNORMAL DREAMS										
Female	54	4	(7.4)	54	1	(1.9)	108	5	(4.6)	.363
Male	55	3	(5.5)	56	2	(3.6)	111	5	(4.5)	.679
Total	109	7	(6.4)	110	3	(2.7)	219	10	(4.6)	.215
BACK PAIN										
Female	54	5	(9.3)	54	5	(9.3)	108	10	(9.3)	1.00
Male	55	1	(1.8)	56	0		111	1	(0.9)	.495
Total	109	6	(5.5)	110	5	(4.5)	219	11	(5.0)	.768

RMP.B1YP.JCLLIB2(AES6JEAB)
RMP.B1YO.HCJEREP(AES6JEAB)
Gender: Patient Gender
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.55. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Gender
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE (continued)

	Flx			Placebo			Total			p-Value*
Gender	N	n	(%)	N	n	(%)	N	n	(%)	
DRY MOUTH										
Female	54	0		54	2	(3.7)	108	2	(1.9)	.495
Male	55	6	(10.9)	56	4	(7.1)	111	10	(9.0)	.527
Total	109	6	(5.5)	110	6	(5.5)	219	12	(5.5)	1.00
EAR PAIN										
Female	54	3	(5.6)	54	2	(3.7)	108	5	(4.6)	1.00
Male	55	3	(5.5)	56	1	(1.8)	111	4	(3.6)	.364
Total	109	6	(5.5)	110	3	(2.7)	219	9	(4.1)	.332

RMP.B1YP.JCLLIB2(AES6JEAB)
RMP.B1YO.HCJEREP(AES6JEAB)
Gender: Patient Gender
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.55. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Gender
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE (continued)

	Flx			Placebo			Total			p-Value*
Gender	N	n	(%)	N	n	(%)	N	n	(%)	
INSOMNIA										
Female	54	3	(5.6)	54	0		108	3	(2.8)	.243
Male	55	3	(5.5)	56	5	(8.9)	111	8	(7.2)	.716
Total	109	6	(5.5)	110	5	(4.5)	219	11	(5.0)	.768
PRURITUS										
Female	54	2	(3.7)	54	1	(1.9)	108	3	(2.8)	1.00
Male	55	4	(7.3)	56	5	(8.9)	111	9	(8.1)	1.00
Total	109	6	(5.5)	110	6	(5.5)	219	12	(5.5)	1.00

RMP.B1YP.JCLLIB2(AES6JEAB)
RMP.B1YO.HCJEREP(AES6JEAB)
Gender: Patient Gender
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.55. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Gender
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE (continued)

	Flx			Placebo			Total			p-Value*
Gender	N	n	(%)	N	n	(%)	N	n	(%)	
EPISTAXIS										
Female	54	2	(3.7)	54	2	(3.7)	108	4	(3.7)	1.00
Male	55	3	(5.5)	56	0		111	3	(2.7)	.118
Total	109	5	(4.6)	110	2	(1.8)	219	7	(3.2)	.280
HOSTILITY										
Female	54	1	(1.9)	54	1	(1.9)	108	2	(1.9)	1.00
Male	55	4	(7.3)	56	4	(7.1)	111	8	(7.2)	1.00
Total	109	5	(4.6)	110	5	(4.5)	219	10	(4.6)	1.00

RMP.B1YP.JCLLIB2(AES6JEAB)
RMP.B1YO.HCJEREP(AES6JEAB)
Gender: Patient Gender
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.55. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Gender
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE (continued)

	Flx			Placebo			Total			p-Value*
Gender	N	n	(%)	N	n	(%)	N	n	(%)	
INFECTION										
Female	54	2	(3.7)	54	4	(7.4)	108	6	(5.6)	.678
Male	55	3	(5.5)	56	1	(1.8)	111	4	(3.6)	.364
Total	109	5	(4.6)	110	5	(4.5)	219	10	(4.6)	1.00
PERSONALITY DISORDER										
Female	54	2	(3.7)	54	0		108	2	(1.9)	.495
Male	55	3	(5.5)	56	2	(3.6)	111	5	(4.5)	.679
Total	109	5	(4.6)	110	2	(1.8)	219	7	(3.2)	.280

RMP.B1YP.JCLLIB2(AES6JEAB)
RMP.B1YO.HCJEREP(AES6JEAB)
Gender: Patient Gender
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.55. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Gender
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE (continued)

	Flx			Placebo			Total			p-Value*
Gender	N	n	(%)	N	n	(%)	N	n	(%)	
SOMNOLENCE										
Female	54	3	(5.6)	54	0		108	3	(2.8)	.243
Male	55	2	(3.6)	56	4	(7.1)	111	6	(5.4)	.679
Total	109	5	(4.6)	110	4	(3.6)	219	9	(4.1)	.748
AGITATION										
Female	54	1	(1.9)	54	0		108	1	(0.9)	1.00
Male	55	3	(5.5)	56	0		111	3	(2.7)	.118
Total	109	4	(3.7)	110	0		219	4	(1.8)	.060

RMP.B1YP.JCLLIB2(AES6JEAB)
RMP.B1YO.HCJEREP(AES6JEAB)
Gender: Patient Gender
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.55. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Gender
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE (continued)

	Flx			Placebo			Total			p-Value*
Gender	N	n	(%)	N	n	(%)	N	n	(%)	
ALLERGIC REACTION										
Female	54	2	(3.7)	54	0		108	2	(1.9)	.495
Male	55	2	(3.6)	56	2	(3.6)	111	4	(3.6)	1.00
Total	109	4	(3.7)	110	2	(1.8)	219	6	(2.7)	.446
DYSMENORRHEA										
Female	54	4	(7.4)	54	4	(7.4)	108	8	(7.4)	1.00
Male	55	0		56	0		111	0		
Total	109	4	(3.7)	110	4	(3.6)	219	8	(3.7)	1.00

RMP.B1YP.JCLLIB2(AES6JEAB)
RMP.B1YO.HCJEREP(AES6JEAB)
Gender: Patient Gender
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.55. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Gender
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE (continued)

	Flx			Placebo			Total			p-Value*
Gender	N	n	(%)	N	n	(%)	N	n	(%)	
DYSPEPSIA										
Female	54	2	(3.7)	54	3	(5.6)	108	5	(4.6)	1.00
Male	55	2	(3.6)	56	2	(3.6)	111	4	(3.6)	1.00
Total	109	4	(3.7)	110	5	(4.5)	219	9	(4.1)	1.00
ECCHYMOSIS										
Female	54	3	(5.6)	54	1	(1.9)	108	4	(3.7)	.618
Male	55	1	(1.8)	56	1	(1.8)	111	2	(1.8)	1.00
Total	109	4	(3.7)	110	2	(1.8)	219	6	(2.7)	.446

RMP.B1YP.JCLLIB2(AES6JEAB)
RMP.B1YO.HCJEREP(AES6JEAB)
Gender: Patient Gender
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.55. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Gender
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE (continued)

	Flx			Placebo			Total			p-Value*
Gender	N	n	(%)	N	n	(%)	N	n	(%)	
FLU SYNDROME										
Female	54	2	(3.7)	54	0		108	2	(1.9)	.495
Male	55	2	(3.6)	56	3	(5.4)	111	5	(4.5)	1.00
Total	109	4	(3.7)	110	3	(2.7)	219	7	(3.2)	.721
HYPERKINESIA										
Female	54	1	(1.9)	54	0		108	1	(0.9)	1.00
Male	55	3	(5.5)	56	1	(1.8)	111	4	(3.6)	.364
Total	109	4	(3.7)	110	1	(0.9)	219	5	(2.3)	.212

RMP.B1YP.JCLLIB2(AES6JEAB)
RMP.B1YO.HCJEREP(AES6JEAB)
Gender: Patient Gender
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.55. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Gender
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE (continued)

	Flx			Placebo			Total			p-Value*
Gender	N	n	(%)	N	n	(%)	N	n	(%)	
PHOTOSENSITIVITY REACTION										
Female	54	2	(3.7)	54	0		108	2	(1.9)	.495
Male	55	2	(3.6)	56	1	(1.8)	111	3	(2.7)	.618
Total	109	4	(3.7)	110	1	(0.9)	219	5	(2.3)	.212
SINUSITIS										
Female	54	3	(5.6)	54	1	(1.9)	108	4	(3.7)	.618
Male	55	1	(1.8)	56	1	(1.8)	111	2	(1.8)	1.00
Total	109	4	(3.7)	110	2	(1.8)	219	6	(2.7)	.446

RMP.B1YP.JCLLIB2(AES6JEAB)
RMP.B1YO.HCJEREP(AES6JEAB)
Gender: Patient Gender
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.55. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Gender
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE (continued)

	Flx			Placebo			Total			p-Value*
Gender	N	n	(%)	N	n	(%)	N	n	(%)	
AKATHISIA										
Female	54	2	(3.7)	54	0		108	2	(1.9)	.495
Male	55	1	(1.8)	56	0		111	1	(0.9)	.495
Total	109	3	(2.8)	110	0		219	3	(1.4)	.122
ASTHMA										
Female	54	0		54	0		108	0		
Male	55	3	(5.5)	56	0		111	3	(2.7)	.118
Total	109	3	(2.8)	110	0		219	3	(1.4)	.122

RMP.B1YP.JCLLIB2(AES6JEAB)
RMP.B1YO.HCJEREP(AES6JEAB)
Gender: Patient Gender
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.55. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Gender
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE (continued)

	Flx			Placebo			Total			p-Value*
Gender	N	n	(%)	N	n	(%)	N	n	(%)	
CHEST PAIN										
Female	54	2	(3.7)	54	1	(1.9)	108	3	(2.8)	1.00
Male	55	1	(1.8)	56	1	(1.8)	111	2	(1.8)	1.00
Total	109	3	(2.8)	110	2	(1.8)	219	5	(2.3)	.683
CONSTIPATION										
Female	54	1	(1.9)	54	2	(3.7)	108	3	(2.8)	1.00
Male	55	2	(3.6)	56	4	(7.1)	111	6	(5.4)	.679
Total	109	3	(2.8)	110	6	(5.5)	219	9	(4.1)	.499

RMP.B1YP.JCLLIB2(AES6JEAB)
RMP.B1YO.HCJEREP(AES6JEAB)
Gender: Patient Gender
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.55. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Gender
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE (continued)

	Flx			Placebo			Total			p-Value*
Gender	N	n	(%)	N	n	(%)	N	n	(%)	
CONTACT DERMATITIS										
Female	54	0		54	0		108	0		
Male	55	3	(5.5)	56	0		111	3	(2.7)	.118
Total	109	3	(2.8)	110	0		219	3	(1.4)	.122
DEPRESSION										
Female	54	3	(5.6)	54	1	(1.9)	108	4	(3.7)	.618
Male	55	0		56	1	(1.8)	111	1	(0.9)	1.00
Total	109	3	(2.8)	110	2	(1.8)	219	5	(2.3)	.683

RMP.B1YP.JCLLIB2(AES6JEAB)
RMP.B1YO.HCJEREP(AES6JEAB)
Gender: Patient Gender
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.55. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Gender
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE (continued)

	Flx			Placebo			Total			p-Value*
Gender	N	n	(%)	N	n	(%)	N	n	(%)	
MYALGIA										
Female	54	2	(3.7)	54	3	(5.6)	108	5	(4.6)	1.00
Male	55	1	(1.8)	56	3	(5.4)	111	4	(3.6)	.618
Total	109	3	(2.8)	110	6	(5.5)	219	9	(4.1)	.499
NECK PAIN										
Female	54	2	(3.7)	54	1	(1.9)	108	3	(2.8)	1.00
Male	55	1	(1.8)	56	0		111	1	(0.9)	.495
Total	109	3	(2.8)	110	1	(0.9)	219	4	(1.8)	.369

RMP.B1YP.JCLLIB2(AES6JEAB)
RMP.B1YO.HCJEREP(AES6JEAB)
Gender: Patient Gender
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.55. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Gender
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE (continued)

	Flx			Placebo			Total			p-Value*
Gender	N	n	(%)	N	n	(%)	N	n	(%)	
SPEECH DISORDER										
Female	54	0		54	1	(1.9)	108	1	(0.9)	1.00
Male	55	3	(5.5)	56	1	(1.8)	111	4	(3.6)	.364
Total	109	3	(2.8)	110	2	(1.8)	219	5	(2.3)	.683
TREMOR										
Female	54	2	(3.7)	54	0		108	2	(1.9)	.495
Male	55	1	(1.8)	56	1	(1.8)	111	2	(1.8)	1.00
Total	109	3	(2.8)	110	1	(0.9)	219	4	(1.8)	.369

RMP.B1YP.JCLLIB2(AES6JEAB)
RMP.B1YO.HCJEREP(AES6JEAB)
Gender: Patient Gender
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.55. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Gender
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE (continued)

	Flx			Placebo			Total			p-Value*
Gender	N	n	(%)	N	n	(%)	N	n	(%)	
ACUTE BRAIN SYNDROME										
Female	54	0		54	0		108	0		
Male	55	2	(3.6)	56	0		111	2	(1.8)	.243
Total	109	2	(1.8)	110	0		219	2	(0.9)	.247
ANXIETY										
Female	54	2	(3.7)	54	0		108	2	(1.9)	.495
Male	55	0		56	0		111	0		
Total	109	2	(1.8)	110	0		219	2	(0.9)	.247

RMP.B1YP.JCLLIB2(AES6JEAB)
RMP.B1YO.HCJEREP(AES6JEAB)
Gender: Patient Gender
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.55. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Gender
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE (continued)

	Flx			Placebo			Total			p-Value*
Gender	N	n	(%)	N	n	(%)	N	n	(%)	
BRONCHITIS										
Female	54	2	(3.7)	54	2	(3.7)	108	4	(3.7)	1.00
Male	55	0		56	0		111	0		
Total	109	2	(1.8)	110	2	(1.8)	219	4	(1.8)	1.00
CHILLS										
Female	54	1	(1.9)	54	1	(1.9)	108	2	(1.9)	1.00
Male	55	1	(1.8)	56	0		111	1	(0.9)	.495
Total	109	2	(1.8)	110	1	(0.9)	219	3	(1.4)	.622

RMP.B1YP.JCLLIB2(AES6JEAB)
RMP.B1YO.HCJEREP(AES6JEAB)
Gender: Patient Gender
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.55. Treatment-Emergent Non-Solicited Adverse Events Subgroup Analysis by Gender All Randomized Patients Subchronic Treatment Phase (Study Periods III-V) B1Y-MC-HCJE (continued)

	Flx			Placebo			Total			p-Value*
Gender	N	n	(%)	N	n	(%)	N	n	(%)	
DRY SKIN										
Female	54	2	(3.7)	54	1	(1.9)	108	3	(2.8)	1.00
Male	55	0		56	2	(3.6)	111	2	(1.8)	.495
Total	109	2	(1.8)	110	3	(2.7)	219	5	(2.3)	1.00
EAR DISORDER										
Female	54	1	(1.9)	54	0		108	1	(0.9)	1.00
Male	55	1	(1.8)	56	1	(1.8)	111	2	(1.8)	1.00
Total	109	2	(1.8)	110	1	(0.9)	219	3	(1.4)	.622

RMP.B1YP.JCLLIB2(AES6JEAB)
RMP.B1YO.HCJEREP(AES6JEAB)
Gender: Patient Gender
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.55. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Gender
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE (continued)

	Flx			Placebo			Total			p-Value*
Gender	N	n	(%)	N	n	(%)	N	n	(%)	
EUPHORIA										
Female	54	1	(1.9)	54	0		108	1	(0.9)	1.00
Male	55	1	(1.8)	56	0		111	1	(0.9)	.495
Total	109	2	(1.8)	110	0		219	2	(0.9)	.247
EYE DISORDER										
Female	54	2	(3.7)	54	0		108	2	(1.9)	.495
Male	55	0		56	0		111	0		
Total	109	2	(1.8)	110	0		219	2	(0.9)	.247

RMP.B1YP.JCLLIB2(AES6JEAB)
RMP.B1YO.HCJEREP(AES6JEAB)
Gender: Patient Gender
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.55. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Gender
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE (continued)

	Flx			Placebo			Total			p-Value*
Gender	N	n	(%)	N	n	(%)	N	n	(%)	
GASTROENTERITIS										
Female	54	1	(1.9)	54	0		108	1	(0.9)	1.00
Male	55	1	(1.8)	56	0		111	1	(0.9)	.495
Total	109	2	(1.8)	110	0		219	2	(0.9)	.247
INCREASED APPETITE										
Female	54	1	(1.9)	54	1	(1.9)	108	2	(1.9)	1.00
Male	55	1	(1.8)	56	2	(3.6)	111	3	(2.7)	1.00
Total	109	2	(1.8)	110	3	(2.7)	219	5	(2.3)	1.00

RMP.B1YP.JCLLIB2(AES6JEAB)
RMP.B1YO.HCJEREP(AES6JEAB)
Gender: Patient Gender
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.55. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Gender
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE (continued)

	Flx			Placebo			Total			p-Value*
Gender	N	n	(%)	N	n	(%)	N	n	(%)	
NECK RIGIDITY										
Female	54	0		54	0		108	0		
Male	55	2	(3.6)	56	1	(1.8)	111	3	(2.7)	.618
Total	109	2	(1.8)	110	1	(0.9)	219	3	(1.4)	.622
OTITIS EXTERNA										
Female	54	1	(1.9)	54	0		108	1	(0.9)	1.00
Male	55	1	(1.8)	56	1	(1.8)	111	2	(1.8)	1.00
Total	109	2	(1.8)	110	1	(0.9)	219	3	(1.4)	.622

RMP.B1YP.JCLLIB2(AES6JEAB)
RMP.B1YO.HCJEREP(AES6JEAB)
Gender: Patient Gender
* Frequencies are analyzed using a Fisher’s Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.55. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Gender
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE (continued)

	Flx			Placebo			Total			p-Value*
Gender	N	n	(%)	N	n	(%)	N	n	(%)	
SLEEP DISORDER										
Female	54	2	(3.7)	54	0		108	2	(1.9)	.495
Male	55	0		56	0		111	0		
Total	109	2	(1.8)	110	0		219	2	(0.9)	.247
SURGICAL PROCEDURE										
Female	54	1	(1.9)	54	1	(1.9)	108	2	(1.9)	1.00
Male	55	1	(1.8)	56	1	(1.8)	111	2	(1.8)	1.00
Total	109	2	(1.8)	110	2	(1.8)	219	4	(1.8)	1.00

RMP.B1YP.JCLLIB2(AES6JEAB)
RMP.B1YO.HCJEREP(AES6JEAB)
Gender: Patient Gender
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.55. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Gender
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE (continued)

	Flx			Placebo			Total			p-Value*
Gender	N	n	(%)	N	n	(%)	N	n	(%)	
SWEATING										
Female	54	1	(1.9)	54	0		108	1	(0.9)	1.00
Male	55	1	(1.8)	56	0		111	1	(0.9)	.495
Total	109	2	(1.8)	110	0		219	2	(0.9)	.247
THINKING ABNORMAL										
Female	54	0		54	1	(1.9)	108	1	(0.9)	1.00
Male	55	2	(3.6)	56	0		111	2	(1.8)	.243
Total	109	2	(1.8)	110	1	(0.9)	219	3	(1.4)	.622

RMP.B1YP.JCLLIB2(AES6JEAB)
RMP.B1YO.HCJEREP(AES6JEAB)
Gender: Patient Gender
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.55. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Gender
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE (continued)

	Flx			Placebo			Total			p-Value*
Gender	N	n	(%)	N	n	(%)	N	n	(%)	
THIRST										
Female	54	2	(3.7)	54	1	(1.9)	108	3	(2.8)	1.00
Male	55	0		56	1	(1.8)	111	1	(0.9)	1.00
Total	109	2	(1.8)	110	2	(1.8)	219	4	(1.8)	1.00
TOOTH DISORDER										
Female	54	2	(3.7)	54	0		108	2	(1.9)	.495
Male	55	0		56	0		111	0		
Total	109	2	(1.8)	110	0		219	2	(0.9)	.247

RMP.B1YP.JCLLIB2(AES6JEAB)
RMP.B1YO.HCJEREP(AES6JEAB)
Gender: Patient Gender
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.55. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Gender
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE (continued)

	Flx			Placebo			Total			p-Value*
Gender	N	n	(%)	N	n	(%)	N	n	(%)	
WEIGHT LOSS										
Female	54	1	(1.9)	54	1	(1.9)	108	2	(1.9)	1.00
Male	55	1	(1.8)	56	0		111	1	(0.9)	.495
Total	109	2	(1.8)	110	1	(0.9)	219	3	(1.4)	.622
YAWN										
Female	54	0		54	0		108	0		
Male	55	2	(3.6)	56	0		111	2	(1.8)	.243
Total	109	2	(1.8)	110	0		219	2	(0.9)	.247

RMP.B1YP.JCLLIB2(AES6JEAB)
RMP.B1YO.HCJEREP(AES6JEAB)
Gender: Patient Gender
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.55. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Gender
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE (continued)

	Flx			Placebo			Total			p-Value*
Gender	N	n	(%)	N	n	(%)	N	n	(%)	
AMBLYOPIA										
Female	54	0		54	0		108	0		
Male	55	1	(1.8)	56	0		111	1	(0.9)	.495
Total	109	1	(0.9)	110	0		219	1	(0.5)	.498
AMNESIA										
Female	54	1	(1.9)	54	1	(1.9)	108	2	(1.9)	1.00
Male	55	0		56	0		111	0		
Total	109	1	(0.9)	110	1	(0.9)	219	2	(0.9)	1.00

RMP.B1YP.JCLLIB2(AES6JEAB)
RMP.B1YO.HCJEREP(AES6JEAB)
Gender: Patient Gender
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.55. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Gender
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE (continued)

	Flx			Placebo			Total			p-Value*
Gender	N	n	(%)	N	n	(%)	N	n	(%)	
ANEMIA										
Female	54	1	(1.9)	54	0		108	1	(0.9)	1.00
Male	55	0		56	0		111	0		
Total	109	1	(0.9)	110	0		219	1	(0.5)	.498
APATHY										
Female	54	0		54	0		108	0		
Male	55	1	(1.8)	56	0		111	1	(0.9)	.495
Total	109	1	(0.9)	110	0		219	1	(0.5)	.498

RMP.B1YP.JCLLIB2(AES6JEAB)
RMP.B1YO.HCJEREP(AES6JEAB)
Gender: Patient Gender
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.55. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Gender
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE (continued)

	Flx			Placebo			Total			p-Value*
Gender	N	n	(%)	N	n	(%)	N	n	(%)	
BRADYCARDIA										
Female	54	1	(1.9)	54	1	(1.9)	108	2	(1.9)	1.00
Male	55	0		56	0		111	0		
Total	109	1	(0.9)	110	1	(0.9)	219	2	(0.9)	1.00
BUCCOGLOSSAL SYNDROME										
Female	54	1	(1.9)	54	0		108	1	(0.9)	1.00
Male	55	0		56	0		111	0		
Total	109	1	(0.9)	110	0		219	1	(0.5)	.498

RMP.B1YP.JCLLIB2(AES6JEAB)
RMP.B1YO.HCJEREP(AES6JEAB)
Gender: Patient Gender
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.55. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Gender
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE (continued)

	Flx			Placebo			Total			p-Value*
Gender	N	n	(%)	N	n	(%)	N	n	(%)	
CARDIOVASCULAR DISORDER										
Female	54	1	(1.9)	54	0		108	1	(0.9)	1.00
Male	55	0		56	0		111	0		
Total	109	1	(0.9)	110	0		219	1	(0.5)	.498
DELUSIONS										
Female	54	0		54	0		108	0		
Male	55	1	(1.8)	56	0		111	1	(0.9)	.495
Total	109	1	(0.9)	110	0		219	1	(0.5)	.498

RMP.B1YP.JCLLIB2(AES6JEAB)
RMP.B1YO.HCJEREP(AES6JEAB)
Gender: Patient Gender
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.55. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Gender
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE (continued)

	Flx			Placebo			Total			p-Value*
Gender	N	n	(%)	N	n	(%)	N	n	(%)	
DYSPHAGIA										
Female	54	1	(1.9)	54	1	(1.9)	108	2	(1.9)	1.00
Male	55	0		56	0		111	0		
Total	109	1	(0.9)	110	1	(0.9)	219	2	(0.9)	1.00
DYSPNEA										
Female	54	1	(1.9)	54	0		108	1	(0.9)	1.00
Male	55	0		56	0		111	0		
Total	109	1	(0.9)	110	0		219	1	(0.5)	.498

RMP.B1YP.JCLLIB2(AES6JEAB)
RMP.B1YO.HCJEREP(AES6JEAB)
Gender: Patient Gender
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.55. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Gender
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE (continued)

	Flx			Placebo			Total			p-Value*
Gender	N	n	(%)	N	n	(%)	N	n	(%)	
EMOTIONAL LABILITY										
Female	54	0		54	0		108	0		
Male	55	1	(1.8)	56	0		111	1	(0.9)	.495
Total	109	1	(0.9)	110	0		219	1	(0.5)	.498
ENDOCRINE DISORDER										
Female	54	1	(1.9)	54	0		108	1	(0.9)	1.00
Male	55	0		56	0		111	0		
Total	109	1	(0.9)	110	0		219	1	(0.5)	.498

RMP.B1YP.JCLLIB2(AES6JEAB)
RMP.B1YO.HCJEREP(AES6JEAB)
Gender: Patient Gender
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.55. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Gender
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE (continued)

	Flx			Placebo			Total			p-Value*
Gender	N	n	(%)	N	n	(%)	N	n	(%)	
ENDOMETRIAL HYPERPLASIA										
Female	54	1	(1.9)	54	0		108	1	(0.9)	1.00
Male	55	0		56	0		111	0		
Total	109	1	(0.9)	110	0		219	1	(0.5)	.498
EYE PAIN										
Female	54	0		54	0		108	0		
Male	55	1	(1.8)	56	0		111	1	(0.9)	.495
Total	109	1	(0.9)	110	0		219	1	(0.5)	.498

RMP.B1YP.JCLLIB2(AES6JEAB)
RMP.B1YO.HCJEREP(AES6JEAB)
Gender: Patient Gender
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.55. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Gender
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE (continued)

	Flx			Placebo			Total			p-Value*
Gender	N	n	(%)	N	n	(%)	N	n	(%)	
FECAL INCONTINENCE										
Female	54	0		54	0		108	0		
Male	55	1	(1.8)	56	0		111	1	(0.9)	.495
Total	109	1	(0.9)	110	0		219	1	(0.5)	.498
FLATULENCE										
Female	54	0		54	0		108	0		
Male	55	1	(1.8)	56	0		111	1	(0.9)	.495
Total	109	1	(0.9)	110	0		219	1	(0.5)	.498

RMP.B1YP.JCLLIB2(AES6JEAB)
RMP.B1YO.HCJEREP(AES6JEAB)
Gender: Patient Gender
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.55. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Gender
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE (continued)

	Flx			Placebo			Total			p-Value*
Gender	N	n	(%)	N	n	(%)	N	n	(%)	
FUNGAL DERMATITIS										
Female	54	0		54	1	(1.9)	108	1	(0.9)	1.00
Male	55	1	(1.8)	56	0		111	1	(0.9)	.495
Total	109	1	(0.9)	110	1	(0.9)	219	2	(0.9)	1.00
GASTROINTESTINAL DISORDER										
Female	54	1	(1.9)	54	1	(1.9)	108	2	(1.9)	1.00
Male	55	0		56	0		111	0		
Total	109	1	(0.9)	110	1	(0.9)	219	2	(0.9)	1.00

RMP.B1YP.JCLLIB2(AES6JEAB)
RMP.B1YO.HCJEREP(AES6JEAB)
Gender: Patient Gender
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.55. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Gender
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE (continued)

	Flx			Placebo			Total			p-Value*
Gender	N	n	(%)	N	n	(%)	N	n	(%)	
HALLUCINATIONS										
Female	54	0		54	0		108	0		
Male	55	1	(1.8)	56	0		111	1	(0.9)	.495
Total	109	1	(0.9)	110	0		219	1	(0.5)	.498
HEPATITIS NONSPECIFIC										
Female	54	0		54	0		108	0		
Male	55	1	(1.8)	56	0		111	1	(0.9)	.495
Total	109	1	(0.9)	110	0		219	1	(0.5)	.498

RMP.B1YP.JCLLIB2(AES6JEAB)
RMP.B1YO.HCJEREP(AES6JEAB)
Gender: Patient Gender
* Frequencies are analyzed using a Fisher’s Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.55. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Gender
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE (continued)

	Flx			Placebo			Total			p-Value*
Gender	N	n	(%)	N	n	(%)	N	n	(%)	
HEPATOMEGALY										
Female	54	0		54	1	(1.9)	108	1	(0.9)	1.00
Male	55	1	(1.8)	56	0		111	1	(0.9)	.495
Total	109	1	(0.9)	110	1	(0.9)	219	2	(0.9)	1.00
HERPES SIMPLEX										
Female	54	1	(1.9)	54	0		108	1	(0.9)	1.00
Male	55	0		56	0		111	0		
Total	109	1	(0.9)	110	0		219	1	(0.5)	.498

RMP.B1YP.JCLLIB2(AES6JEAB)
RMP.B1YO.HCJEREP(AES6JEAB)
Gender: Patient Gender
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.55. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Gender
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE (continued)

	Flx			Placebo			Total			p-Value*
Gender	N	n	(%)	N	n	(%)	N	n	(%)	
HYPERCHOLESTEREMIA										
Female	54	0		54	0		108	0		
Male	55	1	(1.8)	56	0		111	1	(0.9)	.495
Total	109	1	(0.9)	110	0		219	1	(0.5)	.498
HYPERTONIA										
Female	54	1	(1.9)	54	1	(1.9)	108	2	(1.9)	1.00
Male	55	0		56	0		111	0		
Total	109	1	(0.9)	110	1	(0.9)	219	2	(0.9)	1.00

RMP.B1YP.JCLLIB2(AES6JEAB)
RMP.B1YO.HCJEREP(AES6JEAB)
Gender: Patient Gender
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.55. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Gender
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE (continued)

	Flx			Placebo			Total			p-Value*
Gender	N	n	(%)	N	n	(%)	N	n	(%)	
HYPOTENSION										
Female	54	0		54	0		108	0		
Male	55	1	(1.8)	56	0		111	1	(0.9)	.495
Total	109	1	(0.9)	110	0		219	1	(0.5)	.498
INCREASED SALIVATION										
Female	54	0		54	1	(1.9)	108	1	(0.9)	1.00
Male	55	1	(1.8)	56	0		111	1	(0.9)	.495
Total	109	1	(0.9)	110	1	(0.9)	219	2	(0.9)	1.00

RMP.B1YP.JCLLIB2(AES6JEAB)
RMP.B1YO.HCJEREP(AES6JEAB)
Gender: Patient Gender
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.55. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Gender
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE (continued)

	Flx			Placebo			Total			p-Value*
Gender	N	n	(%)	N	n	(%)	N	n	(%)	
INTENTIONAL INJURY										
Female	54	1	(1.9)	54	0		108	1	(0.9)	1.00
Male	55	0		56	1	(1.8)	111	1	(0.9)	1.00
Total	109	1	(0.9)	110	1	(0.9)	219	2	(0.9)	1.00
JOINT DISORDER										
Female	54	0		54	0		108	0		
Male	55	1	(1.8)	56	0		111	1	(0.9)	.495
Total	109	1	(0.9)	110	0		219	1	(0.5)	.498

RMP.B1YP.JCLLIB2(AES6JEAB)
RMP.B1YO.HCJEREP(AES6JEAB)
Gender: Patient Gender
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.55. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Gender
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE (continued)

	Flx			Placebo			Total			p-Value*
Gender	N	n	(%)	N	n	(%)	N	n	(%)	
LARYNGITIS										
Female	54	0		54	1	(1.9)	108	1	(0.9)	1.00
Male	55	1	(1.8)	56	0		111	1	(0.9)	.495
Total	109	1	(0.9)	110	1	(0.9)	219	2	(0.9)	1.00
LEG CRAMPS										
Female	54	0		54	1	(1.9)	108	1	(0.9)	1.00
Male	55	1	(1.8)	56	2	(3.6)	111	3	(2.7)	1.00
Total	109	1	(0.9)	110	3	(2.7)	219	4	(1.8)	.622

RMP.B1YP.JCLLIB2(AES6JEAB)
RMP.B1YO.HCJEREP(AES6JEAB)
Gender: Patient Gender
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.55. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Gender
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE (continued)

	Flx			Placebo			Total			p-Value*
Gender	N	n	(%)	N	n	(%)	N	n	(%)	
LEUKOPENIA										
Female	54	1	(1.9)	54	0		108	1	(0.9)	1.00
Male	55	0		56	0		111	0		
Total	109	1	(0.9)	110	0		219	1	(0.5)	.498
LUNG DISORDER										
Female	54	0		54	0		108	0		
Male	55	1	(1.8)	56	0		111	1	(0.9)	.495
Total	109	1	(0.9)	110	0		219	1	(0.5)	.498

RMP.B1YP.JCLLIB2(AES6JEAB)
RMP.B1YO.HCJEREP(AES6JEAB)
Gender: Patient Gender
* Frequencies are analyzed using a Fisher’s Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.55. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Gender
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE (continued)

	Flx			Placebo			Total			p-Value*
Gender	N	n	(%)	N	n	(%)	N	n	(%)	
LYMPHADENOPATHY										
Female	54	1	(1.9)	54	1	(1.9)	108	2	(1.9)	1.00
Male	55	0		56	0		111	0		
Total	109	1	(0.9)	110	1	(0.9)	219	2	(0.9)	1.00
MACULOPAPULAR RASH										
Female	54	0		54	0		108	0		
Male	55	1	(1.8)	56	1	(1.8)	111	2	(1.8)	1.00
Total	109	1	(0.9)	110	1	(0.9)	219	2	(0.9)	1.00

RMP.B1YP.JCLLIB2(AES6JEAB)
RMP.B1YO.HCJEREP(AES6JEAB)
Gender: Patient Gender
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.55. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Gender
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE (continued)

	Flx			Placebo			Total			p-Value*
Gender	N	n	(%)	N	n	(%)	N	n	(%)	
MANIC REACTION										
Female	54	0		54	0		108	0		
Male	55	1	(1.8)	56	0		111	1	(0.9)	.495
Total	109	1	(0.9)	110	0		219	1	(0.5)	.498
MIGRAINE										
Female	54	1	(1.9)	54	1	(1.9)	108	2	(1.9)	1.00
Male	55	0		56	0		111	0		
Total	109	1	(0.9)	110	1	(0.9)	219	2	(0.9)	1.00

RMP.B1YP.JCLLIB2(AES6JEAB)
RMP.B1YO.HCJEREP(AES6JEAB)
Gender: Patient Gender
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.55. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Gender
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE (continued)

	Flx			Placebo			Total			p-Value*
Gender	N	n	(%)	N	n	(%)	N	n	(%)	
NEUROSIS										
Female	54	1	(1.9)	54	0		108	1	(0.9)	1.00
Male	55	0		56	0		111	0		
Total	109	1	(0.9)	110	0		219	1	(0.5)	.498
OTITIS MEDIA										
Female	54	0		54	0		108	0		
Male	55	1	(1.8)	56	0		111	1	(0.9)	.495
Total	109	1	(0.9)	110	0		219	1	(0.5)	.498

RMP.B1YP.JCLLIB2(AES6JEAB)
RMP.B1YO.HCJEREP(AES6JEAB)
Gender: Patient Gender
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.55. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Gender
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE (continued)

	Flx			Placebo			Total			p-Value*
Gender	N	n	(%)	N	n	(%)	N	n	(%)	
OVERDOSE										
Female	54	0		54	1	(1.9)	108	1	(0.9)	1.00
Male	55	1	(1.8)	56	0		111	1	(0.9)	.495
Total	109	1	(0.9)	110	1	(0.9)	219	2	(0.9)	1.00
PALPITATION										
Female	54	1	(1.9)	54	1	(1.9)	108	2	(1.9)	1.00
Male	55	0		56	0		111	0		
Total	109	1	(0.9)	110	1	(0.9)	219	2	(0.9)	1.00

RMP.B1YP.JCLLIB2(AES6JEAB)
RMP.B1YO.HCJEREP(AES6JEAB)
Gender: Patient Gender
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.55. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Gender
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE (continued)

	Flx			Placebo			Total			p-Value*
Gender	N	n	(%)	N	n	(%)	N	n	(%)	
PNEUMONIA										
Female	54	0		54	0		108	0		
Male	55	1	(1.8)	56	0		111	1	(0.9)	.495
Total	109	1	(0.9)	110	0		219	1	(0.5)	.498
RECTAL HEMORRHAGE										
Female	54	1	(1.9)	54	0		108	1	(0.9)	1.00
Male	55	0		56	0		111	0		
Total	109	1	(0.9)	110	0		219	1	(0.5)	.498

RMP.B1YP.JCLLIB2(AES6JEAB)
RMP.B1YO.HCJEREP(AES6JEAB)
Gender: Patient Gender
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.55. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Gender
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE (continued)

	Flx			Placebo			Total			p-Value*
Gender	N	n	(%)	N	n	(%)	N	n	(%)	
SINUS BRADYCARDIA										
Female	54	0		54	0		108	0		
Male	55	1	(1.8)	56	0		111	1	(0.9)	.495
Total	109	1	(0.9)	110	0		219	1	(0.5)	.498
SYNCOPE										
Female	54	0		54	0		108	0		
Male	55	1	(1.8)	56	0		111	1	(0.9)	.495
Total	109	1	(0.9)	110	0		219	1	(0.5)	.498

RMP.B1YP.JCLLIB2(AES6JEAB)
RMP.B1YO.HCJEREP(AES6JEAB)
Gender: Patient Gender
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.55. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Gender
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE (continued)

	Flx			Placebo			Total			p-Value*
Gender	N	n	(%)	N	n	(%)	N	n	(%)	
TACHYCARDIA										
Female	54	0		54	0		108	0		
Male	55	1	(1.8)	56	0		111	1	(0.9)	.495
Total	109	1	(0.9)	110	0		219	1	(0.5)	.498
THYROID DISORDER										
Female	54	1	(1.9)	54	0		108	1	(0.9)	1.00
Male	55	0		56	0		111	0		
Total	109	1	(0.9)	110	0		219	1	(0.5)	.498

RMP.B1YP.JCLLIB2(AES6JEAB)
RMP.B1YO.HCJEREP(AES6JEAB)
Gender: Patient Gender
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.55. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Gender
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE (continued)

	Flx			Placebo			Total			p-Value*
Gender	N	n	(%)	N	n	(%)	N	n	(%)	
TINNITUS										
Female	54	1	(1.9)	54	0		108	1	(0.9)	1.00
Male	55	0		56	0		111	0		
Total	109	1	(0.9)	110	0		219	1	(0.5)	.498
ULCERATIVE STOMATITIS										
Female	54	0		54	0		108	0		
Male	55	1	(1.8)	56	0		111	1	(0.9)	.495
Total	109	1	(0.9)	110	0		219	1	(0.5)	.498

RMP.B1YP.JCLLIB2(AES6JEAB)
RMP.B1YO.HCJEREP(AES6JEAB)
Gender: Patient Gender
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.55. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Gender
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE (continued)

	Flx			Placebo			Total			p-Value*
Gender	N	n	(%)	N	n	(%)	N	n	(%)	
URINARY FREQUENCY										
Female	54	1	(1.9)	54	1	(1.9)	108	2	(1.9)	1.00
Male	55	0		56	1	(1.8)	111	1	(0.9)	1.00
Total	109	1	(0.9)	110	2	(1.8)	219	3	(1.4)	1.00
URINARY TRACT INFECTION										
Female	54	0		54	1	(1.9)	108	1	(0.9)	1.00
Male	55	1	(1.8)	56	0		111	1	(0.9)	.495
Total	109	1	(0.9)	110	1	(0.9)	219	2	(0.9)	1.00

RMP.B1YP.JCLLIB2(AES6JEAB)
RMP.B1YO.HCJEREP(AES6JEAB)
Gender: Patient Gender
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.55. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Gender
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE (continued)

	Flx			Placebo			Total			p-Value*
Gender	N	n	(%)	N	n	(%)	N	n	(%)	
VASODILATATION										
Female	54	1	(1.9)	54	0		108	1	(0.9)	1.00
Male	55	0		56	0		111	0		
Total	109	1	(0.9)	110	0		219	1	(0.5)	.498
VESICULOBULLOUS RASH										
Female	54	0		54	0		108	0		
Male	55	1	(1.8)	56	0		111	1	(0.9)	.495
Total	109	1	(0.9)	110	0		219	1	(0.5)	.498

RMP.B1YP.JCLLIB2(AES6JEAB)
RMP.B1YO.HCJEREP(AES6JEAB)
Gender: Patient Gender
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.55. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Gender
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE (continued)

	Flx			Placebo			Total			p-Value*
Gender	N	n	(%)	N	n	(%)	N	n	(%)	
ABDOMINAL SYNDROME ACUTE										
Female	54	0		54	0		108	0		
Male	55	0		56	1	(1.8)	111	1	(0.9)	1.00
Total	109	0		110	1	(0.9)	219	1	(0.5)	1.00
ACNE										
Female	54	0		54	1	(1.9)	108	1	(0.9)	1.00
Male	55	0		56	0		111	0		
Total	109	0		110	1	(0.9)	219	1	(0.5)	1.00

RMP.B1YP.JCLLIB2(AES6JEAB)
RMP.B1YO.HCJEREP(AES6JEAB)
Gender: Patient Gender
* Frequencies are analyzed using a Fisher’s Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.55. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Gender
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE (continued)

	Flx			Placebo			Total			p-Value*
Gender	N	n	(%)	N	n	(%)	N	n	(%)	
ALOPECIA										
Female	54	0		54	1	(1.9)	108	1	(0.9)	1.00
Male	55	0		56	0		111	0		
Total	109	0		110	1	(0.9)	219	1	(0.5)	1.00
APHTHOUS STOMATITIS										
Female	54	0		54	1	(1.9)	108	1	(0.9)	1.00
Male	55	0		56	0		111	0		
Total	109	0		110	1	(0.9)	219	1	(0.5)	1.00

RMP.B1YP.JCLLIB2(AES6JEAB)
RMP.B1YO.HCJEREP(AES6JEAB)
Gender: Patient Gender
* Frequencies are analyzed using a Fisher’s Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.55. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Gender
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE (continued)

	Flx			Placebo			Total			p-Value*
Gender	N	n	(%)	N	n	(%)	N	n	(%)	
ARTHRALGIA										
Female	54	0		54	0		108	0		
Male	55	0		56	1	(1.8)	111	1	(0.9)	1.00
Total	109	0		110	1	(0.9)	219	1	(0.5)	1.00
BILIRUBINURIA										
Female	54	0		54	1	(1.9)	108	1	(0.9)	1.00
Male	55	0		56	0		111	0		
Total	109	0		110	1	(0.9)	219	1	(0.5)	1.00

RMP.B1YP.JCLLIB2(AES6JEAB)
RMP.B1YO.HCJEREP(AES6JEAB)
Gender: Patient Gender
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.55. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Gender
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE (continued)

	Flx			Placebo			Total			p-Value*
Gender	N	n	(%)	N	n	(%)	N	n	(%)	
CYSTITIS										
Female	54	0		54	1	(1.9)	108	1	(0.9)	1.00
Male	55	0		56	0		111	0		
Total	109	0		110	1	(0.9)	219	1	(0.5)	1.00
DEHYDRATION										
Female	54	0		54	1	(1.9)	108	1	(0.9)	1.00
Male	55	0		56	1	(1.8)	111	1	(0.9)	1.00
Total	109	0		110	2	(1.8)	219	2	(0.9)	.498

RMP.B1YP.JCLLIB2(AES6JEAB)
RMP.B1YO.HCJEREP(AES6JEAB)
Gender: Patient Gender
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.55. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Gender
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE (continued)

	Flx			Placebo			Total			p-Value*
Gender	N	n	(%)	N	n	(%)	N	n	(%)	
DYSURIA										
Female	54	0		54	1	(1.9)	108	1	(0.9)	1.00
Male	55	0		56	0		111	0		
Total	109	0		110	1	(0.9)	219	1	(0.5)	1.00
FACE EDEMA										
Female	54	0		54	1	(1.9)	108	1	(0.9)	1.00
Male	55	0		56	0		111	0		
Total	109	0		110	1	(0.9)	219	1	(0.5)	1.00

RMP.B1YP.JCLLIB2(AES6JEAB)
RMP.B1YO.HCJEREP(AES6JEAB)
Gender: Patient Gender
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.55. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Gender
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE (continued)

	Flx			Placebo			Total			p-Value*
Gender	N	n	(%)	N	n	(%)	N	n	(%)	
HYPESTHESIA										
Female	54	0		54	1	(1.9)	108	1	(0.9)	1.00
Male	55	0		56	0		111	0		
Total	109	0		110	1	(0.9)	219	1	(0.5)	1.00
HYPOVENTILATION										
Female	54	0		54	0		108	0		
Male	55	0		56	1	(1.8)	111	1	(0.9)	1.00
Total	109	0		110	1	(0.9)	219	1	(0.5)	1.00

RMP.B1YP.JCLLIB2(AES6JEAB)
RMP.B1YO.HCJEREP(AES6JEAB)
Gender: Patient Gender
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.55. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Gender
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE (continued)

	Flx			Placebo			Total			p-Value*
Gender	N	n	(%)	N	n	(%)	N	n	(%)	
LEUKORRHEA										
Female	54	0		54	1	(1.9)	108	1	(0.9)	1.00
Male	55	0		56	0		111	0		
Total	109	0		110	1	(0.9)	219	1	(0.5)	1.00
LYMPHOCYTOSIS										
Female	54	0		54	1	(1.9)	108	1	(0.9)	1.00
Male	55	0		56	0		111	0		
Total	109	0		110	1	(0.9)	219	1	(0.5)	1.00

RMP.B1YP.JCLLIB2(AES6JEAB)
RMP.B1YO.HCJEREP(AES6JEAB)
Gender: Patient Gender
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.55. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Gender
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE (continued)

	Flx			Placebo			Total			p-Value*
Gender	N	n	(%)	N	n	(%)	N	n	(%)	
MENORRHAGIA										
Female	54	0		54	1	(1.9)	108	1	(0.9)	1.00
Male	55	0		56	0		111	0		
Total	109	0		110	1	(0.9)	219	1	(0.5)	1.00
METRORRHAGIA										
Female	54	0		54	1	(1.9)	108	1	(0.9)	1.00
Male	55	0		56	0		111	0		
Total	109	0		110	1	(0.9)	219	1	(0.5)	1.00

RMP.B1YP.JCLLIB2(AES6JEAB)
RMP.B1YO.HCJEREP(AES6JEAB)
Gender: Patient Gender
* Frequencies are analyzed using a Fisher’s Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.55. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Gender
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE (continued)

	Flx			Placebo			Total			p-Value*
Gender	N	n	(%)	N	n	(%)	N	n	(%)	
MOUTH ULCERATION										
Female	54	0		54	0		108	0		
Male	55	0		56	1	(1.8)	111	1	(0.9)	1.00
Total	109	0		110	1	(0.9)	219	1	(0.5)	1.00
PUSTULAR RASH										
Female	54	0		54	1	(1.9)	108	1	(0.9)	1.00
Male	55	0		56	0		111	0		
Total	109	0		110	1	(0.9)	219	1	(0.5)	1.00

RMP.B1YP.JCLLIB2(AES6JEAB)
RMP.B1YO.HCJEREP(AES6JEAB)
Gender: Patient Gender
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.55. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Gender
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE (continued)

	Flx			Placebo			Total			p-Value*
Gender	N	n	(%)	N	n	(%)	N	n	(%)	
SKIN DISCOLORATION										
Female	54	0		54	1	(1.9)	108	1	(0.9)	1.00
Male	55	0		56	0		111	0		
Total	109	0		110	1	(0.9)	219	1	(0.5)	1.00
SKIN ULCER										
Female	54	0		54	1	(1.9)	108	1	(0.9)	1.00
Male	55	0		56	0		111	0		
Total	109	0		110	1	(0.9)	219	1	(0.5)	1.00

RMP.B1YP.JCLLIB2(AES6JEAB)
RMP.B1YO.HCJEREP(AES6JEAB)
Gender: Patient Gender
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.55. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Gender
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE (continued)

	Flx			Placebo			Total			p-Value*
Gender	N	n	(%)	N	n	(%)	N	n	(%)	
SPLENOMEGALY										
Female	54	0		54	1	(1.9)	108	1	(0.9)	1.00
Male	55	0		56	0		111	0		
Total	109	0		110	1	(0.9)	219	1	(0.5)	1.00
SUBCUTANEOUS NODULE										
Female	54	0		54	0		108	0		
Male	55	0		56	1	(1.8)	111	1	(0.9)	1.00
Total	109	0		110	1	(0.9)	219	1	(0.5)	1.00

RMP.B1YP.JCLLIB2(AES6JEAB)
RMP.B1YO.HCJEREP(AES6JEAB)
Gender: Patient Gender
* Frequencies are analyzed using a Fisher’s Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.55. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Gender
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE (continued)

	Flx			Placebo			Total			p-Value*
Gender	N	n	(%)	N	n	(%)	N	n	(%)	
UNEXPECTED BENEFIT										
Female	54	0		54	1	(1.9)	108	1	(0.9)	1.00
Male	55	0		56	0		111	0		
Total	109	0		110	1	(0.9)	219	1	(0.5)	1.00
VERTIGO										
Female	54	0		54	1	(1.9)	108	1	(0.9)	1.00
Male	55	0		56	0		111	0		
Total	109	0		110	1	(0.9)	219	1	(0.5)	1.00

RMP.B1YP.JCLLIB2(AES6JEAB)
RMP.B1YO.HCJEREP(AES6JEAB)
Gender: Patient Gender
* Frequencies are analyzed using a Fisher’s Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.55. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Gender
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE (concluded)

	Flx			Placebo			Total			p-Value*
Gender	N	n	(%)	N	n	(%)	N	n	(%)	
WEIGHT GAIN										
Female	54	0		54	1	(1.9)	108	1	(0.9)	1.00
Male	55	0		56	0		111	0		
Total	109	0		110	1	(0.9)	219	1	(0.5)	1.00

RMP.B1YP.JCLLIB2(AES6JEAB)
RMP.B1YO.HCJEREP(AES6JEAB)
Gender: Patient Gender
* Frequencies are analyzed using a Fisher’s Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.56 presents the incidence of treatment-emergent solicited adverse events from the Side-Effects Checklist examined by gender subgroups for the subchronic treatment phase.

The Breslow-Day test detected a trend towards a significant difference in odds ratios across genders for headache (p=.082). Differences were not detected for any other event. The between-group comparison was significant for females (p=.020) for the event headache, with fluoxetine-treated females (57%) reporting the event more frequently than placebo-treated females (33%). There were no differences detected between treatment groups in males for headache. The between-group comparison was significant (p=.026) for difficulty pronouncing words, with placebo-treated males reporting the event more frequently (34%) than fluoxetine-treated males (15%). There were no differences detected between treatment groups in females for difficulty pronouncing words.

Table 14.56. Treatment-Emergent Solicited Adverse Events
Side Effects Checklist Subgroup Analysis by Gender
Significant (p<.05) Difference in Odds Ratio
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE

SECL Event - Have you had trouble with:	GENDER	Flx N	Flx n	Flx (%)	Placebo N	Placebo n	Placebo (%)	p-Values: Homogeneity of Odds Ratio p-Value*	p-Values: Between Group Comparison p-Value**
01. EATING	Female	54	22	(40.7)	54	22	(40.7)	.447	1.00
	Male	55	12	(21.8)	56	17	(30.4)		.388
02. DRINKING	Female	54	11	(20.4)	54	11	(20.4)	.301	1.00
	Male	55	5	(9.1)	56	10	(17.9)		.267
03. DRY MOUTH AND LIPS	Female	54	20	(37.0)	54	21	(38.9)	.398	1.00
	Male	55	14	(25.5)	56	21	(37.5)		.221
04. WETNESS IN MOUTH	Female	54	5	(9.3)	54	15	(27.8)	.266	.024
	Male	55	6	(10.9)	56	9	(16.1)		.580
05. CONSTIPATION	Female	54	6	(11.1)	54	6	(11.1)	.552	1.00
	Male	55	5	(9.1)	56	8	(14.3)		.557
06. DIARRHEA	Female	54	15	(27.8)	54	10	(18.5)	.435	.362
	Male	55	13	(23.6)	56	13	(23.2)		1.00
07. STOMACHACHES	Female	54	25	(46.3)	54	24	(44.4)	.727	1.00
	Male	55	23	(41.8)	56	25	(44.6)		.849

* The homogeneity of odds ratio p-Value is derived from the Breslow-Day test.
**The between group comparison within strata p-Value is from the Fisher's Exact Test.
Treatment-Emergent Solicited = was present at baseline and worsened as defined by increase in score on the side-effects checklist or new occurrence after baseline.
RMP.B1YP.SASPGM(CUSJESG1)
RMP.B1YO.HCJEREP(CUSTJEMQ)

Table 14.56. Treatment-Emergent Solicited Adverse Events
Side Effects Checklist Subgroup Analysis by Gender
Significant (p<.05) Difference in Odds Ratio
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE (continued)

SECL Event - Have you had trouble with:	GENDER	Flx N	Flx n	Flx (%)	Placebo N	Placebo n	Placebo (%)	p-Values: Homogeneity of Odds Ratio p-Value*	p-Values: Between Group Comparison p-Value**
08. MUSCLE CRAMPS	Female	54	19	(35.2)	54	19	(35.2)	.352	1.00
	Male	55	16	(29.1)	56	23	(41.1)		.234
09. BEING SICK TO YOUR STOMACH	Female	54	24	(44.4)	54	21	(38.9)	.941	.696
	Male	55	20	(36.4)	56	18	(32.1)		.692
10. WETTING THE BED	Female	54	1	(1.9)	54	2	(3.7)	.843	1.00
	Male	55	2	(3.6)	56	3	(5.4)		1.00
11. URINATING	Female	54	6	(11.1)	54	10	(18.5)	.334	.417
	Male	55	4	(7.3)	56	3	(5.4)		.716
12. ITCHY OR SCRATCHY SKIN	Female	54	20	(37.0)	54	19	(35.2)	.374	1.00
	Male	55	12	(21.8)	56	17	(30.4)		.388
13. RASHES	Female	54	13	(24.1)	54	14	(25.9)	.273	1.00
	Male	55	5	(9.1)	56	11	(19.6)		.176
14. COLD OR SNIFFLES	Female	54	26	(48.1)	54	32	(59.3)	.309	.335
	Male	55	25	(45.5)	56	24	(42.9)		.849

* The homogeneity of odds ratio p-Value is derived from the Breslow-Day test.
**The between group comparison within strata p-Value is from the Fisher's Exact Test.
Treatment-Emergent Solicited = was present at baseline and worsened as defined by increase in score on the side-effects checklist or new occurrence after baseline.
RMP.B1YP.SASPGM(CUSJESG1)
RMP.B1YO.HCJEREP(CUSTJEMQ)

Table 14.56. Treatment-Emergent Solicited Adverse Events
Side Effects Checklist Subgroup Analysis by Gender
Significant (p<.05) Difference in Odds Ratio
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE (continued)

SECL Event - Have you had trouble with:	GENDER	Flx N	Flx n	Flx (%)	Placebo N	Placebo n	Placebo (%)	p-Values: Homogeneity of Odds Ratio p-Value*	p-Values: Between Group Comparison p-Value**
15. HEADACHE	Female	54	31	(57.4)	54	18	(33.3)	.082	.020
	Male	55	26	(47.3)	56	26	(46.4)		1.00
16. DIZZINESS	Female	54	24	(44.4)	54	18	(33.3)	.450	.324
	Male	55	14	(25.5)	56	14	(25.0)		1.00
17. PLAYING SPORTS	Female	54	8	(14.8)	54	10	(18.5)	.680	.797
	Male	55	11	(20.0)	56	11	(19.6)		1.00
18. SHAKINESS	Female	54	16	(29.6)	54	14	(25.9)	.804	.830
	Male	55	10	(18.2)	56	10	(17.9)		1.00
19. PRONOUNCING WORDS	Female	54	10	(18.5)	54	14	(25.9)	.312	.488
	Male	55	8	(14.5)	56	19	(33.9)		.026
20. DOING THINGS WITH YOUR HANDS	Female	54	9	(16.7)	54	12	(22.2)	.450	.628
	Male	55	6	(10.9)	56	13	(23.2)		.129
21. SITTING STILL	Female	54	15	(27.8)	54	17	(31.5)	.580	.833
	Male	55	19	(34.5)	56	26	(46.4)		.247

* The homogeneity of odds ratio p-Value is derived from the Breslow-Day test.
**The between group comparison within strata p-Value is from the Fisher's Exact Test.
Treatment-Emergent Solicited = was present at baseline and worsened as defined by increase in score on the side-effects checklist or new occurrence after baseline.
RMP.B1YP.SASPGM(CUSJESG1)
RMP.B1YO.HCJEREP(CUSTJEMQ)

Table 14.56. Treatment-Emergent Solicited Adverse Events
Side Effects Checklist Subgroup Analysis by Gender
Significant (p<.05) Difference in Odds Ratio
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE (continued)

SECL Event - Have you had trouble with:	GENDER	Flx N	Flx n	Flx (%)	Placebo N	Placebo n	Placebo (%)	p-Values: Homogeneity of Odds Ratio p-Value*	p-Values: Between Group Comparison p-Value**
22. TIREDNESS	Female	54	30	(55.6)	54	24	(44.4)	.531	.336
	Male	55	25	(45.5)	56	24	(42.9)		.849
23. FEELING SLEEPY	Female	54	31	(57.4)	54	27	(50.0)	.934	.563
	Male	55	25	(45.5)	56	22	(39.3)		.567
24. SLEEPING	Female	54	24	(44.4)	54	24	(44.4)	.535	1.00
	Male	55	21	(38.2)	56	26	(46.4)		.444
25. BAD DREAMS	Female	54	17	(31.5)	54	23	(42.6)	.317	.319
	Male	55	13	(23.6)	56	12	(21.4)		.823
26. GETTING ALONG WITH PARENTS	Female	54	26	(48.1)	54	23	(42.6)	.724	.699
	Male	55	25	(45.5)	56	25	(44.6)		1.00
27. GETTING ALONG WITH KIDS	Female	54	14	(25.9)	54	15	(27.8)	.633	1.00
	Male	55	20	(36.4)	56	18	(32.1)		.692
28. CRYING	Female	54	25	(46.3)	54	25	(46.3)	.636	1.00
	Male	55	22	(40.0)	56	19	(33.9)		.558

* The homogeneity of odds ratio p-Value is derived from the Breslow-Day test.
**The between group comparison within strata p-Value is from the Fisher’s Exact Test.
Treatment-Emergent Solicited = was present at baseline and worsened as defined by increase in score on the side-effects checklist or new occurrence after baseline.
RMP.B1YP.SASPGM(CUSJESG1)
RMP.B1YO.HCJEREP(CUSTJEMQ)

Table 14.56. Treatment-Emergent Solicited Adverse Events
Side Effects Checklist Subgroup Analysis by Gender
Significant (p<.05) Difference in Odds Ratio
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE (concluded)

SECL Event - Have you had trouble with:	GENDER	Flx N	Flx n	Flx (%)	Placebo N	Placebo n	Placebo (%)	p-Values: Homogeneity of Odds Ratio p-Value*	p-Values: Between Group Comparison p-Value**
29. GETTING MAD	Female	54	25	(46.3)	54	25	(46.3)	.446	1.00
	Male	55	20	(36.4)	56	26	(46.4)		.337
30. NOT BEING HAPPY	Female	54	24	(44.4)	54	19	(35.2)	.520	.432
	Male	55	20	(36.4)	56	20	(35.7)		1.00
31. BEING SAD	Female	54	23	(42.6)	54	20	(37.0)	.446	.694
	Male	55	24	(43.6)	56	16	(28.6)		.116
32. PAYING ATTENTION	Female	54	23	(42.6)	54	18	(33.3)	.977	.428
	Male	55	24	(43.6)	56	19	(33.9)		.333

* The homogeneity of odds ratio p-Value is derived from the Breslow-Day test.
**The between group comparison within strata p-Value is from the Fisher's Exact Test.
Treatment-Emergent Solicited = was present at baseline and worsened as defined by increase in score on the side-effects checklist or new occurrence after baseline.
RMP.B1YP.SASPGM(CUSJESG1)
RMP.B1YO.HCJEREP(CUSTJEMQ)

14.3.2.2.3. By Family History of Depression

Table 14.57 presents the incidence of treatment-emergent non-solicited adverse events analyzed by family history of depression subgroups for the subchronic treatment phase.

There was a statistically significant difference between treatment groups in the number of patients with a negative family history of depression reporting treatment-emergent non-solicited adverse events (p=.035) and a trend for patients with a positive family history of depression (p=.075). Overall, more fluoxetine-treated patients with a negative family history (93%) reported at least one treatment-emergent non-solicited adverse event than placebo-treated patients with a negative family history (74%). Despite the overall difference in reporting frequencies, there were no statistically significant differences between family history of depression subgroups for any individual treatment-emergent non-solicited adverse event.

Table 14.57. Treatment-Emergent Non-Solicited Adverse Events Subgroup Analysis by Family History of Depression All Randomized Patients Subchronic Treatment Phase (Study Periods III-V) B1Y-MC-HCJE

DEPRESSION (Visit: 1)	Flx N	Flx n (%)	Placebo N	Placebo n (%)	Total N	Total n (%)	p-Value*
PATIENTS WITH >= 1 TESS							
NO	41	38 (92.7)	39	29 (74.4)	80	67 (83.8)	.035
YES	61	58 (95.1)	60	51 (85.0)	121	109 (90.1)	.075
Total	102	96 (94.1)	99	80 (80.8)	201	176 (87.6)	.005
PATIENTS WITH NO TESS							
NO	41	3 (7.3)	39	10 (25.6)	80	13 (16.3)	.035
YES	61	3 (4.9)	60	9 (15.0)	121	12 (9.9)	.075
Total	102	6 (5.9)	99	19 (19.2)	201	25 (12.4)	.005

RMP.B1YP.JCLLIB2(AES6JEAF)
RMP.B1YO.HCJEREP(AES6JEAF)
DEPRESSION: FAMILY DEPRESSION (Visit: 1)
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.57. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Family History of Depression
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE (continued)

DEPRESSION (Visit: 1)	Flx N	Flx n (%)	Placebo N	Placebo n (%)	Total N	Total n (%)	p-Value*
HEADACHE							
NO	41	15 (36.6)	39	8 (20.5)	80	23 (28.8)	.141
YES	61	20 (32.8)	60	12 (20.0)	121	32 (26.4)	.149
Total	102	35 (34.3)	99	20 (20.2)	201	55 (27.4)	.028
RHINITIS							
NO	41	14 (34.1)	39	6 (15.4)	80	20 (25.0)	.071
YES	61	19 (31.1)	60	20 (33.3)	121	39 (32.2)	.847
Total	102	33 (32.4)	99	26 (26.3)	201	59 (29.4)	.357

RMP.B1YP.JCLLIB2(AES6JEAF)
RMP.B1YO.HCJEREP(AES6JEAF)
DEPRESSION: FAMILY DEPRESSION (Visit: 1)
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.57. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Family History of Depression
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE (continued)

DEPRESSION (Visit: 1)	Flx N	Flx n (%)	Placebo N	Placebo n (%)	Total N	Total n (%)	p-Value*
ABDOMINAL PAIN							
NO	41	8 (19.5)	39	10 (25.6)	80	18 (22.5)	.597
YES	61	12 (19.7)	60	11 (18.3)	121	23 (19.0)	1.00
Total	102	20 (19.6)	99	21 (21.2)	201	41 (20.4)	.862
PHARYNGITIS							
NO	41	7 (17.1)	39	4 (10.3)	80	11 (13.8)	.520
YES	61	13 (21.3)	60	7 (11.7)	121	20 (16.5)	.221
Total	102	20 (19.6)	99	11 (11.1)	201	31 (15.4)	.119

RMP.B1YP.JCLLIB2(AES6JEAF)
RMP.B1YO.HCJEREP(AES6JEAF)
DEPRESSION: FAMILY DEPRESSION (Visit: 1)
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.57. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Family History of Depression
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE (continued)

DEPRESSION (Visit: 1)	Flx N	Flx n (%)	Placebo N	Placebo n (%)	Total N	Total n (%)	p-Value*
ACCIDENTAL INJURY							
NO	41	4 (9.8)	39	0	80	4 (5.0)	.116
YES	61	13 (21.3)	60	10 (16.7)	121	23 (19.0)	.644
Total	102	17 (16.7)	99	10 (10.1)	201	27 (13.4)	.216
COUGH INCREASED							
NO	41	6 (14.6)	39	3 (7.7)	80	9 (11.3)	.483
YES	61	8 (13.1)	60	5 (8.3)	121	13 (10.7)	.559
Total	102	14 (13.7)	99	8 (8.1)	201	22 (10.9)	.260

RMP.B1YP.JCLLIB2(AES6JEAF)
RMP.B1YO.HCJEREP(AES6JEAF)
DEPRESSION: FAMILY DEPRESSION (Visit: 1)
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.57. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Family History of Depression
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE (continued)

DEPRESSION (Visit: 1)	Flx N	Flx n (%)	Placebo N	Placebo n (%)	Total N	Total n (%)	p-Value*
DIARRHEA							
NO	41	9 (22.0)	39	6 (15.4)	80	15 (18.8)	.570
YES	61	4 (6.6)	60	6 (10.0)	121	10 (8.3)	.529
Total	102	13 (12.7)	99	12 (12.1)	201	25 (12.4)	1.00
RASH							
NO	41	5 (12.2)	39	4 (10.3)	80	9 (11.3)	1.00
YES	61	8 (13.1)	60	6 (10.0)	121	14 (11.6)	.777
Total	102	13 (12.7)	99	10 (10.1)	201	23 (11.4)	.659

RMP.B1YP.JCLLIB2(AES6JEAF)
RMP.B1YO.HCJEREP(AES6JEAF)
DEPRESSION: FAMILY DEPRESSION (Visit: 1)
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.57. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Family History of Depression
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE (continued)

DEPRESSION (Visit: 1)	Flx N	Flx n (%)	Placebo N	Placebo n (%)	Total N	Total n (%)	p-Value*
DIZZINESS							
NO	41	5 (12.2)	39	6 (15.4)	80	11 (13.8)	.753
YES	61	6 (9.8)	60	1 (1.7)	121	7 (5.8)	.114
Total	102	11 (10.8)	99	7 (7.1)	201	18 (9.0)	.461
NERVOUSNESS							
NO	41	4 (9.8)	39	1 (2.6)	80	5 (6.3)	.360
YES	61	7 (11.5)	60	4 (6.7)	121	11 (9.1)	.529
Total	102	11 (10.8)	99	5 (5.1)	201	16 (8.0)	.192

RMP.B1YP.JCLLIB2(AES6JEAF)
RMP.B1YO.HCJEREP(AES6JEAF)
DEPRESSION: FAMILY DEPRESSION (Visit: 1)
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.57. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Family History of Depression
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE (continued)

DEPRESSION (Visit: 1)	Flx N	Flx n (%)	Placebo N	Placebo n (%)	Total N	Total n (%)	p-Value*
VOMITING							
NO	41	3 (7.3)	39	5 (12.8)	80	8 (10.0)	.476
YES	61	8 (13.1)	60	6 (10.0)	121	14 (11.6)	.777
Total	102	11 (10.8)	99	11 (11.1)	201	22 (10.9)	1.00
ANOREXIA							
NO	41	4 (9.8)	39	5 (12.8)	80	9 (11.3)	.734
YES	61	6 (9.8)	60	2 (3.3)	121	8 (6.6)	.272
Total	102	10 (9.8)	99	7 (7.1)	201	17 (8.5)	.614

RMP.B1YP.JCLLIB2(AES6JEAF)
RMP.B1YO.HCJEREP(AES6JEAF)
DEPRESSION: FAMILY DEPRESSION (Visit: 1)
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.57. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Family History of Depression
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE (continued)

DEPRESSION (Visit: 1)	Flx N	Flx n (%)	Placebo N	Placebo n (%)	Total N	Total n (%)	p-Value*
ASTHENIA							
NO	41	3 (7.3)	39	2 (5.1)	80	5 (6.3)	1.00
YES	61	7 (11.5)	60	4 (6.7)	121	11 (9.1)	.529
Total	102	10 (9.8)	99	6 (6.1)	201	16 (8.0)	.436
FEVER							
NO	41	4 (9.8)	39	3 (7.7)	80	7 (8.8)	1.00
YES	61	6 (9.8)	60	4 (6.7)	121	10 (8.3)	.743
Total	102	10 (9.8)	99	7 (7.1)	201	17 (8.5)	.614

RMP.B1YP.JCLLIB2(AES6JEAF)
RMP.B1YO.HCJEREP(AES6JEAF)
DEPRESSION: FAMILY DEPRESSION (Visit: 1)
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.57. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Family History of Depression
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE (continued)

DEPRESSION (Visit: 1)	Flx N	Flx n (%)	Placebo N	Placebo n (%)	Total N	Total n (%)	p-Value*
PAIN							
NO	41	4 (9.8)	39	3 (7.7)	80	7 (8.8)	1.00
YES	61	6 (9.8)	60	7 (11.7)	121	13 (10.7)	.777
Total	102	10 (9.8)	99	10 (10.1)	201	20 (10.0)	1.00
NAUSEA							
NO	41	6 (14.6)	39	5 (12.8)	80	11 (13.8)	1.00
YES	61	2 (3.3)	60	5 (8.3)	121	7 (5.8)	.272
Total	102	8 (7.8)	99	10 (10.1)	201	18 (9.0)	.628

RMP.B1YP.JCLLIB2(AES6JEAF)
RMP.B1YO.HCJEREP(AES6JEAF)
DEPRESSION: FAMILY DEPRESSION (Visit: 1)
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.57. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Family History of Depression
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE (continued)

DEPRESSION (Visit: 1)	Flx N	Flx n	Flx (%)	Placebo N	Placebo n	Placebo (%)	Total N	Total n	Total (%)	p-Value*
ABNORMAL DREAMS										
NO	41	1	(2.4)	39	2	(5.1)	80	3	(3.8)	.611
YES	61	6	(9.8)	60	1	(1.7)	121	7	(5.8)	.114
Total	102	7	(6.9)	99	3	(3.0)	201	10	(5.0)	.332
EAR PAIN										
NO	41	4	(9.8)	39	0		80	4	(5.0)	.116
YES	61	2	(3.3)	60	1	(1.7)	121	3	(2.5)	1.00
Total	102	6	(5.9)	99	1	(1.0)	201	7	(3.5)	.119

RMP.B1YP.JCLLIB2(AES6JEAF)
RMP.B1YO.HCJEREP(AES6JEAF)
DEPRESSION: FAMILY DEPRESSION (Visit: 1)
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.57. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Family History of Depression
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE (continued)

DEPRESSION (Visit: 1)	Flx N	Flx n	Flx (%)	Placebo N	Placebo n	Placebo (%)	Total N	Total n	Total (%)	p-Value*
INSOMNIA										
NO	41	4	(9.8)	39	1	(2.6)	80	5	(6.3)	.360
YES	61	2	(3.3)	60	4	(6.7)	121	6	(5.0)	.439
Total	102	6	(5.9)	99	5	(5.1)	201	11	(5.5)	1.00
BACK PAIN										
NO	41	1	(2.4)	39	2	(5.1)	80	3	(3.8)	.611
YES	61	4	(6.6)	60	1	(1.7)	121	5	(4.1)	.365
Total	102	5	(4.9)	99	3	(3.0)	201	8	(4.0)	.721

RMP.B1YP.JCLLIB2(AES6JEAF)
RMP.B1YO.HCJEREP(AES6JEAF)
DEPRESSION: FAMILY DEPRESSION (Visit: 1)
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.57. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Family History of Depression
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE (continued)

DEPRESSION (Visit: 1)	Flx N	Flx n	Flx (%)	Placebo N	Placebo n	Placebo (%)	Total N	Total n	Total (%)	p-Value*
DRY MOUTH										
NO	41	2	(4.9)	39	4	(10.3)	80	6	(7.5)	.426
YES	61	3	(4.9)	60	2	(3.3)	121	5	(4.1)	1.00
Total	102	5	(4.9)	99	6	(6.1)	201	11	(5.5)	.765
EPISTAXIS										
NO	41	2	(4.9)	39	0		80	2	(2.5)	.494
YES	61	3	(4.9)	60	2	(3.3)	121	5	(4.1)	1.00
Total	102	5	(4.9)	99	2	(2.0)	201	7	(3.5)	.445

RMP.B1YP.JCLLIB2(AES6JEAF)
RMP.B1YO.HCJEREP(AES6JEAF)
DEPRESSION: FAMILY DEPRESSION (Visit: 1)
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.57. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Family History of Depression
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE (continued)

DEPRESSION (Visit: 1)	Flx N	Flx n	Flx (%)	Placebo N	Placebo n	Placebo (%)	Total N	Total n	Total (%)	p-Value*
HOSTILITY										
NO	41	2	(4.9)	39	2	(5.1)	80	4	(5.0)	1.00
YES	61	3	(4.9)	60	3	(5.0)	121	6	(5.0)	1.00
Total	102	5	(4.9)	99	5	(5.1)	201	10	(5.0)	1.00
PERSONALITY DISORDER										
NO	41	3	(7.3)	39	1	(2.6)	80	4	(5.0)	.616
YES	61	2	(3.3)	60	1	(1.7)	121	3	(2.5)	1.00
Total	102	5	(4.9)	99	2	(2.0)	201	7	(3.5)	.445

RMP.B1YP.JCLLIB2(AES6JEAF)
RMP.B1YO.HCJEREP(AES6JEAF)
DEPRESSION: FAMILY DEPRESSION (Visit: 1)
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.57. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Family History of Depression
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE (continued)

DEPRESSION (Visit: 1)	Flx N	Flx n	Flx (%)	Placebo N	Placebo n	Placebo (%)	Total N	Total n	Total (%)	p-Value*
PRURITUS										
NO	41	1	(2.4)	39	1	(2.6)	80	2	(2.5)	1.00
YES	61	4	(6.6)	60	5	(8.3)	121	9	(7.4)	.743
Total	102	5	(4.9)	99	6	(6.1)	201	11	(5.5)	.765
SOMNOLENCE										
NO	41	1	(2.4)	39	0		80	1	(1.3)	1.00
YES	61	4	(6.6)	60	4	(6.7)	121	8	(6.6)	1.00
Total	102	5	(4.9)	99	4	(4.0)	201	9	(4.5)	1.00

RMP.B1YP.JCLLIB2(AES6JEAF)
RMP.B1YO.HCJEREP(AES6JEAF)
DEPRESSION: FAMILY DEPRESSION (Visit: 1)
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.57. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Family History of Depression
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE (continued)

DEPRESSION (Visit: 1)	Flx N	Flx n	Flx (%)	Placebo N	Placebo n	Placebo (%)	Total N	Total n	Total (%)	p-Value*
AGITATION										
NO	41	2	(4.9)	39	0		80	2	(2.5)	.494
YES	61	2	(3.3)	60	0		121	2	(1.7)	.496
Total	102	4	(3.9)	99	0		201	4	(2.0)	.121
ALLERGIC REACTION										
NO	41	0		39	0		80	0		
YES	61	4	(6.6)	60	2	(3.3)	121	6	(5.0)	.680
Total	102	4	(3.9)	99	2	(2.0)	201	6	(3.0)	.683

RMP.B1YP.JCLLIB2(AES6JEAF)
RMP.B1YO.HCJEREP(AES6JEAF)
DEPRESSION: FAMILY DEPRESSION (Visit: 1)
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.57. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Family History of Depression
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE (continued)

DEPRESSION (Visit: 1)	Flx N	Flx n	Flx (%)	Placebo N	Placebo n	Placebo (%)	Total N	Total n	Total (%)	p-Value*
DYSMENORRHEA										
NO	41	4	(9.8)	39	1	(2.6)	80	5	(6.3)	.360
YES	61	0		60	2	(3.3)	121	2	(1.7)	.244
Total	102	4	(3.9)	99	3	(3.0)	201	7	(3.5)	1.00
DYSPEPSIA										
NO	41	2	(4.9)	39	1	(2.6)	80	3	(3.8)	1.00
YES	61	2	(3.3)	60	3	(5.0)	121	5	(4.1)	.680
Total	102	4	(3.9)	99	4	(4.0)	201	8	(4.0)	1.00

RMP.B1YP.JCLLIB2(AES6JEAF)
RMP.B1YO.HCJEREP(AES6JEAF)
DEPRESSION: FAMILY DEPRESSION (Visit: 1)
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.57. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Family History of Depression
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE (continued)

DEPRESSION (Visit: 1)	Flx N	Flx n	Flx (%)	Placebo N	Placebo n	Placebo (%)	Total N	Total n	Total (%)	p-Value*
ECCHYMOSIS										
NO	41	1	(2.4)	39	0		80	1	(1.3)	1.00
YES	61	3	(4.9)	60	1	(1.7)	121	4	(3.3)	.619
Total	102	4	(3.9)	99	1	(1.0)	201	5	(2.5)	.369
FLU SYNDROME										
NO	41	1	(2.4)	39	0		80	1	(1.3)	1.00
YES	61	3	(4.9)	60	3	(5.0)	121	6	(5.0)	1.00
Total	102	4	(3.9)	99	3	(3.0)	201	7	(3.5)	1.00

RMP.B1YP.JCLLIB2(AES6JEAF)
RMP.B1YO.HCJEREP(AES6JEAF)
DEPRESSION: FAMILY DEPRESSION (Visit: 1)
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.57. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Family History of Depression
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE (continued)

DEPRESSION (Visit: 1)	Flx N	Flx n	Flx (%)	Placebo N	Placebo n	Placebo (%)	Total N	Total n	Total (%)	p-Value*
HYPERKINESIA										
NO	41	1	(2.4)	39	0		80	1	(1.3)	1.00
YES	61	3	(4.9)	60	1	(1.7)	121	4	(3.3)	.619
Total	102	4	(3.9)	99	1	(1.0)	201	5	(2.5)	.369
INFECTION										
NO	41	1	(2.4)	39	1	(2.6)	80	2	(2.5)	1.00
YES	61	3	(4.9)	60	2	(3.3)	121	5	(4.1)	1.00
Total	102	4	(3.9)	99	3	(3.0)	201	7	(3.5)	1.00

RMP.B1YP.JCLLIB2(AES6JEAF)
RMP.B1YO.HCJEREP(AES6JEAF)
DEPRESSION: FAMILY DEPRESSION (Visit: 1)
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.57. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Family History of Depression
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE (continued)

DEPRESSION (Visit: 1)	Flx N	Flx n	Flx (%)	Placebo N	Placebo n	Placebo (%)	Total N	Total n	Total (%)	p-Value*
PHOTOSENSITIVITY REACTION										
NO	41	2	(4.9)	39	0		80	2	(2.5)	.494
YES	61	2	(3.3)	60	1	(1.7)	121	3	(2.5)	1.00
Total	102	4	(3.9)	99	1	(1.0)	201	5	(2.5)	.369
SINUSITIS										
NO	41	0		39	1	(2.6)	80	1	(1.3)	.488
YES	61	4	(6.6)	60	1	(1.7)	121	5	(4.1)	.365
Total	102	4	(3.9)	99	2	(2.0)	201	6	(3.0)	.683

RMP.B1YP.JCLLIB2(AES6JEAF)
RMP.B1YO.HCJEREP(AES6JEAF)
DEPRESSION: FAMILY DEPRESSION (Visit: 1)
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.57. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Family History of Depression
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE (continued)

DEPRESSION (Visit: 1)	Flx N	Flx n	Flx (%)	Placebo N	Placebo n	Placebo (%)	Total N	Total n	Total (%)	p-Value*
AKATHISIA										
NO	41	3	(7.3)	39	0		80	3	(3.8)	.241
YES	61	0		60	0		121	0		
Total	102	3	(2.9)	99	0		201	3	(1.5)	.246
ASTHMA										
NO	41	2	(4.9)	39	0		80	2	(2.5)	.494
YES	61	1	(1.6)	60	0		121	1	(0.8)	1.00
Total	102	3	(2.9)	99	0		201	3	(1.5)	.246

RMP.B1YP.JCLLIB2(AES6JEAF)
RMP.B1YO.HCJEREP(AES6JEAF)
DEPRESSION: FAMILY DEPRESSION (Visit: 1)
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.57. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Family History of Depression
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE (continued)

DEPRESSION (Visit: 1)	Flx N	Flx n	Flx (%)	Placebo N	Placebo n	Placebo (%)	Total N	Total n	Total (%)	p-Value*
CHEST PAIN										
NO	41	1	(2.4)	39	0		80	1	(1.3)	1.00
YES	61	2	(3.3)	60	2	(3.3)	121	4	(3.3)	1.00
Total	102	3	(2.9)	99	2	(2.0)	201	5	(2.5)	1.00
CONSTIPATION										
NO	41	2	(4.9)	39	1	(2.6)	80	3	(3.8)	1.00
YES	61	1	(1.6)	60	4	(6.7)	121	5	(4.1)	.207
Total	102	3	(2.9)	99	5	(5.1)	201	8	(4.0)	.494

RMP.B1YP.JCLLIB2(AES6JEAF)
RMP.B1YO.HCJEREP(AES6JEAF)
DEPRESSION: FAMILY DEPRESSION (Visit: 1)
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.57. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Family History of Depression
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE (continued)

DEPRESSION (Visit: 1)	Flx N	Flx n	Flx (%)	Placebo N	Placebo n	Placebo (%)	Total N	Total n	Total (%)	p-Value*
CONTACT DERMATITIS										
NO	41	1	(2.4)	39	0		80	1	(1.3)	1.00
YES	61	2	(3.3)	60	0		121	2	(1.7)	.496
Total	102	3	(2.9)	99	0		201	3	(1.5)	.246
DEPRESSION										
NO	41	1	(2.4)	39	0		80	1	(1.3)	1.00
YES	61	2	(3.3)	60	2	(3.3)	121	4	(3.3)	1.00
Total	102	3	(2.9)	99	2	(2.0)	201	5	(2.5)	1.00

RMP.B1YP.JCLLIB2(AES6JEAF)
RMP.B1YO.HCJEREP(AES6JEAF)
DEPRESSION: FAMILY DEPRESSION (Visit: 1)
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.57. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Family History of Depression
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE (continued)

DEPRESSION (Visit: 1)	Flx N	Flx n	Flx (%)	Placebo N	Placebo n	Placebo (%)	Total N	Total n	Total (%)	p-Value*
MYALGIA										
NO	41	1	(2.4)	39	0		80	1	(1.3)	1.00
YES	61	2	(3.3)	60	4	(6.7)	121	6	(5.0)	.439
Total	102	3	(2.9)	99	4	(4.0)	201	7	(3.5)	.718
NECK PAIN										
NO	41	1	(2.4)	39	1	(2.6)	80	2	(2.5)	1.00
YES	61	2	(3.3)	60	0		121	2	(1.7)	.496
Total	102	3	(2.9)	99	1	(1.0)	201	4	(2.0)	.621

RMP.B1YP.JCLLIB2(AES6JEAF)
RMP.B1YO.HCJEREP(AES6JEAF)
DEPRESSION: FAMILY DEPRESSION (Visit: 1)
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.57. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Family History of Depression
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE (continued)

DEPRESSION (Visit: 1)	Flx N	Flx n	Flx (%)	Placebo N	Placebo n	Placebo (%)	Total N	Total n	Total (%)	p-Value*
SPEECH DISORDER										
NO	41	1	(2.4)	39	1	(2.6)	80	2	(2.5)	1.00
YES	61	2	(3.3)	60	0		121	2	(1.7)	.496
Total	102	3	(2.9)	99	1	(1.0)	201	4	(2.0)	.621
TREMOR										
NO	41	2	(4.9)	39	0		80	2	(2.5)	.494
YES	61	1	(1.6)	60	1	(1.7)	121	2	(1.7)	1.00
Total	102	3	(2.9)	99	1	(1.0)	201	4	(2.0)	.621

RMP.B1YP.JCLLIB2(AES6JEAF)
RMP.B1YO.HCJEREP(AES6JEAF)
DEPRESSION: FAMILY DEPRESSION (Visit: 1)
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.57. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Family History of Depression
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE (continued)

DEPRESSION (Visit: 1)	Flx N	Flx n	Flx (%)	Placebo N	Placebo n	Placebo (%)	Total N	Total n	Total (%)	p-Value*
ACUTE BRAIN SYNDROME										
NO	41	0		39	0		80	0		
YES	61	2	(3.3)	60	0		121	2	(1.7)	.496
Total	102	2	(2.0)	99	0		201	2	(1.0)	.498
ANXIETY										
NO	41	1	(2.4)	39	0		80	1	(1.3)	1.00
YES	61	1	(1.6)	60	0		121	1	(0.8)	1.00
Total	102	2	(2.0)	99	0		201	2	(1.0)	.498

RMP.B1YP.JCLLIB2(AES6JEAF)
RMP.B1YO.HCJEREP(AES6JEAF)
DEPRESSION: FAMILY DEPRESSION (Visit: 1)
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.57. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Family History of Depression
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE (continued)

DEPRESSION (Visit: 1)	Flx N	Flx n	Flx (%)	Placebo N	Placebo n	Placebo (%)	Total N	Total n	Total (%)	p-Value*
BRONCHITIS										
NO	41	1	(2.4)	39	2	(5.1)	80	3	(3.8)	.611
YES	61	1	(1.6)	60	0		121	1	(0.8)	1.00
Total	102	2	(2.0)	99	2	(2.0)	201	4	(2.0)	1.00
CHILLS										
NO	41	1	(2.4)	39	1	(2.6)	80	2	(2.5)	1.00
YES	61	1	(1.6)	60	0		121	1	(0.8)	1.00
Total	102	2	(2.0)	99	1	(1.0)	201	3	(1.5)	1.00

RMP.B1YP.JCLLIB2(AES6JEAF)
RMP.B1YO.HCJEREP(AES6JEAF)
DEPRESSION: FAMILY DEPRESSION (Visit: 1)
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.57. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Family History of Depression
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE (continued)

DEPRESSION (Visit: 1)	Flx N	Flx n	Flx (%)	Placebo N	Placebo n	Placebo (%)	Total N	Total n	Total (%)	p-Value*
DRY SKIN										
NO	41	0		39	1	(2.6)	80	1	(1.3)	.488
YES	61	2	(3.3)	60	1	(1.7)	121	3	(2.5)	1.00
Total	102	2	(2.0)	99	2	(2.0)	201	4	(2.0)	1.00
EAR DISORDER										
NO	41	0		39	0		80	0		
YES	61	2	(3.3)	60	0		121	2	(1.7)	.496
Total	102	2	(2.0)	99	0		201	2	(1.0)	.498

RMP.B1YP.JCLLIB2(AES6JEAF)
RMP.B1YO.HCJEREP(AES6JEAF)
DEPRESSION: FAMILY DEPRESSION (Visit: 1)
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.57. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Family History of Depression
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE (continued)

DEPRESSION (Visit: 1)	Flx N	Flx n	Flx (%)	Placebo N	Placebo n	Placebo (%)	Total N	Total n	Total (%)	p-Value*
EUPHORIA										
NO	41	0		39	0		80	0		
YES	61	2	(3.3)	60	0		121	2	(1.7)	.496
Total	102	2	(2.0)	99	0		201	2	(1.0)	.498
EYE DISORDER										
NO	41	0		39	0		80	0		
YES	61	2	(3.3)	60	0		121	2	(1.7)	.496
Total	102	2	(2.0)	99	0		201	2	(1.0)	.498

RMP.B1YP.JCLLIB2(AES6JEAF)
RMP.B1YO.HCJEREP(AES6JEAF)
DEPRESSION: FAMILY DEPRESSION (Visit: 1)
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.57. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Family History of Depression
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE (continued)

DEPRESSION (Visit: 1)	Flx N	Flx n	Flx (%)	Placebo N	Placebo n	Placebo (%)	Total N	Total n	Total (%)	p-Value*
GASTROENTERITIS										
NO	41	1	(2.4)	39	0		80	1	(1.3)	1.00
YES	61	1	(1.6)	60	0		121	1	(0.8)	1.00
Total	102	2	(2.0)	99	0		201	2	(1.0)	.498
NECK RIGIDITY										
NO	41	0		39	0		80	0		
YES	61	2	(3.3)	60	1	(1.7)	121	3	(2.5)	1.00
Total	102	2	(2.0)	99	1	(1.0)	201	3	(1.5)	1.00

RMP.B1YP.JCLLIB2(AES6JEAF)
RMP.B1YO.HCJEREP(AES6JEAF)
DEPRESSION: FAMILY DEPRESSION (Visit: 1)
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.57. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Family History of Depression
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE (continued)

DEPRESSION (Visit: 1)	Flx N	Flx n	Flx (%)	Placebo N	Placebo n	Placebo (%)	Total N	Total n	Total (%)	p-Value*
OTITIS EXTERNA										
NO	41	1	(2.4)	39	1	(2.6)	80	2	(2.5)	1.00
YES	61	1	(1.6)	60	0		121	1	(0.8)	1.00
Total	102	2	(2.0)	99	1	(1.0)	201	3	(1.5)	1.00
SLEEP DISORDER										
NO	41	1	(2.4)	39	0		80	1	(1.3)	1.00
YES	61	1	(1.6)	60	0		121	1	(0.8)	1.00
Total	102	2	(2.0)	99	0		201	2	(1.0)	.498

RMP.B1YP.JCLLIB2(AES6JEAF)
RMP.B1YO.HCJEREP(AES6JEAF)
DEPRESSION: FAMILY DEPRESSION (Visit: 1)
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.57. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Family History of Depression
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE (continued)

DEPRESSION (Visit: 1)	Flx N	Flx n	Flx (%)	Placebo N	Placebo n	Placebo (%)	Total N	Total n	Total (%)	p-Value*
SURGICAL PROCEDURE										
NO	41	2	(4.9)	39	0		80	2	(2.5)	.494
YES	61	0		60	2	(3.3)	121	2	(1.7)	.244
Total	102	2	(2.0)	99	2	(2.0)	201	4	(2.0)	1.00
SWEATING										
NO	41	2	(4.9)	39	0		80	2	(2.5)	.494
YES	61	0		60	0		121	0		
Total	102	2	(2.0)	99	0		201	2	(1.0)	.498

RMP.B1YP.JCLLIB2(AES6JEAF)
RMP.B1YO.HCJEREP(AES6JEAF)
DEPRESSION: FAMILY DEPRESSION (Visit: 1)
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.57. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Family History of Depression
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE (continued)

DEPRESSION (Visit: 1)	Flx N	Flx n	Flx (%)	Placebo N	Placebo n	Placebo (%)	Total N	Total n	Total (%)	p-Value*
THINKING ABNORMAL										
NO	41	0		39	1	(2.6)	80	1	(1.3)	.488
YES	61	2	(3.3)	60	0		121	2	(1.7)	.496
Total	102	2	(2.0)	99	1	(1.0)	201	3	(1.5)	1.00
THIRST										
NO	41	2	(4.9)	39	1	(2.6)	80	3	(3.8)	1.00
YES	61	0		60	1	(1.7)	121	1	(0.8)	.496
Total	102	2	(2.0)	99	2	(2.0)	201	4	(2.0)	1.00

RMP.B1YP.JCLLIB2(AES6JEAF)
RMP.B1YO.HCJEREP(AES6JEAF)
DEPRESSION: FAMILY DEPRESSION (Visit: 1)
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.57. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Family History of Depression
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE (continued)

DEPRESSION (Visit: 1)	Flx N	Flx n	Flx (%)	Placebo N	Placebo n	Placebo (%)	Total N	Total n	Total (%)	p-Value*
TOOTH DISORDER										
NO	41	0		39	0		80	0		
YES	61	2	(3.3)	60	0		121	2	(1.7)	.496
Total	102	2	(2.0)	99	0		201	2	(1.0)	.498
YAWN										
NO	41	0		39	0		80	0		
YES	61	2	(3.3)	60	0		121	2	(1.7)	.496
Total	102	2	(2.0)	99	0		201	2	(1.0)	.498

RMP.B1YP.JCLLIB2(AES6JEAF)
RMP.B1YO.HCJEREP(AES6JEAF)
DEPRESSION: FAMILY DEPRESSION (Visit: 1)
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.57. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Family History of Depression
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE (continued)

DEPRESSION (Visit: 1)	Flx N	Flx n	Flx (%)	Placebo N	Placebo n	Placebo (%)	Total N	Total n	Total (%)	p-Value*
AMBLYOPIA										
NO	41	0		39	0		80	0		
YES	61	1	(1.6)	60	0		121	1	(0.8)	1.00
Total	102	1	(1.0)	99	0		201	1	(0.5)	1.00
AMNESIA										
NO	41	0		39	0		80	0		
YES	61	1	(1.6)	60	0		121	1	(0.8)	1.00
Total	102	1	(1.0)	99	0		201	1	(0.5)	1.00

RMP.B1YP.JCLLIB2(AES6JEAF)
RMP.B1YO.HCJEREP(AES6JEAF)
DEPRESSION: FAMILY DEPRESSION (Visit: 1)
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.57. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Family History of Depression
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE (continued)

DEPRESSION (Visit: 1)	Flx N	Flx n	Flx (%)	Placebo N	Placebo n	Placebo (%)	Total N	Total n	Total (%)	p-Value*
ANEMIA										
NO	41	1	(2.4)	39	0		80	1	(1.3)	1.00
YES	61	0		60	0		121	0		
Total	102	1	(1.0)	99	0		201	1	(0.5)	1.00
BRADYCARDIA										
NO	41	0		39	0		80	0		
YES	61	1	(1.6)	60	0		121	1	(0.8)	1.00
Total	102	1	(1.0)	99	0		201	1	(0.5)	1.00

RMP.B1YP.JCLLIB2(AES6JEAF)
RMP.B1YO.HCJEREP(AES6JEAF)
DEPRESSION: FAMILY DEPRESSION (Visit: 1)
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.57. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Family History of Depression
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE (continued)

DEPRESSION (Visit: 1)	Flx N	Flx n	Flx (%)	Placebo N	Placebo n	Placebo (%)	Total N	Total n	Total (%)	p-Value*
BUCCOGLOSSAL SYNDROME										
NO	41	0		39	0		80	0		
YES	61	1	(1.6)	60	0		121	1	(0.8)	1.00
Total	102	1	(1.0)	99	0		201	1	(0.5)	1.00
CARDIOVASCULAR DISORDER										
NO	41	0		39	0		80	0		
YES	61	1	(1.6)	60	0		121	1	(0.8)	1.00
Total	102	1	(1.0)	99	0		201	1	(0.5)	1.00

RMP.B1YP.JCLLIB2(AES6JEAF)
RMP.B1YO.HCJEREP(AES6JEAF)
DEPRESSION: FAMILY DEPRESSION (Visit: 1)
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.57. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Family History of Depression
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE (continued)

DEPRESSION (Visit: 1)	Flx N	Flx n	Flx (%)	Placebo N	Placebo n	Placebo (%)	Total N	Total n	Total (%)	p-Value*
DELUSIONS										
NO	41	1	(2.4)	39	0		80	1	(1.3)	1.00
YES	61	0		60	0		121	0		
Total	102	1	(1.0)	99	0		201	1	(0.5)	1.00
DYSPHAGIA										
NO	41	0		39	0		80	0		
YES	61	1	(1.6)	60	1	(1.7)	121	2	(1.7)	1.00
Total	102	1	(1.0)	99	1	(1.0)	201	2	(1.0)	1.00

RMP.B1YP.JCLLIB2(AES6JEAF)
RMP.B1YO.HCJEREP(AES6JEAF)
DEPRESSION: FAMILY DEPRESSION (Visit: 1)
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.57. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Family History of Depression
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE (continued)

DEPRESSION (Visit: 1)	Flx N	Flx n	Flx (%)	Placebo N	Placebo n	Placebo (%)	Total N	Total n	Total (%)	p-Value*
DYSPNEA										
NO	41	0		39	0		80	0		
YES	61	1	(1.6)	60	0		121	1	(0.8)	1.00
Total	102	1	(1.0)	99	0		201	1	(0.5)	1.00
EMOTIONAL LABILITY										
NO	41	1	(2.4)	39	0		80	1	(1.3)	1.00
YES	61	0		60	0		121	0		
Total	102	1	(1.0)	99	0		201	1	(0.5)	1.00

RMP.B1YP.JCLLIB2(AES6JEAF)
RMP.B1YO.HCJEREP(AES6JEAF)
DEPRESSION: FAMILY DEPRESSION (Visit: 1)
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.57. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Family History of Depression
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE (continued)

DEPRESSION (Visit: 1)	Flx N	Flx n	Flx (%)	Placebo N	Placebo n	Placebo (%)	Total N	Total n	Total (%)	p-Value*
ENDOCRINE DISORDER										
NO	41	1	(2.4)	39	0		80	1	(1.3)	1.00
YES	61	0		60	0		121	0		
Total	102	1	(1.0)	99	0		201	1	(0.5)	1.00
ENDOMETRIAL HYPERPLASIA										
NO	41	1	(2.4)	39	0		80	1	(1.3)	1.00
YES	61	0		60	0		121	0		
Total	102	1	(1.0)	99	0		201	1	(0.5)	1.00

RMP.B1YP.JCLLIB2(AES6JEAF)
RMP.B1YO.HCJEREP(AES6JEAF)
DEPRESSION: FAMILY DEPRESSION (Visit: 1)
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.57. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Family History of Depression
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE (continued)

DEPRESSION (Visit: 1)	Flx N	Flx n	Flx (%)	Placebo N	Placebo n	Placebo (%)	Total N	Total n	Total (%)	p-Value*
FLATULENCE										
NO	41	1	(2.4)	39	0		80	1	(1.3)	1.00
YES	61	0		60	0		121	0		
Total	102	1	(1.0)	99	0		201	1	(0.5)	1.00
FUNGAL DERMATITIS										
NO	41	0		39	1	(2.6)	80	1	(1.3)	.488
YES	61	1	(1.6)	60	0		121	1	(0.8)	1.00
Total	102	1	(1.0)	99	1	(1.0)	201	2	(1.0)	1.00

RMP.B1YP.JCLLIB2(AES6JEAF)
RMP.B1YO.HCJEREP(AES6JEAF)
DEPRESSION: FAMILY DEPRESSION (Visit: 1)
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.57. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Family History of Depression
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE (continued)

DEPRESSION (Visit: 1)	Flx N	Flx n	Flx (%)	Placebo N	Placebo n	Placebo (%)	Total N	Total n	Total (%)	p-Value*
GASTROINTESTINAL DISORDER										
NO	41	0		39	0		80	0		
YES	61	1	(1.6)	60	1	(1.7)	121	2	(1.7)	1.00
Total	102	1	(1.0)	99	1	(1.0)	201	2	(1.0)	1.00
HALLUCINATIONS										
NO	41	1	(2.4)	39	0		80	1	(1.3)	1.00
YES	61	0		60	0		121	0		
Total	102	1	(1.0)	99	0		201	1	(0.5)	1.00

RMP.B1YP.JCLLIB2(AES6JEAF)
RMP.B1YO.HCJEREP(AES6JEAF)
DEPRESSION: FAMILY DEPRESSION (Visit: 1)
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.57. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Family History of Depression
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE (continued)

DEPRESSION (Visit: 1)	Flx N	Flx n	Flx (%)	Placebo N	Placebo n	Placebo (%)	Total N	Total n	Total (%)	p-Value*
HEPATITIS NONSPECIFIC										
NO	41	1	(2.4)	39	0		80	1	(1.3)	1.00
YES	61	0		60	0		121	0		
Total	102	1	(1.0)	99	0		201	1	(0.5)	1.00
HEPATOMEGALY										
NO	41	1	(2.4)	39	1	(2.6)	80	2	(2.5)	1.00
YES	61	0		60	0		121	0		
Total	102	1	(1.0)	99	1	(1.0)	201	2	(1.0)	1.00

RMP.B1YP.JCLLIB2(AES6JEAF)
RMP.B1YO.HCJEREP(AES6JEAF)
DEPRESSION: FAMILY DEPRESSION (Visit: 1)
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.57. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Family History of Depression
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE (continued)

DEPRESSION (Visit: 1)	Flx N	Flx n	Flx (%)	Placebo N	Placebo n	Placebo (%)	Total N	Total n	Total (%)	p-Value*
HERPES SIMPLEX										
NO	41	1	(2.4)	39	0		80	1	(1.3)	1.00
YES	61	0		60	0		121	0		
Total	102	1	(1.0)	99	0		201	1	(0.5)	1.00
HYPERTONIA										
NO	41	0		39	1	(2.6)	80	1	(1.3)	.488
YES	61	1	(1.6)	60	0		121	1	(0.8)	1.00
Total	102	1	(1.0)	99	1	(1.0)	201	2	(1.0)	1.00

RMP.B1YP.JCLLIB2(AES6JEAF)
RMP.B1YO.HCJEREP(AES6JEAF)
DEPRESSION: FAMILY DEPRESSION (Visit: 1)
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.57. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Family History of Depression
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE (continued)

DEPRESSION (Visit: 1)	Flx N	Flx n	Flx (%)	Placebo N	Placebo n	Placebo (%)	Total N	Total n	Total (%)	p-Value*
HYPOTENSION										
NO	41	1	(2.4)	39	0		80	1	(1.3)	1.00
YES	61	0		60	0		121	0		
Total	102	1	(1.0)	99	0		201	1	(0.5)	1.00
INCREASED APPETITE										
NO	41	1	(2.4)	39	0		80	1	(1.3)	1.00
YES	61	0		60	2	(3.3)	121	2	(1.7)	.244
Total	102	1	(1.0)	99	2	(2.0)	201	3	(1.5)	.618

RMP.B1YP.JCLLIB2(AES6JEAF)
RMP.B1YO.HCJEREP(AES6JEAF)
DEPRESSION: FAMILY DEPRESSION (Visit: 1)
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.57. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Family History of Depression
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE (continued)

DEPRESSION (Visit: 1)	Flx N	Flx n	Flx (%)	Placebo N	Placebo n	Placebo (%)	Total N	Total n	Total (%)	p-Value*
INCREASED SALIVATION										
NO	41	0		39	1	(2.6)	80	1	(1.3)	.488
YES	61	1	(1.6)	60	0		121	1	(0.8)	1.00
Total	102	1	(1.0)	99	1	(1.0)	201	2	(1.0)	1.00
INTENTIONAL INJURY										
NO	41	0		39	0		80	0		
YES	61	1	(1.6)	60	1	(1.7)	121	2	(1.7)	1.00
Total	102	1	(1.0)	99	1	(1.0)	201	2	(1.0)	1.00

RMP.B1YP.JCLLIB2(AES6JEAF)
RMP.B1YO.HCJEREP(AES6JEAF)
DEPRESSION: FAMILY DEPRESSION (Visit: 1)
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.57. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Family History of Depression
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE (continued)

DEPRESSION (Visit: 1)	Flx N	Flx n	Flx (%)	Placebo N	Placebo n	Placebo (%)	Total N	Total n	Total (%)	p-Value*
JOINT DISORDER										
NO	41	0		39	0		80	0		
YES	61	1	(1.6)	60	0		121	1	(0.8)	1.00
Total	102	1	(1.0)	99	0		201	1	(0.5)	1.00
LEG CRAMPS										
NO	41	0		39	1	(2.6)	80	1	(1.3)	.488
YES	61	1	(1.6)	60	2	(3.3)	121	3	(2.5)	.619
Total	102	1	(1.0)	99	3	(3.0)	201	4	(2.0)	.364

RMP.B1YP.JCLLIB2(AES6JEAF)
RMP.B1YO.HCJEREP(AES6JEAF)
DEPRESSION: FAMILY DEPRESSION (Visit: 1)
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.57. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Family History of Depression
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE (continued)

DEPRESSION (Visit: 1)	Flx N	Flx n	Flx (%)	Placebo N	Placebo n	Placebo (%)	Total N	Total n	Total (%)	p-Value*
LEUKOPENIA										
NO	41	1	(2.4)	39	0		80	1	(1.3)	1.00
YES	61	0		60	0		121	0		
Total	102	1	(1.0)	99	0		201	1	(0.5)	1.00
LUNG DISORDER										
NO	41	0		39	0		80	0		
YES	61	1	(1.6)	60	0		121	1	(0.8)	1.00
Total	102	1	(1.0)	99	0		201	1	(0.5)	1.00

RMP.B1YP.JCLLIB2(AES6JEAF)
RMP.B1YO.HCJEREP(AES6JEAF)
DEPRESSION: FAMILY DEPRESSION (Visit: 1)
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.57. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Family History of Depression
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE (continued)

DEPRESSION (Visit: 1)	Flx N	Flx n	Flx (%)	Placebo N	Placebo n	Placebo (%)	Total N	Total n	Total (%)	p-Value*
LYMPHADENOPATHY										
NO	41	0		39	0		80	0		
YES	61	1	(1.6)	60	1	(1.7)	121	2	(1.7)	1.00
Total	102	1	(1.0)	99	1	(1.0)	201	2	(1.0)	1.00
MANIC REACTION										
NO	41	1	(2.4)	39	0		80	1	(1.3)	1.00
YES	61	0		60	0		121	0		
Total	102	1	(1.0)	99	0		201	1	(0.5)	1.00

RMP.B1YP.JCLLIB2(AES6JEAF)
RMP.B1YO.HCJEREP(AES6JEAF)
DEPRESSION: FAMILY DEPRESSION (Visit: 1)
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.57. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Family History of Depression
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE (continued)

DEPRESSION (Visit: 1)	Flx N	Flx n	Flx (%)	Placebo N	Placebo n	Placebo (%)	Total N	Total n	Total (%)	p-Value*
MIGRAINE										
NO	41	1	(2.4)	39	0		80	1	(1.3)	1.00
YES	61	0		60	1	(1.7)	121	1	(0.8)	.496
Total	102	1	(1.0)	99	1	(1.0)	201	2	(1.0)	1.00
NEUROSIS										
NO	41	0		39	0		80	0		
YES	61	1	(1.6)	60	0		121	1	(0.8)	1.00
Total	102	1	(1.0)	99	0		201	1	(0.5)	1.00

RMP.B1YP.JCLLIB2(AES6JEAF)
RMP.B1YO.HCJEREP(AES6JEAF)
DEPRESSION: FAMILY DEPRESSION (Visit: 1)
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.57. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Family History of Depression
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE (continued)

DEPRESSION (Visit: 1)	Flx N	Flx n (%)	Placebo N	Placebo n (%)	Total N	Total n (%)	p-Value*
OTITIS MEDIA							
NO	41	0	39	0	80	0	
YES	61	1 (1.6)	60	0	121	1 (0.8)	1.00
Total	102	1 (1.0)	99	0	201	1 (0.5)	1.00
OVERDOSE							
NO	41	0	39	0	80	0	
YES	61	1 (1.6)	60	1 (1.7)	121	2 (1.7)	1.00
Total	102	1 (1.0)	99	1 (1.0)	201	2 (1.0)	1.00

RMP.B1YP.JCLLIB2(AES6JEAF)
RMP.B1YO.HCJEREP(AES6JEAF)
DEPRESSION: FAMILY DEPRESSION (Visit: 1)
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.57. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Family History of Depression
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE (continued)

DEPRESSION (Visit: 1)	Flx N	Flx n	Flx (%)	Placebo N	Placebo n	Placebo (%)	Total N	Total n	Total (%)	p-Value*
PALPITATION										
NO	41	0		39	0		80	0		
YES	61	1	(1.6)	60	1	(1.7)	121	2	(1.7)	1.00
Total	102	1	(1.0)	99	1	(1.0)	201	2	(1.0)	1.00
PNEUMONIA										
NO	41	1	(2.4)	39	0		80	1	(1.3)	1.00
YES	61	0		60	0		121	0		
Total	102	1	(1.0)	99	0		201	1	(0.5)	1.00

RMP.B1YP.JCLLIB2(AES6JEAF)
RMP.B1YO.HCJEREP(AES6JEAF)
DEPRESSION: FAMILY DEPRESSION (Visit: 1)
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.57. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Family History of Depression
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE (continued)

DEPRESSION (Visit: 1)	Flx N	Flx n	Flx (%)	Placebo N	Placebo n	Placebo (%)	Total N	Total n	Total (%)	p-Value*
RECTAL HEMORRHAGE										
NO	41	0		39	0		80	0		
YES	61	1	(1.6)	60	0		121	1	(0.8)	1.00
Total	102	1	(1.0)	99	0		201	1	(0.5)	1.00
SINUS BRADYCARDIA										
NO	41	0		39	0		80	0		
YES	61	1	(1.6)	60	0		121	1	(0.8)	1.00
Total	102	1	(1.0)	99	0		201	1	(0.5)	1.00

RMP.B1YP.JCLLIB2(AES6JEAF)
RMP.B1YO.HCJEREP(AES6JEAF)
DEPRESSION: FAMILY DEPRESSION (Visit: 1)
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.57. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Family History of Depression
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE (continued)

DEPRESSION (Visit: 1)	Flx N	Flx n	Flx (%)	Placebo N	Placebo n	Placebo (%)	Total N	Total n	Total (%)	p-Value*
SYNCOPE										
NO	41	0		39	0		80	0		
YES	61	1	(1.6)	60	0		121	1	(0.8)	1.00
Total	102	1	(1.0)	99	0		201	1	(0.5)	1.00
TACHYCARDIA										
NO	41	1	(2.4)	39	0		80	1	(1.3)	1.00
YES	61	0		60	0		121	0		
Total	102	1	(1.0)	99	0		201	1	(0.5)	1.00

RMP.B1YP.JCLLIB2(AES6JEAF)
RMP.B1YO.HCJEREP(AES6JEAF)
DEPRESSION: FAMILY DEPRESSION (Visit: 1)
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.57. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Family History of Depression
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE (continued)

DEPRESSION (Visit: 1)	Flx N	Flx n	Flx (%)	Placebo N	Placebo n	Placebo (%)	Total N	Total n	Total (%)	p-Value*
THYROID DISORDER										
NO	41	1	(2.4)	39	0		80	1	(1.3)	1.00
YES	61	0		60	0		121	0		
Total	102	1	(1.0)	99	0		201	1	(0.5)	1.00
TINNITUS										
NO	41	1	(2.4)	39	0		80	1	(1.3)	1.00
YES	61	0		60	0		121	0		
Total	102	1	(1.0)	99	0		201	1	(0.5)	1.00

RMP.B1YP.JCLLIB2(AES6JEAF)
RMP.B1YO.HCJEREP(AES6JEAF)
DEPRESSION: FAMILY DEPRESSION (Visit: 1)
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.57. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Family History of Depression
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE (continued)

DEPRESSION (Visit: 1)	Flx N	Flx n	Flx (%)	Placebo N	Placebo n	Placebo (%)	Total N	Total n	Total (%)	p-Value*
ULCERATIVE STOMATITIS										
NO	41	0		39	0		80	0		
YES	61	1	(1.6)	60	0		121	1	(0.8)	1.00
Total	102	1	(1.0)	99	0		201	1	(0.5)	1.00
URINARY FREQUENCY										
NO	41	0		39	0		80	0		
YES	61	1	(1.6)	60	0		121	1	(0.8)	1.00
Total	102	1	(1.0)	99	0		201	1	(0.5)	1.00

RMP.B1YP.JCLLIB2(AES6JEAF)
RMP.B1YO.HCJEREP(AES6JEAF)
DEPRESSION: FAMILY DEPRESSION (Visit: 1)
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.57. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Family History of Depression
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE (continued)

DEPRESSION (Visit: 1)	Flx N	Flx n	Flx (%)	Placebo N	Placebo n	Placebo (%)	Total N	Total n	Total (%)	p-Value*
URINARY TRACT INFECTION										
NO	41	0		39	0		80	0		
YES	61	1	(1.6)	60	1	(1.7)	121	2	(1.7)	1.00
Total	102	1	(1.0)	99	1	(1.0)	201	2	(1.0)	1.00
VASODILATATION										
NO	41	0		39	0		80	0		
YES	61	1	(1.6)	60	0		121	1	(0.8)	1.00
Total	102	1	(1.0)	99	0		201	1	(0.5)	1.00

RMP.B1YP.JCLLIB2(AES6JEAF)
RMP.B1YO.HCJEREP(AES6JEAF)
DEPRESSION: FAMILY DEPRESSION (Visit: 1)
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.57. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Family History of Depression
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE (continued)

DEPRESSION (Visit: 1)	Flx N	Flx n	Flx (%)	Placebo N	Placebo n	Placebo (%)	Total N	Total n	Total (%)	p-Value*
WEIGHT LOSS										
NO	41	1	(2.4)	39	1	(2.6)	80	2	(2.5)	1.00
YES	61	0		60	0		121	0		
Total	102	1	(1.0)	99	1	(1.0)	201	2	(1.0)	1.00
ABDOMINAL SYNDROME ACUTE										
NO	41	0		39	1	(2.6)	80	1	(1.3)	.488
YES	61	0		60	0		121	0		
Total	102	0		99	1	(1.0)	201	1	(0.5)	.493

RMP.B1YP.JCLLIB2(AES6JEAF)
RMP.B1YO.HCJEREP(AES6JEAF)
DEPRESSION: FAMILY DEPRESSION (Visit: 1)
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.57. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Family History of Depression
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE (continued)

DEPRESSION (Visit: 1)	Flx N	Flx n (%)	Placebo N	Placebo n (%)	Total N	Total n (%)	p-Value*
ACNE							
NO	41	0	39	0	80	0	
YES	61	0	60	1 (1.7)	121	1 (0.8)	.496
Total	102	0	99	1 (1.0)	201	1 (0.5)	.493
ALOPECIA							
NO	41	0	39	0	80	0	
YES	61	0	60	1 (1.7)	121	1 (0.8)	.496
Total	102	0	99	1 (1.0)	201	1 (0.5)	.493

RMP.B1YP.JCLLIB2(AES6JEAF)
RMP.B1YO.HCJEREP(AES6JEAF)
DEPRESSION: FAMILY DEPRESSION (Visit: 1)
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.57. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Family History of Depression
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE (continued)

DEPRESSION (Visit: 1)	Flx N	Flx n (%)	Placebo N	Placebo n (%)	Total N	Total n (%)	p-Value*
ARTHRALGIA							
NO	41	0	39	1 (2.6)	80	1 (1.3)	.488
YES	61	0	60	0	121	0	
Total	102	0	99	1 (1.0)	201	1 (0.5)	.493
BILIRUBINURIA							
NO	41	0	39	1 (2.6)	80	1 (1.3)	.488
YES	61	0	60	0	121	0	
Total	102	0	99	1 (1.0)	201	1 (0.5)	.493

RMP.B1YP.JCLLIB2(AES6JEAF)
RMP.B1YO.HCJEREP(AES6JEAF)
DEPRESSION: FAMILY DEPRESSION (Visit: 1)
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.57. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Family History of Depression
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE (continued)

DEPRESSION (Visit: 1)	Flx N	Flx n (%)	Placebo N	Placebo n (%)	Total N	Total n (%)	p-Value*
CYSTITIS							
NO	41	0	39	1 (2.6)	80	1 (1.3)	.488
YES	61	0	60	0	121	0	
Total	102	0	99	1 (1.0)	201	1 (0.5)	.493
DEHYDRATION							
NO	41	0	39	0	80	0	
YES	61	0	60	1 (1.7)	121	1 (0.8)	.496
Total	102	0	99	1 (1.0)	201	1 (0.5)	.493

RMP.B1YP.JCLLIB2(AES6JEAF)
RMP.B1YO.HCJEREP(AES6JEAF)
DEPRESSION: FAMILY DEPRESSION (Visit: 1)
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.57. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Family History of Depression
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE (continued)

DEPRESSION (Visit: 1)	Flx N	Flx n (%)	Placebo N	Placebo n (%)	Total N	Total n (%)	p-Value*
FACE EDEMA							
NO	41	0	39	0	80	0	
YES	61	0	60	1 (1.7)	121	1 (0.8)	.496
Total	102	0	99	1 (1.0)	201	1 (0.5)	.493
HYPESTHESIA							
NO	41	0	39	1 (2.6)	80	1 (1.3)	.488
YES	61	0	60	0	121	0	
Total	102	0	99	1 (1.0)	201	1 (0.5)	.493

RMP.B1YP.JCLLIB2(AES6JEAF)
RMP.B1YO.HCJEREP(AES6JEAF)
DEPRESSION: FAMILY DEPRESSION (Visit: 1)
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.57. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Family History of Depression
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE (continued)

DEPRESSION (Visit: 1)	Flx N	Flx n (%)	Placebo N	Placebo n (%)	Total N	Total n (%)	p-Value*
HYPOVENTILATION							
NO	41	0	39	1 (2.6)	80	1 (1.3)	.488
YES	61	0	60	0	121	0	
Total	102	0	99	1 (1.0)	201	1 (0.5)	.493
LARYNGITIS							
NO	41	0	39	0	80	0	
YES	61	0	60	1 (1.7)	121	1 (0.8)	.496
Total	102	0	99	1 (1.0)	201	1 (0.5)	.493

RMP.B1YP.JCLLIB2(AES6JEAF)
RMP.B1YO.HCJEREP(AES6JEAF)
DEPRESSION: FAMILY DEPRESSION (Visit: 1)
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.57. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Family History of Depression
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE (continued)

DEPRESSION (Visit: 1)	Flx N	Flx n (%)	Placebo N	Placebo n (%)	Total N	Total n (%)	p-Value*
LYMPHOCYTOSIS							
NO	41	0	39	1 (2.6)	80	1 (1.3)	.488
YES	61	0	60	0	121	0	
Total	102	0	99	1 (1.0)	201	1 (0.5)	.493
MACULOPAPULAR RASH							
NO	41	0	39	0	80	0	
YES	61	0	60	1 (1.7)	121	1 (0.8)	.496
Total	102	0	99	1 (1.0)	201	1 (0.5)	.493

RMP.B1YP.JCLLIB2(AES6JEAF)
RMP.B1YO.HCJEREP(AES6JEAF)
DEPRESSION: FAMILY DEPRESSION (Visit: 1)
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.57. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Family History of Depression
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE (continued)

DEPRESSION (Visit: 1)	Flx N	Flx n (%)	Placebo N	Placebo n (%)	Total N	Total n (%)	p-Value*
METRORRHAGIA							
NO	41	0	39	0	80	0	
YES	61	0	60	1 (1.7)	121	1 (0.8)	.496
Total	102	0	99	1 (1.0)	201	1 (0.5)	.493
MOUTH ULCERATION							
NO	41	0	39	0	80	0	
YES	61	0	60	1 (1.7)	121	1 (0.8)	.496
Total	102	0	99	1 (1.0)	201	1 (0.5)	.493

RMP.B1YP.JCLLIB2(AES6JEAF)
RMP.B1YO.HCJEREP(AES6JEAF)
DEPRESSION: FAMILY DEPRESSION (Visit: 1)
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.57. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Family History of Depression
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE (continued)

DEPRESSION (Visit: 1)	Flx N	Flx n (%)	Placebo N	Placebo n (%)	Total N	Total n (%)	p-Value*
PUSTULAR RASH							
NO	41	0	39	0	80	0	
YES	61	0	60	1 (1.7)	121	1 (0.8)	.496
Total	102	0	99	1 (1.0)	201	1 (0.5)	.493
SPLENOMEGALY							
NO	41	0	39	1 (2.6)	80	1 (1.3)	.488
YES	61	0	60	0	121	0	
Total	102	0	99	1 (1.0)	201	1 (0.5)	.493

RMP.B1YP.JCLLIB2(AES6JEAF)
RMP.B1YO.HCJEREP(AES6JEAF)
DEPRESSION: FAMILY DEPRESSION (Visit: 1)
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.57. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Family History of Depression
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE (continued)

DEPRESSION (Visit: 1)	Flx N	Flx n (%)	Placebo N	Placebo n (%)	Total N	Total n (%)	p-Value*
SUBCUTANEOUS NODULE							
NO	41	0	39	0	80	0	
YES	61	0	60	1 (1.7)	121	1 (0.8)	.496
Total	102	0	99	1 (1.0)	201	1 (0.5)	.493
UNEXPECTED BENEFIT							
NO	41	0	39	0	80	0	
YES	61	0	60	1 (1.7)	121	1 (0.8)	.496
Total	102	0	99	1 (1.0)	201	1 (0.5)	.493

RMP.B1YP.JCLLIB2(AES6JEAF)
RMP.B1YO.HCJEREP(AES6JEAF)
DEPRESSION: FAMILY DEPRESSION (Visit: 1)
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.57. Treatment-Emergent Non-Solicited Adverse Events
Subgroup Analysis by Family History of Depression
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE (concluded)

DEPRESSION (Visit: 1)	Flx N	Flx n (%)	Placebo N	Placebo n (%)	Total N	Total n (%)	p-Value*
WEIGHT GAIN							
NO	41	0	39	0	80	0	
YES	61	0	60	1 (1.7)	121	1 (0.8)	.496
Total	102	0	99	1 (1.0)	201	1 (0.5)	.493

RMP.B1YP.JCLLIB2(AES6JEAF)
RMP.B1YO.HCJEREP(AES6JEAF)
DEPRESSION: FAMILY DEPRESSION (Visit: 1)
* Frequencies are analyzed using a Fisher's Exact test.
Note: N = Total number of patients in the treatment group having the optional variable characteristic(s).
XAES0006

Table 14.58 presents the incidence of treatment-emergent solicited adverse events from the Side-Effects Checklist examined by family history of depression subgroups for the subchronic treatment phase.

Statistically significant differences across family history of depression subgroups were observed for two treatment-emergent solicited adverse events when testing for homogeneity of odds ratios using the Breslow-Day test. The Breslow-Day test for trouble urinating was statistically significant (p=.050); however, neither of the between-treatment group comparisons were statistically significant. The Breslow-Day test for trouble playing sports was also statistically significant (p=.040); however, neither of the between-treatment group comparisons were statistically significant. The Breslow-Day test also noted a trend towards significance for trouble drinking (p=.071); however, neither of the between-treatment group comparisons were statistically significant.

Table 14.58. Treatment-Emergent Solicited Adverse Events
Side Effects Checklist Subgroup Analysis by Family History of Depression
Significant (p<.05) Difference in Odds Ratio
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE

SECL Event - Have you had trouble with:	DEPRESSION	Flx N	Flx n	Flx (%)	Placebo N	Placebo n	Placebo (%)	p-Values: Homogeneity of Odds Ratio p-Value*	p-Values: Between Group Comparison p-Value**
01. EATING	No	41	10	(24.4)	39	12	(30.8)	.722	.619
	Yes	61	22	(36.1)	60	23	(38.3)		.852
02. DRINKING	No	41	8	(19.5)	39	4	(10.3)	.071	.350
	Yes	61	8	(13.1)	60	14	(23.3)		.164
03. DRY MOUTH AND LIPS	No	41	9	(22.0)	39	16	(41.0)	.196	.092
	Yes	61	21	(34.4)	60	22	(36.7)		.851
04. WETNESS IN MOUTH	No	41	3	(7.3)	39	9	(23.1)	.396	.063
	Yes	61	8	(13.1)	60	13	(21.7)		.239
05. CONSTIPATION	No	41	4	(9.8)	39	3	(7.7)	.368	1.00
	Yes	61	6	(9.8)	60	10	(16.7)		.296
06. DIARRHEA	No	41	9	(22.0)	39	7	(17.9)	1.00	.782
	Yes	61	16	(26.2)	60	13	(21.7)		.671
07. STOMACHACHES	No	41	15	(36.6)	39	18	(46.2)	.531	.496
	Yes	61	27	(44.3)	60	27	(45.0)		1.00

* The homogeneity of odds ratio p-Value is derived from the Breslow-Day test.
**The between group comparison within strata p-Value is from the Fisher's Exact Test.
Treatment-Emergent Solicited = was present at baseline and worsened as defined by increase in score on the side-effects checklist or new occurrence after baseline.
RMP.B1YP.SASPGM(CUSJESG2)
RMP.B1YO.HCJEREP(CUSTJEMR)

Table 14.58. Treatment-Emergent Solicited Adverse Events
Side Effects Checklist Subgroup Analysis by Family History of Depression
Significant (p<.05) Difference in Odds Ratio
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE (continued)

SECL Event - Have you had trouble with:	DEPRESSION	Flx N	Flx n	Flx (%)	Placebo N	Placebo n	Placebo (%)	p-Values: Homogeneity of Odds Ratio p-Value*	p-Values: Between Group Comparison p-Value**
08. MUSCLE CRAMPS	No	41	8	(19.5)	39	14	(35.9)	.166	.134
	Yes	61	24	(39.3)	60	23	(38.3)		1.00
09. BEING SICK TO YOUR STOMACH	No	41	13	(31.7)	39	13	(33.3)	.445	1.00
	Yes	61	27	(44.3)	60	21	(35.0)		.354
10. WETTING THE BED	No	41	0		39	1	(2.6)	.263	.488
	Yes	61	3	(4.9)	60	2	(3.3)		1.00
11. URINATING	No	41	2	(4.9)	39	5	(12.8)	.050	.258
	Yes	61	8	(13.1)	60	3	(5.0)		.205
12. ITCHY OR SCRATCHY SKIN	No	41	8	(19.5)	39	11	(28.2)	.630	.435
	Yes	61	21	(34.4)	60	23	(38.3)		.708
13. RASHES	No	41	5	(12.2)	39	8	(20.5)	.598	.373
	Yes	61	12	(19.7)	60	14	(23.3)		.663
14. COLD OR SNIFFLES	No	41	18	(43.9)	39	20	(51.3)	.569	.655
	Yes	61	31	(50.8)	60	30	(50.0)		1.00

* The homogeneity of odds ratio p-Value is derived from the Breslow-Day test.
**The between group comparison within strata p-Value is from the Fisher’s Exact Test.
Treatment-Emergent Solicited = was present at baseline and worsened as defined by increase in score on the side-effects checklist or new occurrence after baseline.
RMP.B1YP.SASPGM(CUSJESG2)
RMP.B1YO.HCJEREP(CUSTJEMR)

Table 14.58. Treatment-Emergent Solicited Adverse Events
Side Effects Checklist Subgroup Analysis by Family History of Depression
Significant (p<.05) Difference in Odds Ratio
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE (continued)

SECL Event - Have you had trouble with:	DEPRESSION	Flx N	Flx n	Flx (%)	Placebo N	Placebo n	Placebo (%)	p-Values: Homogeneity of Odds Ratio p-Value*	p-Values: Between Group Comparison p-Value**
15. HEADACHE	No	41	19	(46.3)	39	15	(38.5)	.517	.506
	Yes	61	35	(57.4)	60	24	(40.0)		.070
16. DIZZINESS	No	41	11	(26.8)	39	13	(33.3)	.160	.628
	Yes	61	25	(41.0)	60	17	(28.3)		.182
17. PLAYING SPORTS	No	41	10	(24.4)	39	4	(10.3)	.040	.142
	Yes	61	9	(14.8)	60	14	(23.3)		.255
18. SHAKINESS	No	41	6	(14.6)	39	7	(17.9)	.372	.767
	Yes	61	18	(29.5)	60	13	(21.7)		.406
19. PRONOUNCING WORDS	No	41	3	(7.3)	39	9	(23.1)	.315	.063
	Yes	61	14	(23.0)	60	20	(33.3)		.230
20. DOING THINGS WITH YOUR HANDS	No	41	5	(12.2)	39	7	(17.9)	.798	.542
	Yes	61	9	(14.8)	60	15	(25.0)		.178
21. SITTING STILL	No	41	10	(24.4)	39	17	(43.6)	.249	.098
	Yes	61	22	(36.1)	60	24	(40.0)		.710

* The homogeneity of odds ratio p-Value is derived from the Breslow-Day test.
**The between group comparison within strata p-Value is from the Fisher's Exact Test.
Treatment-Emergent Solicited = was present at baseline and worsened as defined by increase in score on the side-effects checklist or new occurrence after baseline.
RMP.B1YP.SASPGM(CUSJESG2)
RMP.B1YO.HCJEREP(CUSTJEMR)

Table 14.58. Treatment-Emergent Solicited Adverse Events
Side Effects Checklist Subgroup Analysis by Family History of Depression
Significant (p<.05) Difference in Odds Ratio
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE (continued)

SECL Event - Have you had trouble with:	DEPRESSION	Flx N	Flx n	Flx (%)	Placebo N	Placebo n	Placebo (%)	p-Values: Homogeneity of Odds Ratio p-Value*	p-Values: Between Group Comparison p-Value**
22. TIREDNESS	No	41	17	(41.5)	39	18	(46.2)	.192	.822
	Yes	61	34	(55.7)	60	25	(41.7)		.147
23. FEELING SLEEPY	No	41	17	(41.5)	39	18	(46.2)	.236	.822
	Yes	61	35	(57.4)	60	27	(45.0)		.205
24. SLEEPING	No	41	15	(36.6)	39	14	(35.9)	.580	1.00
	Yes	61	26	(42.6)	60	30	(50.0)		.468
25. BAD DREAMS	No	41	10	(24.4)	39	12	(30.8)	.732	.619
	Yes	61	18	(29.5)	60	19	(31.7)		.845
26. GETTING ALONG WITH PARENTS	No	41	16	(39.0)	39	13	(33.3)	.980	.647
	Yes	61	32	(52.5)	60	28	(46.7)		.587
27. GETTING ALONG WITH KIDS	No	41	14	(34.1)	39	10	(25.6)	.492	.469
	Yes	61	19	(31.1)	60	19	(31.7)		1.00
28. CRYING	No	41	17	(41.5)	39	13	(33.3)	.602	.495
	Yes	61	26	(42.6)	60	25	(41.7)		1.00

* The homogeneity of odds ratio p-Value is derived from the Breslow-Day test.
**The between group comparison within strata p-Value is from the Fisher’s Exact Test.
Treatment-Emergent Solicited = was present at baseline and worsened as defined by increase in score on the side-effects checklist or new occurrence after baseline.
RMP.B1YP.SASPGM(CUSJESG2)
RMP.B1YO.HCJEREP(CUSTJEMR)

Table 14.58. Treatment-Emergent Solicited Adverse Events
Side Effects Checklist Subgroup Analysis by Family History of Depression
Significant (p<.05) Difference in Odds Ratio
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE (concluded)

SECL Event - Have you had trouble with:	DEPRESSION	Flx N	Flx n	Flx (%)	Placebo N	Placebo n	Placebo (%)	p-Values: Homogeneity of Odds Ratio p-Value*	p-Values: Between Group Comparison p-Value**
29. GETTING MAD	No	41	16	(39.0)	39	14	(35.9)	.398	.820
	Yes	61	25	(41.0)	60	30	(50.0)		.364
30. NOT BEING HAPPY	No	41	14	(34.1)	39	12	(30.8)	.789	.814
	Yes	61	27	(44.3)	60	22	(36.7)		.460
31. BEING SAD	No	41	16	(39.0)	39	13	(33.3)	.392	.647
	Yes	61	28	(45.9)	60	17	(28.3)		.060
32. PAYING ATTENTION	No	41	17	(41.5)	39	10	(25.6)	.508	.161
	Yes	61	27	(44.3)	60	22	(36.7)		.460

* The homogeneity of odds ratio p-Value is derived from the Breslow-Day test.
**The between group comparison within strata p-Value is from the Fisher's Exact Test.
Treatment-Emergent Solicited = was present at baseline and worsened as defined by increase in score on the side-effects checklist or new occurrence after baseline.
RMP.B1YP.SASPGM(CUSJESG2)
RMP.B1YO.HCJEREP(CUSTJEMR)

14.3.3. Listings of Deaths, Other Serious, and Nonserious Clinically Significant Adverse Events

No patients died during Study Periods I through V. As the 32-week relapse prevention phase (Study Period VI) is ongoing, analyses of this phase will be submitted in a future clinical study report.

Nine serious adverse events occurred in 9 patients (3 not randomized, 2 fluoxetine-treated, 4 placebo-treated). Serious adverse events led to the discontinuation of 5 patients (1 not randomized, 1 fluoxetine-treated, 3 placebo-treated). Three of the nine serious adverse events occurred during the diagnostic evaluation and placebo washout phases of the study, prior to randomization to study treatment. The remaining six serious adverse events occurred during double-blind treatment in 2 fluoxetine-treated and 4 placebo-treated patients.

A total of 23 patients discontinued due to adverse events (including the 5 patients discontinued due to serious adverse events) during Study Periods I through V (1 not randomized, 11 fluoxetine-treated, 11 placebo-treated).

Further details are provided in Section 12.3. Table 14.59 presents a by-patient listing of these events. See Appendix 16.2.2 for documentation of visit discontinued and days in therapy at discontinuation.

Table 14.59. Listing of Serious Adverse Events, Deaths, and Adverse Events Leading to Discontinuation All Randomized Patients B1Y-MC-HCJE

Body System: BODY AS A WHOLE
Event Classification: ABDOMINAL PAIN
Protocol: B1Y-MC-HCJE

Inv	Pat	Onset Visit	Therapy Group	Onset(First Occur.)Rel. Day of Ther.	Stop(Last Occur.)Rel. Day of Ther.	Event Cause Disc.	Serious Criteria	Actual Term
4	432	7	Placebo	13	15	YES	NONE	STOMACH ACHE

RMP.B1YP.JCLLIB2(AEL1JEAA)
RMP.B1YO.X065REP(AEL1JEAA)
Code: CA-Congenital Anomaly CN-Cancer DI-Died HO-Hospitalized LT-Life-threatening OD-Overdose PD-Permanently Disabled
OTH-Other Serious Criteria
XAEL0001

Table 14.59. Listing of Serious Adverse Events, Deaths, and Adverse Events Leading to Discontinuation All Randomized Patients B1Y-MC-HCJE (continued)

Body System: BODY AS A WHOLE
Event Classification: ABDOMINAL SYNDROME ACUTE
Protocol: B1Y-MC-HCJE

Inv	Pat	Onset Visit	Therapy Group	Onset(First Occur.)Rel. Day of Ther.	Stop(Last Occur.)Rel. Day of Ther.	Event Cause Disc.	Serious Criteria	Actual Term
16	1656	9	Placebo	43	44	NO	HO	ABDOMINAL PAIN/APPENDICITIS

RMP.B1YP.JCLLIB2(AEL1JEAA)
RMP.B1YO.X065REP(AEL1JEAA)
Code: CA-Congenital Anomaly CN-Cancer DI-Died HO-Hospitalized LT-Life-threatening OD-Overdose PD-Permanently Disabled
OTH-Other Serious Criteria
XAEL0001

Table 14.59. Listing of Serious Adverse Events, Deaths, and Adverse Events Leading to Discontinuation All Randomized Patients B1Y-MC-HCJE (continued)

Body System: BODY AS A WHOLE
Event Classification: HEADACHE
Protocol: B1Y-MC-HCJE

Inv	Pat	Onset Visit	Therapy Group	Onset(First Occur.)Rel. Day of Ther.	Stop(Last Occur.)Rel. Day of Ther.	Event Cause Disc.	Serious Criteria	Actual Term
4	427	7	Placebo	19	26	YES	NONE	HEADACHE

RMP.B1YP.JCLLIB2(AEL1JEAA)
RMP.B1YO.X065REP(AEL1JEAA)
Code: CA-Congenital Anomaly CN-Cancer DI-Died HO-Hospitalized LT-Life-threatening OD-Overdose PD-Permanently Disabled
OTH-Other Serious Criteria
XAEL0001

Table 14.59. Listing of Serious Adverse Events, Deaths, and Adverse Events Leading to Discontinuation All Randomized Patients B1Y-MC-HCJE (continued)

Body System: BODY AS A WHOLE
Event Classification: INFECTION
Protocol: B1Y-MC-HCJE

Inv	Pat	Onset Visit	Therapy Group	Onset(First Occur.)Rel. Day of Ther.	Stop(Last Occur.)Rel. Day of Ther.	Event Cause Disc.	Serious Criteria	Actual Term
22	2213	10	Placebo	66	ONGOING	YES	HO	KIDNEY INFECTION

RMP.B1YP.JCLLIB2(AEL1JEAA)
RMP.B1YO.X065REP(AEL1JEAA)
Code: CA-Congenital Anomaly CN-Cancer DI-Died HO-Hospitalized LT-Life-threatening OD-Overdose PD-Permanently Disabled
OTH-Other Serious Criteria
XAEL0001

Table 14.59. Listing of Serious Adverse Events, Deaths, and Adverse Events Leading to Discontinuation All Randomized Patients B1Y-MC-HCJE (continued)

Body System: BODY AS A WHOLE
Event Classification: INTENTIONAL INJURY
Protocol: B1Y-MC-HCJE

Inv	Pat	Onset Visit	Therapy Group	Onset(First Occur.)Rel. Day of Ther.	Stop(Last Occur.)Rel. Day of Ther.	Event Cause Disc.	Serious Criteria	Actual Term
8	806	1	Placebo		ONGOING	YES	HO	SELF-MUTILATORY BEHAVIOR

RMP.B1YP.JCLLIB2(AEL1JEAA)
RMP.B1YO.X065REP(AEL1JEAA)
Code: CA-Congenital Anomaly CN-Cancer DI-Died HO-Hospitalized LT-Life-threatening OD-Overdose PD-Permanently Disabled
OTH-Other Serious Criteria
XAEL0001

Table 14.59. Listing of Serious Adverse Events, Deaths, and Adverse Events Leading to Discontinuation All Randomized Patients B1Y-MC-HCJE (continued)

Body System: CARDIOVASCULAR SYSTEM
Event Classification: MIGRAINE
Protocol: B1Y-MC-HCJE

Inv	Pat	Onset Visit	Therapy Group	Onset(First Occur.)Rel. Day of Ther.	Stop(Last Occur.)Rel. Day of Ther.	Event Cause Disc.	Serious Criteria	Actual Term
22	2220	1	Flx		ONGOING	YES	NONE	INTERMITTENT MIGRAINE

RMP.B1YP.JCLLIB2(AEL1JEAA)
RMP.B1YO.X065REP(AEL1JEAA)
Code: CA-Congenital Anomaly CN-Cancer DI-Died HO-Hospitalized LT-Life-threatening OD-Overdose PD-Permanently Disabled
OTH-Other Serious Criteria
XAEL0001

Table 14.59. Listing of Serious Adverse Events, Deaths, and Adverse Events Leading to Discontinuation All Randomized Patients B1Y-MC-HCJE (continued)

Body System: DIGESTIVE SYSTEM
Event Classification: CONSTIPATION
Protocol: B1Y-MC-HCJE

Inv	Pat	Onset Visit	Therapy Group	Onset(First Occur.)Rel. Day of Ther.	Stop(Last Occur.)Rel. Day of Ther.	Event Cause Disc.	Serious Criteria	Actual Term
3	332	7	Flx	12	40	YES	NONE	INTERMITTENT CONSTIPATION

RMP.B1YP.JCLLIB2(AEL1JEAA)
RMP.B1YO.X065REP(AEL1JEAA)
Code: CA-Congenital Anomaly CN-Cancer DI-Died HO-Hospitalized LT-Life-threatening OD-Overdose PD-Permanently Disabled
OTH-Other Serious Criteria
XAEL0001

Table 14.59. Listing of Serious Adverse Events, Deaths, and Adverse Events Leading to Discontinuation All Randomized Patients B1Y-MC-HCJE (continued)

Body System: DIGESTIVE SYSTEM
Event Classification: NAUSEA
Protocol: B1Y-MC-HCJE

Inv	Pat	Onset Visit	Therapy Group	Onset(First Occur.)Rel. Day of Ther.	Stop(Last Occur.)Rel. Day of Ther.	Event Cause Disc.	Serious Criteria	Actual Term
13	1308	13	Placebo	92	98	YES	NONE	NAUSEA

RMP.B1YP.JCLLIB2(AEL1JEAA)
RMP.B1YO.X065REP(AEL1JEAA)
Code: CA-Congenital Anomaly CN-Cancer DI-Died HO-Hospitalized LT-Life-threatening OD-Overdose PD-Permanently Disabled
OTH-Other Serious Criteria
XAEL0001

Table 14.59. Listing of Serious Adverse Events, Deaths, and Adverse Events Leading to Discontinuation All Randomized Patients B1Y-MC-HCJE (continued)

Body System: HEMIC AND LYMPHATIC SYSTEM
Event Classification: LYMPHOCYTOSIS
Protocol: B1Y-MC-HCJE

Inv	Pat	Onset Visit	Therapy Group	Onset(First Occur.)Rel. Day of Ther.	Stop(Last Occur.)Rel. Day of Ther.	Event Cause Disc.	Serious Criteria	Actual Term
3	303	14	Placebo	120		YES	NONE	INFECTIOUS MONONUCLEOSIS

RMP.B1YP.JCLLIB2(AEL1JEAA)
RMP.B1YO.X065REP(AEL1JEAA)
Code: CA-Congenital Anomaly CN-Cancer DI-Died HO-Hospitalized LT-Life-threatening OD-Overdose PD-Permanently Disabled
OTH-Other Serious Criteria
XAEL0001

Table 14.59. Listing of Serious Adverse Events, Deaths, and Adverse Events Leading to Discontinuation All Randomized Patients B1Y-MC-HCJE (continued)

Body System: NERVOUS SYSTEM
Event Classification: AGITATION
Protocol: B1Y-MC-HCJE

Inv	Pat	Onset Visit	Therapy Group	Onset(First Occur.)Rel. Day of Ther.	Stop(Last Occur.)Rel. Day of Ther.	Event Cause Disc.	Serious Criteria	Actual Term
16	1603	8	Flx	28	ONGOING	YES	NONE	AGITATION

RMP.B1YP.JCLLIB2(AEL1JEAA)
RMP.B1YO.X065REP(AEL1JEAA)
Code: CA-Congenital Anomaly CN-Cancer DI-Died HO-Hospitalized LT-Life-threatening OD-Overdose PD-Permanently Disabled
OTH-Other Serious Criteria
XAEL0001

Table 14.59. Listing of Serious Adverse Events, Deaths, and Adverse Events Leading to Discontinuation All Randomized Patients B1Y-MC-HCJE (continued)

Body System: NERVOUS SYSTEM
Event Classification: ANXIETY
Protocol: B1Y-MC-HCJE

Inv	Pat	Onset Visit	Therapy Group	Onset(First Occur.)Rel. Day of Ther.	Stop(Last Occur.)Rel. Day of Ther.	Event Cause Disc.	Serious Criteria	Actual Term
2	201	4	Placebo	-1	7	YES	NONE	ANXIOUS

RMP.B1YP.JCLLIB2(AEL1JEAA)
RMP.B1YO.X065REP(AEL1JEAA)
Code: CA-Congenital Anomaly CN-Cancer DI-Died HO-Hospitalized LT-Life-threatening OD-Overdose PD-Permanently Disabled
OTH-Other Serious Criteria
XAEL0001

Table 14.59. Listing of Serious Adverse Events, Deaths, and Adverse Events Leading to Discontinuation All Randomized Patients B1Y-MC-HCJE (continued)

Body System: NERVOUS SYSTEM
Event Classification: DEPRESSION
Protocol: B1Y-MC-HCJE

Inv	Pat	Onset Visit	Therapy Group	Onset(First Occur.)Rel. Day of Ther.	Stop(Last Occur.)Rel. Day of Ther.	Event Cause Disc.	Serious Criteria	Actual Term
4	419	1	Flx	-89	ONGOING	YES	HO	SUICIDAL IDEATION
11	1132	3	NON-RAND	.	.	NO	HO	SUICIDAL IDEATION

RMP.B1YP.JCLLIB2(AEL1JEAA)
RMP.B1YO.X065REP(AEL1JEAA)
Code: CA-Congenital Anomaly CN-Cancer DI-Died HO-Hospitalized LT-Life-threatening OD-Overdose PD-Permanently Disabled
OTH-Other Serious Criteria
XAEL0001

Table 14.59. Listing of Serious Adverse Events, Deaths, and Adverse Events Leading to Discontinuation All Randomized Patients B1Y-MC-HCJE (continued)

Body System: NERVOUS SYSTEM
Event Classification: DIZZINESS
Protocol: B1Y-MC-HCJE

Inv	Pat	Onset Visit	Therapy Group	Onset(First Occur.)Rel. Day of Ther.	Stop(Last Occur.)Rel. Day of Ther.	Event Cause Disc.	Serious Criteria	Actual Term
16	1653	7	Placebo	21	34	YES	NONE	DIZZY

RMP.B1YP.JCLLIB2(AEL1JEAA)
RMP.B1YO.X065REP(AEL1JEAA)
Code: CA-Congenital Anomaly CN-Cancer DI-Died HO-Hospitalized LT-Life-threatening OD-Overdose PD-Permanently Disabled
OTH-Other Serious Criteria
XAEL0001

Table 14.59. Listing of Serious Adverse Events, Deaths, and Adverse Events Leading to Discontinuation All Randomized Patients B1Y-MC-HCJE (continued)

Body System: NERVOUS SYSTEM
Event Classification: EUPHORIA
Protocol: B1Y-MC-HCJE

Inv	Pat	Onset Visit	Therapy Group	Onset(First Occur.)Rel. Day of Ther.	Stop(Last Occur.)Rel. Day of Ther.	Event Cause Disc.	Serious Criteria	Actual Term
16	1652	11	Flx	65	ONGOING	YES	NONE	ELEVATED MOOD

RMP.B1YP.JCLLIB2(AEL1JEAA)
RMP.B1YO.X065REP(AEL1JEAA)
Code: CA-Congenital Anomaly CN-Cancer DI-Died HO-Hospitalized LT-Life-threatening OD-Overdose PD-Permanently Disabled
OTH-Other Serious Criteria
XAEL0001

Table 14.59. Listing of Serious Adverse Events, Deaths, and Adverse Events Leading to Discontinuation All Randomized Patients B1Y-MC-HCJE (continued)

Body System: NERVOUS SYSTEM
Event Classification: HOSTILITY
Protocol: B1Y-MC-HCJE

Inv	Pat	Onset Visit	Therapy Group	Onset(First Occur.)Rel. Day of Ther.	Stop(Last Occur.)Rel. Day of Ther.	Event Cause Disc.	Serious Criteria	Actual Term
2	207	1	NON-RAND	.	ONGOING	YES	HO	EXPLOSIVE AGGRESSION
16	1602	13	Flx	98	ONGOING	YES	NONE	PHYSICALLY AGGRESSIVE
22	2201	1	Placebo		ONGOING	YES	HO	AGGRESSIVE BEHAVIOR

RMP.B1YP.JCLLIB2(AEL1JEAA)
RMP.B1YO.X065REP(AEL1JEAA)
Code: CA-Congenital Anomaly CN-Cancer DI-Died HO-Hospitalized LT-Life-threatening OD-Overdose PD-Permanently Disabled
OTH-Other Serious Criteria
XAEL0001

Table 14.59. Listing of Serious Adverse Events, Deaths, and Adverse Events Leading to Discontinuation All Randomized Patients B1Y-MC-HCJE (continued)

Body System: NERVOUS SYSTEM
Event Classification: HYPERKINESIA
Protocol: B1Y-MC-HCJE

Inv	Pat	Onset Visit	Therapy Group	Onset(First Occur.)Rel. Day of Ther.	Stop(Last Occur.)Rel. Day of Ther.	Event Cause Disc.	Serious Criteria	Actual Term
2	202	7	Flx	18	ONGOING	YES	NONE	INCREASED HYPERACTIVITY

RMP.B1YP.JCLLIB2(AEL1JEAA)
RMP.B1YO.X065REP(AEL1JEAA)
Code: CA-Congenital Anomaly CN-Cancer DI-Died HO-Hospitalized LT-Life-threatening OD-Overdose PD-Permanently Disabled
OTH-Other Serious Criteria
XAEL0001

Table 14.59. Listing of Serious Adverse Events, Deaths, and Adverse Events Leading to Discontinuation All Randomized Patients B1Y-MC-HCJE (continued)

Body System: NERVOUS SYSTEM
Event Classification: MANIC REACTION
Protocol: B1Y-MC-HCJE

Inv	Pat	Onset Visit	Therapy Group	Onset(First Occur.)Rel. Day of Ther.	Stop(Last Occur.)Rel. Day of Ther.	Event Cause Disc.	Serious Criteria	Actual Term
2	208	8	Flx	32	ONGOING	YES	NONE	MANIA

RMP.B1YP.JCLLIB2(AEL1JEAA)
RMP.B1YO.X065REP(AEL1JEAA)
Code: CA-Congenital Anomaly CN-Cancer DI-Died HO-Hospitalized LT-Life-threatening OD-Overdose PD-Permanently Disabled
OTH-Other Serious Criteria
XAEL0001

Table 14.59. Listing of Serious Adverse Events, Deaths, and Adverse Events Leading to Discontinuation All Randomized Patients B1Y-MC-HCJE (continued)

Body System: NERVOUS SYSTEM
Event Classification: PERSONALITY DISORDER
Protocol: B1Y-MC-HCJE

Inv	Pat	Onset Visit	Therapy Group	Onset(First Occur.)Rel. Day of Ther.	Stop(Last Occur.)Rel. Day of Ther.	Event Cause Disc.	Serious Criteria	Actual Term
4	401	11	Flx	73	ONGOING	YES	NONE	BEHAVIORAL DISINHIBITION

RMP.B1YP.JCLLIB2(AEL1JEAA)
RMP.B1YO.X065REP(AEL1JEAA)
Code: CA-Congenital Anomaly CN-Cancer DI-Died HO-Hospitalized LT-Life-threatening OD-Overdose PD-Permanently Disabled
OTH-Other Serious Criteria
XAEL0001

Table 14.59. Listing of Serious Adverse Events, Deaths, and Adverse Events Leading to Discontinuation All Randomized Patients B1Y-MC-HCJE (continued)

Body System: NERVOUS SYSTEM
Event Classification: PSYCHOSIS
Protocol: B1Y-MC-HCJE

Inv	Pat	Onset Visit	Therapy Group	Onset(First Occur.)Rel. Day of Ther.	Stop(Last Occur.)Rel. Day of Ther.	Event Cause Disc.	Serious Criteria	Actual Term
1	128	1	NON-RAND		ONGOING	NO	HO	PSYCHOTIC SYMPTOMS

RMP.B1YP.JCLLIB2(AEL1JEAA)
RMP.B1YO.X065REP(AEL1JEAA)
Code: CA-Congenital Anomaly CN-Cancer DI-Died HO-Hospitalized LT-Life-threatening OD-Overdose PD-Permanently Disabled
OTH-Other Serious Criteria
XAEL0001

Table 14.59. Listing of Serious Adverse Events, Deaths, and Adverse Events Leading to Discontinuation All Randomized Patients B1Y-MC-HCJE (continued)

Body System: RESPIRATORY SYSTEM
Event Classification: PHARYNGITIS
Protocol: B1Y-MC-HCJE

Inv	Pat	Onset Visit	Therapy Group	Onset(First Occur.)Rel. Day of Ther.	Stop(Last Occur.)Rel. Day of Ther.	Event Cause Disc.	Serious Criteria	Actual Term
16	1609	6	Flx	11	93	NO	HO	SWOLLEN TONSILS

RMP.B1YP.JCLLIB2(AEL1JEAA)
RMP.B1YO.X065REP(AEL1JEAA)
Code: CA-Congenital Anomaly CN-Cancer DI-Died HO-Hospitalized LT-Life-threatening OD-Overdose PD-Permanently Disabled
OTH-Other Serious Criteria
XAEL0001

Table 14.59. Listing of Serious Adverse Events, Deaths, and Adverse Events Leading to Discontinuation All Randomized Patients B1Y-MC-HCJE (continued)

Body System: SKIN AND APPENDAGES
Event Classification: ALOPECIA
Protocol: B1Y-MC-HCJE

Inv	Pat	Onset Visit	Therapy Group	Onset(First Occur.)Rel. Day of Ther.	Stop(Last Occur.)Rel. Day of Ther.	Event Cause Disc.	Serious Criteria	Actual Term
15	1504	5	Placebo	1	ONGOING	YES	NONE	HAIR LOSS

RMP.B1YP.JCLLIB2(AEL1JEAA)
RMP.B1YO.X065REP(AEL1JEAA)
Code: CA-Congenital Anomaly CN-Cancer DI-Died HO-Hospitalized LT-Life-threatening OD-Overdose PD-Permanently Disabled
OTH-Other Serious Criteria
XAEL0001

Table 14.59. Listing of Serious Adverse Events, Deaths, and Adverse Events Leading to Discontinuation All Randomized Patients B1Y-MC-HCJE (continued)

Body System: SKIN AND APPENDAGES
Event Classification: RASH
Protocol: B1Y-MC-HCJE

Inv	Pat	Onset Visit	Therapy Group	Onset(First Occur.)Rel. Day of Ther.	Stop(Last Occur.)Rel. Day of Ther.	Event Cause Disc.	Serious Criteria	Actual Term
1	103	7	Placebo	15	ONGOING	YES	NONE	RASH
12	1215	6	Flx	14	21	YES	NONE	GENERALIZED PRURITIC RASH

RMP.B1YP.JCLLIB2(AEL1JEAA)
RMP.B1YO.X065REP(AEL1JEAA)
Code: CA-Congenital Anomaly CN-Cancer DI-Died HO-Hospitalized LT-Life-threatening OD-Overdose PD-Permanently Disabled
OTH-Other Serious Criteria
XAEL0001

Table 14.59. Listing of Serious Adverse Events, Deaths, and Adverse Events Leading to Discontinuation All Randomized Patients B1Y-MC-HCJE (concluded)

Body System: UROGENITAL SYSTEM
Event Classification: ENDOMETRIAL HYPERPLASIA
Protocol: B1Y-MC-HCJE

Inv	Pat	Onset Visit	Therapy Group	Onset(First Occur.)Rel. Day of Ther.	Stop(Last Occur.)Rel. Day of Ther.	Event Cause Disc.	Serious Criteria	Actual Term
12	1211	10	Flx	59	83	YES	NONE	ENDOMETRIAL HYPERPLASIA

RMP.B1YP.JCLLIB2(AEL1JEAA)
RMP.B1YO.X065REP(AEL1JEAA)
Code: CA-Congenital Anomaly CN-Cancer DI-Died HO-Hospitalized LT-Life-threatening OD-Overdose PD-Permanently Disabled
OTH-Other Serious Criteria
XAEL0001

14.3.4. Narratives of Deaths, Other Serious, and Nonserious Clinically Significant Adverse Events

One patient (Patient 1656) reported the serious adverse abdominal pain/appendicitis at Visit 9 and did not discontinue due to this event. The patient did discontinue during the relapse prevention phase due to the event viral infection. The narrative for this patient includes details for both events.

Protocol: B1Y-MC-HCJE Discontinued Due To Adverse Event
Patient : 001-0103

Study Medication: Therapy 1: 26 May 1998-Placebo

Age: 10.73 years Sex: Female
Origin: African Descent Weight: 34.93 kg

Event: Actual Term - RASH
Class Term - RASH
Severity - Moderate
Serious? - No

Onset from initial therapy: 15

Abnormal Labs

Analyte	Result	Units	Lo Limit	Hi Limit
MCV	(H) 96	fl	76	93
ALKPH	(H) 322	u/l	51	300

Adverse Events

Classification Term (Actual)	Onset	Relative Onset	Duration
STRABISMUS (ESOTROPIA)	94----		
HEADACHE (OCCASIONAL HEADACHE)	95----		
ABDOMINAL PAIN (OCCASIONAL STOMACHACHE)	96----		
ANOREXIA (DECREASED APPETITE)	980519	-7	7
WEIGHT LOSS (WEIGHT LOSS)	980519	-7	7
FUNGAL DERMATITIS (RING WORM ON RIGHT KNEE)	980607	12	1
RASH (RASH)	980610	15	7

* denotes event was classified as serious.

Concomitant Medications

Drug	Start Date	Stop Date
GLYCEROL/CAMPHOR/DIPHENHYDRAMI	980610	980617

Summary Paragraph

Patient was randomized to placebo treatment on 26-May-1998. Patient reported rash starting on 10-June-1998 and was discontinued at visit 8 on 1-July-1998 by the investigator. Patient had 36 days of study drug therapy at the time of discontinuation and in the investigator’s opinion the rash was possibly related to the study drug.

Protocol: B1Y-MC-HCJE Serious Adverse Event
Patient : 001-0128

Study Medication: Patient Not Randomized

Age: 13.34 years Sex: Male
Origin: Hispanic Weight: 53.98 kg

Event: Actual Term - PSYCHOTIC SYMPTOMS
Class Term - PSYCHOSIS
Severity - Moderate
Serious? - Yes

Abnormal Labs

Analyte	Result		Units	Lo Limit	Hi Limit
HGB	(H)	8.75	mml/L-Fe	6.52	8.38
POLYS	(L)	3.33	GI/L	4	13.5
LYMPHS	(L)	2.54	GI/L	4	12
BICARB	(H)	31.5	mmol/L	12	28

Adverse Events

Classification Term (Actual)	Onset	Relative Onset	Duration
HYPERKINESIA (ADHD)	90----		
* PSYCHOSIS (PSYCHOTIC SYMPTOMS)	9809--		

* denotes event was classified as serious.

Concomitant Medications

Drug	Start Date	Stop Date
METHYLPHENIDATE HYDROCHLORIDE	95----	981123

Summary Paragraph

Patient evaluated at visit 1 on 15-December-1998. The investigator excluded patient from the study due to the severity of the depression and the pre-existing psychotic symptoms. Patient was not randomized and hospitalization was recommended for patient. Patient was hospitalized on 17-December 1998.

Protocol: B1Y-MC-HCJE Discontinued Due To Adverse Event
Patient : 002-0201

Study Medication: Therapy 1: 12 Oct 1998-Placebo

Age: 16.51 years Sex: Male
Origin: Caucasian Weight: 76.43 kg

Event: Actual Term - ANXIOUS
Class Term - ANXIETY
Severity - Mild
Serious? - No

Onset from initial therapy: 0

Abnormal Labs

Analyte	Result		Units	Lo Limit	Hi Limit
CPK	(H)	549	U/L	94	499
ALBUM	(H)	48	g/l	29	47
CHOL	(L)	2.92218	mmol/L	2.95	5.12

Adverse Events

Classification Term (Actual)	Onset	Relative Onset	Duration
HEADACHE (HEADACHES)	9702--		
SOMNOLENCE (SLEEPINESS)	981009	-3	1
PAIN (ACHES)	981010	-2	1
ANXIETY (ANXIOUS)	981011	-1	1
NAUSEA (NAUSEA)	981013	1	6
ASTHENIA (EXHAUSTION)	981015	3	3

* denotes event was classified as serious.

Concomitant Medications

Drug	Start Date	Stop Date
PARACETAMOL	9702--	-

Summary Paragraph

Patient was randomized to placebo treatment on 12-October-1998. Patient presented on 19-October-1998 for visit 5 and was agitated and yelling at his mother. Patient stated that the study medication made him nervous, gave him a headache, and made him sick to his stomach. Patient demanded to be withdrawn from the study. Patient had 7 days of study drug therapy at the time of discontinuation and in the investigator’s opinion the anxiety was possibly related to the study drug.

Protocol: B1Y-MC-HCJE Discontinued Due To Adverse Event
Patient : 002-0202

Study Medication: Therapy 1: 22 Oct 1998-Fluoxetine

Age: 9.3 years Sex: Female
Origin: Caucasian Weight: 20.87 kg

Event: Actual Term - INCREASED HYPERACTIVITY
Class Term - HYPERKINESIA
Severity - Severe
Serious? - No

Onset from initial therapy: 18

Abnormal Labs

Analyte	Result	Units	Lo Limit	Hi Limit
TPROT	(H) 87	g/l	61	84
ALBUM	(H) 51	g/l	29	47

Adverse Events

Classification Term (Actual)	Onset	Relative Onset	Duration
EYE DISORDER (EXOPHORIA OS)	981001	-21	1
HYPERKINESIA (INCREASED HYPERACTIVITY)	981109	18	4

* denotes event was classified as serious.

Concomitant Medications

Drug	Start Date	Stop Date
METHYLPHENIDATE HYDROCHLORIDE	96----	9807--
DEXAMFETAMINE/AMFETAMINE/DEXAM	9807--	980928

Summary Paragraph

Patient with a long history of ADHD was randomized to fluoxetine treatment on 22-October-1998. Patient arrived for visit 7 on 13-November-1998 with parents and depressive symptoms were mild, however, according to the mother and teacher the patient’s ADHD symptoms were extreme. Patient's symptoms were consistent with increased hyperactivity. Patient had 22 days of study drug therapy at the time of discontinuation and in the investigator's opinion the increased hyperactivity was possibly related to the study drug.

Protocol: B1Y-MC-HCJE Discontinued Due To Adverse Event

Patient : 002-0207 Serious Adverse Event

Study Medication: Patient Not Randomized

Age: 10.63 years Sex: Male
Origin: African Descent Weight: Not Obtained

Event: Actual Term - EXPLOSIVE AGGRESSION
Class Term - HOSTILITY
Severity - Severe
Serious? - Yes

Adverse Events

Classification Term (Actual)	Onset	Relative Onset	Duration
* HOSTILITY (EXPLOSIVE AGGRESSION)	990206		1

* denotes event was classified as serious.

Concomitant Medications

Drug	Start Date	Stop Date
VALPROATE SEMISODIUM	990206	-

Summary Paragraph

Patient evaluated at visit 1 on 6-February-1999. Prior to randomization, patient was hospitalized on 6-February-1999 within hours of evaluation for explosive aggression. Investigator decided not to continue patient in study due to his instability.

Protocol: B1Y-MC-HCJE Discontinued Due To Adverse Event
Patient : 002-0208

Study Medication: Therapy 1: 29 May 1999-Fluoxetine

Age: 12.78 years Sex: Male
Origin: African Descent Weight: 48.53 kg

Event: Actual Term - MANIA
Class Term - MANIC REACTION
Severity - Severe
Serious? - No

Onset from initial therapy: 32

Abnormal Labs

Analyte	Result		Units	Lo Limit	Hi Limit
HCT	(L)	0.36	1	0.39	0.54
HCT	(L)	0.37	1	0.39	0.54
HGB	(L)	7.26	mm/L-Fe	7.88	11.23
HGB	(L)	7.7	mm/L-Fe	7.88	11.23
WBC	(L)	2.8	GI/L	4.35	13.15
WBC	(L)	4.1	GI/L	4.35	13.15
WBC	(L)	3.1	GI/L	4.35	13.15
POLYS	(L)	1.18	GI/L	1.65	8.15
POLYS	(L)	1.38	GI/L	1.65	8.15
LYMPHS	(L)	0.73	GI/L	0.95	5.25
ANISO	(A)	-	No Units	-	-
U-SPGR	(L)	1.008	No Units	1.01	1.034
U-SPGR	(L)	1.007	No Units	1.01	1.034

Adverse Events

Classification Term (Actual)	Onset	Relative Onset	Duration
ALLERGIC REACTION (BEE STING ALLERGY)	93----		
RHINITIS (ALLERGIC RHINNORHEA INTERMITTENT)	990514	-15	1
HEADACHE (HEADACHE)	990602	4	1
ABDOMINAL PAIN (STOMACH ACHE)	990602	4	1
NERVOUSNESS (IRRITABILITY)	990630	32	9
AGITATION (AGITATION)	990630	32	9
INSOMNIA (DECREASED SLEEP)	990630	32	9
SPEECH DISORDER (PRESSURED SPEECH)	990630	32	9
DELUSIONS (DELUSIONS)	990630	32	9
MANIC REACTION (MANIA)	990630	32	9

* denotes event was classified as serious.

Concomitant Medications

Drug	Start Date	Stop Date

GUANFACINE HYDROCHLORIDE	9810--	9812--
OXYMETAZOLINE HYDROCHLORIDE	990527	990615

Summary Paragraph

Patient was randomized to fluoxetine treatment on 29-May-1999. On 9-July-1999 at visit 8, the patient had symptoms of mania that had started 7-10 days prior to visit 8. The investigator decided to discontinue patient from study. The patient had 41 days of study drug therapy at the time of discontinuation and in the investigator’s opinion the mania symptoms were possibly related to the study drug. The investigator reported at a follow up visit, on 12-July-1999, that the patient’s manic symptoms had resolved off medication.

Protocol: B1Y-MC-HCJE Discontinued Due To Adverse Event
Patient : 003-0303

Study Medication: Therapy 1: 06 Aug 1998-Placebo
Therapy 2: Placebo Continued
Age: 10.66 years Sex: Female
Origin: Caucasian Weight: 37.19 kg

Event: Actual Term - INFECTIOUS MONONUCLEOSIS
Class Term - LYMPHOCYTOSIS
Severity - Severe
Serious? - No

Onset from initial therapy: 120

Abnormal Labs

Analyte	Result		Units	Lo Limit	Hi Limit
POLYS	(L)	1.11	GI/L	1.35	8.15
U-SPGR	(L)	1.008	No Units	1.01	1.034
AST	(H)	58	U/L	10	40
ALT	(H)	80	U/L	6	34
CPK	(L)	90	U/L	91	391
CPK	(L)	50	U/L	91	391
ALKPH	(H)	302	U/L	51	300
ALKPH	(H)	356	U/L	51	300
GGT	(H)	52	U/L	0	33
T.BILI	(H)	27	umol/L	3	21

Adverse Events

Classification Term (Actual)	Onset	Relative Onset	Duration
RHINITIS (COLD SYNDROME)	980716	-21	1
PHARYNGITIS (SORE THROAT)	980716	-21	1
PAIN (BODY ACHES)	980716	-21	1
SALIVARY GLAND ENLARGEMENT (SWOLLEN SUBMANDIBULAR GLANDS)	980717	-20	1
LYMPHOCYTOSIS (INFECTIOUS MONONUCLEOSIS)	981204	120	1
FEVER (FEVER)	981204	120	1
ABDOMINAL PAIN (ABDOMINAL PAIN)	981204	120	1
ASTHENIA (FATIGUE)	981204	120	1
RASH (FULL BODY RASH)	981204	120	1
BILIRUBINURIA (BILIRUBIN IN URINE)	981204	120	1
HEPATOMEGALY (ENLARGED LIVER)	981204	120	1
SPLENOMEGALY (ENLARGED SPLEEN)	981204	120	1

* denotes event was classified as serious.

Concomitant Medications

Drug	Start Date	Stop Date
PARACETAMOL	981204	-

Summary Paragraph

Patient was randomized to placebo treatment on 6-August-1998. Patient discontinued from the study on 5-December-1998 at visit 14 for mononucleosis. Patient had 119 days of study drug therapy at the time of discontinuation and in the investigator’s opinion the mononucleosis was not related to the study drug. Investigator referred patient to a pediatrician for follow up care and treatment of the mononucleosis.

Protocol: B1Y-MC-HCJE Discontinued Due To Adverse Event
Patient : 003-0332

Study Medication: Therapy 1: 05 Jan 1999-Fluoxetine

Age: 9.45 years Sex: Male
Origin: Other Weight: 36.29 kg

Event: Actual Term - INTERMITTENT CONSTIPATION
Class Term - CONSTIPATION
Severity - Severe
Serious? - No

Onset from initial therapy: 12

Abnormal Labs

Analyte	Result		Units	Lo Limit	Hi Limit
CPK	(L)	60	U/L	150	489
CPK	(L)	80	U/L	150	489
CHOL	(H)	6.65	mmol/L	3.26	4.94
CHOL	(H)	6.88	mmol/L	3.26	4.94

Adverse Events

Classification Term (Actual)	Onset	Relative Onset	Duration
RHINITIS (ALLERGIC RHINITIS)	9101--		
RASH (ALLERGIC DERMATITIS)	9101--		
DIARRHEA (INTERMITTENT DIARRHEA)	990117	12	8
CONSTIPATION (INTERMITTENT CONSTIPATION)	990117	12	8
NAUSEA (NAUSEA)	990117	12	4
FLATULENCE (INTESTINAL GAS)	990201	27	1

* denotes event was classified as serious.

Concomitant Medications

Drug	Start Date	Stop Date
CORTISONE	9102--	-
FLUTICASONE PROPIONATE	9806--	-
PSEUDOEPHEDRINE/BROMPHENIRAMIN	9810--	-
MAGNESIUM/ALUMINIUM HYDROXIDE	990201	990201
SENNA FRUIT	990204	990208
MINERAL	990208	990214

Summary Paragraph

Patient was randomized to fluoxetine treatment on 5-January-1999. Investigator discussed the problems the patient was having with constipation with patient’s mother by telephone, on 9-February-1999. The patient and parent decided to discontinue study drug with the last dose occurring on 8-February-1999. Patient returned on 20-February-1999, Visit 9, for the termination or last visit. Patient had 34 days of study drug therapy at the time of discontinuation and in the

investigator’s opinion the constipation was possibly related to the study drug.

Protocol: B1Y-MC-HCJE Discontinued Due To Adverse Event
Patient : 004-0401

Study Medication: Therapy 1: 21 May 1998-Fluoxetine
Therapy 2: 23 Jul 1998-Fluoxetine 20mg

Age: 12.78 years Sex: Male
Origin: Caucasian Weight: 71.67 kg

Event: Actual Term - BEHAVIORAL DISINHIBITION
Class Term - PERSONALITY DISORDER
Severity - Moderate
Serious? - No

Onset from initial therapy: 73

Historical Diagnoses
SURGICAL PROCEDURE

Abnormal Labs

Analyte	Result		Units	Lo Limit	Hi Limit
MCV	(L)	75	fl	79	96
MCV	(L)	73	f/l	79	96
ANISO	(A)	-	No Units	-	-
MICRO	(A)	-	No Units	-	-
MICRO	(A)	-	No Units	-	-

Adverse Events

Classification Term (Actual)	Onset	Relative Onset	Duration
ALLERGIC REACTION (SEASONAL ALLERGIES)	8605--		
MIGRAINE (MIGRAINE HEADACHES)	9704--		
PAIN (ORTHODONTIC PAIN)	980429	-22	1
ABDOMINAL PAIN (STOMACH ACHE)	980515	-6	1
ANOREXIA (DECREASED APPETITE)	980521	0	1
PHOTOSENSITIVITY REACTION (SUN BURN)	980602	12	2
DIARRHEA (DIARRHEA)	980604	14	1
RASH (MOSQUITO BITES)	980624	34	1
ACCIDENTAL INJURY (ABRASION ON HEEL)	980624	34	1
DIARRHEA (DIARRHEA)	980703	43	6
EAR PAIN (EARACHE)	980730	70	2
RHINITIS (RUNNY NOSE)	980730	70	2
PERSONALITY DISORDER (BEHAVIORAL DISINHIBITION)	980802	73	4

* denotes event was classified as serious.

Concomitant Medications

Drug	Start Date	Stop Date
SERTRALINE HYDROCHLORIDE	9712--	9804--
PARACETAMOL	980429	980429
PARACETAMOL	980602	980602
POLYMYXIN B SULFATE/GRAMICIDIN	980626	980730
PARACETAMOL	980730	980731

Summary Paragraph

Patient was randomized to fluoxetine treatment on 21-May-1998. On 23-July-1998 (visit 10) patient was classified as a non-responder, determined by the response rate on the CDRS-R, and was re-randomized to the treatment that continued on fluoxetine 20mg. Patient returned to site on 14-August-1998 for an unscheduled visit to have investigator assess emerging behavioral disinhibition. Site attempted to lower dose of study drug through TriaLine, the study drug phone dispensing system. Due to the treatment arm the patient was on, the system did not allow the dose of study drug to be lowered. The system then discontinued patient from the study due to patient not tolerating study drug, as noted by investigator as behavioral disinhibition. The unscheduled visit then became the patient’s final or last visit, visit 12. Patient had 85 days of study drug therapy at the time of discontinuation and in the investigator’s opinion the behavioral disinhibition was possibly related to the study drug.

Protocol: B1Y-MC-HCJE Discontinued Due To Adverse Event

Patient : 004-0419 Serious Adverse Event

Study Medication: Therapy 1: 05 Feb 1999-Fluoxetine
Therapy 2: Fluoxetine Continued

Age: 13.26 years Sex: Female
Origin: Caucasian Weight: Not Obtained

Event: Actual Term - SUICIDAL IDEATION
Class Term - DEPRESSION
Severity - Severe
Serious? - Yes

Onset from initial therapy: 0

Abnormal Labs

Analyte	Result	Units	Lo Limit	Hi Limit
CPK	(L) 60	U/L	91	391

Adverse Events

Classification Term (Actual)	Onset	Relative Onset	Duration
SPECIAL SENSES CONGENITAL ANOMALY (USHERS SYNDROME)	9310--		
* DEPRESSION (SUICIDAL IDEATION)	981108	-89	61
INSOMNIA (INSOMNIA)	990108	-28	1
NERVOUSNESS (INCREASED IRRITABILITY)	990204	-1	1
RHINITIS (STUFFY NOSE)	990215	10	5
HEADACHE (HEADACHE)	990219	14	1
FEVER (FEVER)	990220	15	2

* denotes event was classified as serious.

Concomitant Medications

Drug	Start Date	Stop Date
PARACETAMOL/CHLORPHENAMINE/DEX	990216	990216
PARACETAMOL	990220	990221

Summary Paragraph

Patient was randomized to fluoxetine treatment on 5-February-1999. On 9-April-1999, visit 10, patient was classified as a responder, as determined by the response rate on the CDRS-R, and remained in the fluoxetine 20 mg responder group. On 13-April-1999, parent (mother) phoned site to report patient was hospitalized on 12-April-1999 for suicidal ideation. Patient had a history of suicidal ideation with an onset of 8-November-1998, prior to study entry. Investigator decided to discontinue patient from study due to an increase in the patient’s suicidal ideation. Patient did not return for final or summary visit scheduled on 16-April-1999 and unable to reschedule visit with parent. Patient had 70 days of study drug therapy at the time of discontinuation

and in the investigator’s opinion the increase in severity of suicidal ideation was possibly related to the study drug.

Protocol: B1Y-MC-HCJE Discontinued Due To Adverse Event
Patient : 004-0427

Study Medication: Therapy 1: 21 Apr 1999-Placebo

Age: 14.12 years Sex: Female
Origin: Caucasian Weight: 70.31 kg

Event: Actual Term - HEADACHE
Class Term - HEADACHE
Severity - Mild
Serious? - No

Onset from initial therapy: 19

Abnormal Labs

Analyte	Result	Units	Lo Limit	Hi Limit
CPK	(L) 71	U/L	91	391

Adverse Events

Classification Term (Actual)	Onset	Relative Onset	Duration
NAUSEA (NAUSEA)	990415	-6	2
DIZZINESS (DIZZINESS)	990415	-6	2
HEADACHE (HEADACHE)	990424	3	1
HEADACHE (HEADACHE)	990510	19	2
NAUSEA (NAUSEA)	990510	19	2
VOMITING (VOMITING)	990511	20	1
DIARRHEA (DIARRHEA)	990511	20	1

* denotes event was classified as serious.

Concomitant Medications

Drug	Start Date	Stop Date
PARACETAMOL	990424	990424
IBUPROFEN	990510	990510

Summary Paragraph

Patient was randomized to placebo treatment on 21-April-1999. On 12-May-1999 at visit 7 the patient reported a headache that had started on 10-May-1999. Patient’s mother contacted the site and reported the severity of the headache was preventing the patient from attending school, therefore, the study medication was on stopped on 13-May-1999. Mother reported on 17-May-1990 to the site that the headache had stopped and had not reoccurred. Site attempted to schedule a summary visit for the patient, at that time the parent stated that 3 days after stopping the study medication the patient was started open label Prozac. Furthermore, the parent did not want the patient to miss any more days of school so she would be unable to bring the patient in for the summary visit until after 9-June-1999. The decision was made not to bring patient back for summary visit due to the length of time there would be

between visit 7 and the summary visit and due to the initiation of the open label medication reported to be Prozac. The reason for discontinuation of the patient from study was listed as an adverse event of headache. The patient had 22 days of study drug therapy at the time of discontinuation and in the investigator’s opinion the headache was possibly related to the study drug.

Protocol: B1Y-MC-HCJE Discontinued Due To Adverse Event
Patient : 004-0432

Study Medication: Therapy 1: 14 May 1999-Placebo

Age: 8.17 years Sex: Female
Origin: Caucasian Weight: 30.84 kg

Event: Actual Term - STOMACHACHE
Class Term - ABDOMINAL PAIN
Severity - Moderate
Serious? - No

Onset from initial therapy: 13

Historical Diagnoses
FLU SYNDROME

Abnormal Labs

Analyte	Result		Units	Lo Limit	Hi Limit
MONOS	(H)	0.93	GI/L	0.12	0.92
ANISO	(A)	-	No Units	-	-
T.BILI	(H)	26	umol/L	3	21

Adverse Events

Classification Term (Actual)	Onset	Relative Onset	Duration
EAR PAIN (EARACHE)	990503	-11	1
RASH (HEAT RASH-INNER THIGHS)	990503	-11	4
ABDOMINAL PAIN (STOMACHACHE)	990508	-6	6
NAUSEA (NAUSEA)	990513	-1	1
VOMITING (VOMITING)	990513	-1	1
ABDOMINAL PAIN (STOMACH ACHE)	990527	13	3

* denotes event was classified as serious.

Concomitant Medications

Drug	Start Date	Stop Date
CLOTRIMAZOLE	990503	-
CALCIUM/MAGNESIUM/MAGNESIUM TR	990514	990514

Summary Paragraph

Patient was randomized to placebo treatment on 14-May-1999. Patient had experienced a stomachache prior to enrolling in study (pre-randomization). Parent called on 27-May-1999 and reported the worsening of the stomachache and that it had caused the patient to miss school on 27-May-1999. The investigator advised parent to have the patient stop taking the study drug and scheduled a summary visit (visit 7) for 3-June-1999. The parent reported on 9-June-1999 that the stomachache symptoms had stopped on 29-May-1999 after stopping study medication and that she (mother) would be unable to bring patient back for the final or summary visit. The reason for discontinuation of the patient from study

was listed as an adverse event of stomachache. The patient had 20 days of study drug therapy at the time of discontinuation and in the investigator’s opinion the stomachache was possibly related to the study drug.

Protocol: B1Y-MC-HCJE Discontinued Due To Adverse Event

Patient : 008-0806 Serious Adverse Event

Study Medication: Therapy 1: 22 Dec 1998-Placebo

Age: 14.88 years Sex: Male
Origin: Caucasian Weight: 77.11 kg

Event: Actual Term - SELF-MUTILATORY BEHAVIOR
Class Term - INTENTIONAL INJURY
Severity - Severe
Serious? - Yes

Onset from initial therapy: 0

Abnormal Labs

Analyte	Result	Units	Lo Limit	Hi Limit
CPK	(L) 89	U/L	94	499

Adverse Events

Classification Term (Actual)	Onset	Relative Onset	Duration
ABDOMINAL PAIN (STOMACHACHE)	9101--		
ASTHMA (ASTHMA (EXERCISE INDUCED))	96----		
* INTENTIONAL INJURY (SELF-MUTILATORY BEHAVIOR)	98----		
RHINITIS (HEAD COLD)	981224	2	4
HOSTILITY (HOMICIDAL IDEATION)	990128	37	1

* denotes event was classified as serious.

Concomitant Medications

Drug	Start Date	Stop Date
BISMUTH SUBSALICYLATE	9101--	-
ASCORBIC ACID	981224	981231
ECHINACEA EXTRACT	981224	981231

Summary Paragraph

This patient with a prior history of self-mutilatory behavior was randomized to placebo treatment on 22-December-1998. Patient was hospitalized for suicidal ideation and self-mutilatory behavior on 28-January-1999. Investigator discontinued patient from study due to this condition. The patient had 37 days of study drug therapy at the time of discontinuation and in the investigator’s opinion the event was not related to the study drug.

Protocol: B1Y-MC-HCJE Serious Adverse Event
Patient : 011-1132

Study Medication: Patient Not Randomized

Age: 15.78 years Sex: Male
Origin: African Descent Weight: 60.78 kg

Event: Actual Term - SUICIDAL IDEATION
Class Term - DEPRESSION
Severity - Moderate
Serious? - Yes

Abnormal Labs

Analyte	Result		Units	Lo Limit	Hi Limit
HGB	(H)	10.18	mml/L-Fe	6.52	8.38
WBC	(L)	4.7	GI/L	6	11
POLYS	(L)	2.07	GI/L	4	13.5
LYMPHS	(L)	2.37	GI/L	4	12
T4-RIA	(L)	81	nmol/L	93	201
TPROT	(H)	77	g/L	55	71

Adverse Events

Classification Term (Actual)	Onset	Relative Onset	Duration
* DEPRESSION (SUICIDAL IDEATION)	981227		2

* denotes event was classified as serious.

Summary Paragraph

Patient was in the evaluation phase of the study and was hospitalized on 27-December-1998 for suicidal ideation. This event occurred after visit 2 but prior to the scheduled visit 3. Investigator discontinued patient from the study due to the serious suicidal risk, which is protocol exclusion number 20. Patient was not randomized.

Protocol: B1Y-MC-HCJE Discontinued Due To Adverse Event
Patient : 012-1211

Study Medication: Therapy 1: 24 Sep 1998-Fluoxetine
Therapy 2: Fluoxetine Continued

Age: 15.06 years Sex: Female
Origin: Hispanic Weight: 68.95 kg

Event: Actual Term - ENDOMETRIAL HYPERPLASIA
Class Term - ENDOMETRIAL HYPERPLASIA
Severity - Moderate
Serious? - No

Onset from initial therapy: 59

Abnormal Labs

Analyte	Result	Units	Lo Limit	Hi Limit
U-BLD	(A) -	No Units	-	-

Adverse Events

Classification Term (Actual)	Onset	Relative Onset	Duration
HEADACHE (HEADACHES)	96----		
PAIN (SHOULDER SORENESS)	980904	-20	1
ECCHYMOSIS (BRUISE ON RIGHT HEEL)	980904	-20	1
PRURITUS (ITCHING BETWEEN TOES)	980909	-15	1
NAUSEA (NAUSEA)	980921	-3	1
AKATHISIA (AKATHESIA)	981009	15	1
BACK PAIN (BACK PAIN)	981024	30	3
PAIN (PAIN FROM INFECTED TOOTH)	981108	45	4
ENDOMETRIAL HYPERPLASIA (ENDOMETRIAL HYPERPLASIA)	981122	59	11
ENDOCRINE DISORDER (HORMONAL IRREGULARITY)	981214	81	3
ANEMIA (ANEMIA)	990105	103	1

* denotes event was classified as serious.

Concomitant Medications

Drug	Start Date	Stop Date
IBUPROFEN	96----	-
CEFALEXIN	981109	981111
MEDROXYPROGESTERONE ACETATE	981125	981125
ERGOCALCIFEROL/ASCORBIC ACID/F	981210	-
EVENING PRIMROSE OIL	981210	-
ESTRADIOL	981214	990103
IRON	990106	-

Summary Paragraph

Patient was randomized to fluoxetine treatment on 24-September-1998. The patient was classified as a responder on 3-December-1998 at visit 10, as determined by the response rate on the CDRS-R and remained in the fluoxetine 20 mg responder group. At visit 10, patient reported having endometrial hyperplasia hat started on 22-November-1998. On 17-December-1998, visit 11, patient reported the continuation of endometrial hyperplasia. The investigator advised the parent to have the patient not take any further doses of study medication until the investigator spoke with the Lilly physician. Patient was discontinued from the study as a precautionary measure, after the investigator spoke with the Lilly physician on 18-December-1998. Patient returned for the final or discontinuation visit on 6-January-1999 and reported at that time the endometrial hyperplasia had stopped on 16-December-1998, 1 day prior to discontinuing study drug. The patient had 84 days of study drug therapy at the time the study drug was discontinued and in the investigator’s opinion the event was possibly related to the study drug.

Protocol: B1Y-MC-HCJE Discontinued Due To Adverse Event
Patient : 012-1215

Study Medication: Therapy 1: 02 Dec 1998-Fluoxetine

Age: 13.5 years Sex: Male
Origin: Hispanic Weight: 68.95 kg

Event: Actual Term - GENERALIZED PRURITIC RASH
Class Term - RASH
Severity - Moderate
Serious? - No

Onset from initial therapy: 14

Abnormal Labs

Analyte	Result		Units	Lo Limit	Hi Limit
HCT	(L)	0.37	1	0.39	0.54
HCT	(L)	0.38	1	0.39	0.54
MCV	(L)	73	fl	79	96
ANISO	(A)	-	No Units	-	-
M-RBC	(A)	-	No Units	-	-
U-BLD	(A)	-	No Units	-	-

Adverse Events

Classification Term (Actual)	Onset	Relative Onset	Duration
HEADACHE (DAILY HEADACHES)	9808--		
ABDOMINAL PAIN (DAILY STOMACH ACHES)	9808--		
PHARYNGITIS (SORE THROAT)	981208	6	1
RASH (GENERALIZED PRURITIC RASH)	981216	14	2

* denotes event was classified as serious.

Concomitant Medications

Drug	Start Date	Stop Date
PARACETAMOL	981117	981117
ACETYLSALICYLIC ACID	981124	981124
HYDROCORTISONE	981216	981219

Summary Paragraph

Patient was randomized to fluoxetine treatment on 2-December-1998. At visit 6 on 18-December-1998, the patient reported a generalized pruritic rash that had started on 16-December-1998. The investigator decided to discontinue patient and study medication was stopped at that time. The patient was unable to return for the final visit until 19-January-1999 and reported at that time that the rash had stopped on 23-December-1998. The patient had 16 days of study drug therapy at the time of discontinuation and in the investigator’s opinion the rash was possibly related to the study drug.

Protocol: B1Y-MC-HCJE Discontinued Due To Adverse Event
Patient : 013-1308

Study Medication: Therapy 1: 26 May 1999-Placebo
Therapy 2: Placebo continued

Age: 17.06 years Sex: Female
Origin: African Descent Weight: 73.94 kg

Event: Actual Term - NAUSEA
Class Term - NAUSEA
Severity - Moderate
Serious? - No

Onset from initial therapy: 92

Abnormal Labs

Analyte	Result	Units	Lo Limit	Hi Limit
M-WBC	(A) -	No Units	-	-
M-BACT	(A) -	No Units	-	-

Adverse Events

Classification Term (Actual)	Onset	Relative Onset	Duration
HEADACHE (HEADACHE)	990519	-7	1
AMBLYOPIA (BLURRED VISION)	990521	-5	1
MYALGIA (MUSCLE CRAMPS)	990609	14	1
HEADACHE (HEADACHE)	990609	14	1
HEADACHE (HEADACHE)	990615	20	1
SPEECH DISORDER (STUTTERING)	990702	37	13
DYSMENORRHEA (MENSTRUAL CRAMPS)	990702	37	1
NERVOUSNESS (RESTLESSNESS)	990704	39	3
AMNESIA (FORGETFULNESS)	990704	39	11
NAUSEA (NAUSEA)	990730	65	13
PAIN (BODY ACHES)	990730	65	13
HEADACHE (HEADACHE)	990730	65	13
VERTIGO (VERTIGO)	990730	65	13
NAUSEA (NAUSEA)	990826	92	7
PAIN (BODY ACHES)	990826	92	7
HEADACHE (HEADACHE)	990826	92	7
VERTIGO (VERTIGO)	990826	92	7

* denotes event was classified as serious.

Concomitant Medications

Drug	Start Date	Stop Date
PARACETAMOL	990519	990519
PARACETAMOL	990609	990609
PSEUDOEPHEDRINE/IBUPROFEN	990615	990615
PARACETAMOL	990702	990702

Summary Paragraph

Patient was randomized to placebo treatment on 26-May-1999. Patient reported that at visit 13 on 8-September-1999 the study drug had been stopped on 28-August-1999 due to nausea, body aches, headache and vertigo. These conditions were repetitive of what the patient had experienced on 30-July-99 and patient did not want to continue on medication any longer. Patient was subsequently discontinued from study. Patient had 93 days of study drug therapy at the time of discontinuation and in the investigator’s opinion the nausea was possibly related to the study drug.

Protocol: B1Y-MC-HCJE Discontinued Due To Adverse Event
Patient : 015-1504

Study Medication: Therapy 1: 29 Jan 1999-Placebo

Age: 14.7 years Sex: Female
Origin: Hispanic Weight: 55.34 kg

Event: Actual Term - HAIR LOSS
Class Term - ALOPECIA
Severity - Mild
Serious? - No

Onset from initial therapy: 1

Abnormal Labs

Analyte	Result		Units	Lo Limit	Hi Limit
HGB	(L)	7.01	mml/L-Fe	7.2	10.18
M-BACT	(A)	-	No Units	-	-
CPK	(L)	55	U/L	91	391
CPK	(L)	87	U/L	91	391

Adverse Events

Classification Term (Actual)	Onset	Relative Onset	Duration
HEADACHE (HEADACHE)	990124	-5	1
SOMNOLENCE (SLEEPY)	990125	-4	1
HOSTILITY (AGGRESSIVE)	990125	-4	1
ALOPECIA (HAIR LOSS)	990130	1	6
METRORRHAGIA (IRREGULAR MENSES)	990201	3	4
HEADACHE (HEADACHE)	990210	12	2
RHINITIS (SINUS CONGESTION)	990210	12	2
UNEXPECTED BENEFIT (UNEXPECTED BENEFIT-IMPROVED MOOD)	990214	16	5
UNEXPECTED BENEFIT (UNEXPECTED BENEFIT-DECREASE IN IRRITABILITY)	990214	16	5
RASH (SKIN RASH)	990220	22	13

* denotes event was classified as serious.

Concomitant Medications

Drug	Start Date	Stop Date
DIPHENHYDRAMINE HYDROCHLORIDE	990210	990210

Summary Paragraph

Patient was randomized to placebo treatment on 29-January-1999. Patient reported at visit 5 on 5-February-1999 as having hair loss and irregular menses. Patient reported at visit 9 on 2-April-1999 that study medication had been stopped on 12-March-1999 and patient wanted to discontinue from study because of the hair loss and irregular menses.

Patient had 42 days of study drug therapy at the time of discontinuation and in the investigator’s opinion the events were possibly related to the study drug.

Protocol: B1Y-MC-HCJE Discontinued Due To Adverse Event
Patient : 016-1602

Study Medication: Therapy 1: 16 Dec 1998-Fluoxetine
Therapy 2: 22 Feb 1999-Fluoxetine 20 mg

Age: 9.6 years Sex: Female
Origin: Caucasian Weight: 40.37 kg

Event: Actual Term - PHYSICALLY AGGRESSIVE
Class Term - HOSTILITY
Severity - Moderate
Serious? - No

Onset from initial therapy: 98

Abnormal Labs

Analyte	Result		Units	Lo Limit	Hi Limit
PLTCT	(H)	414	GI/L	130	394
U-SPGR	(L)	1.009	No Units	1.01	1.034
UR AC	(L)	131	umol/L	161	393
UR AC	(L)	119	umol/L	161	393

Adverse Events

Classification Term (Actual)	Onset	Relative Onset	Duration
ALLERGIC REACTION (ALLERGY TO METAL - NICKEL)	96----		
ASTHENIA (FATIGUE)	981125	-21	1
THINKING ABNORMAL (DECREASED CONCENTRATION)	981125	-21	1
INSOMNIA (SLEEP-WAKES FREQUENTLY)	981125	-21	1
NERVOUSNESS (IRRITABILITY)	981125	-21	1
DRY MOUTH (DRY MOUTH)	981216	0	1
THIRST (INCREASE THIRST)	981216	0	1
DIARRHEA (DIARRHEA)	981216	0	1
ABDOMINAL PAIN (STOMACH ACHE)	981218	2	5
PRURITUS (ITCHING)	981223	7	1
DRY SKIN (DRY SKIN)	981223	7	1
PHARYNGITIS (DRY THROAT)	981223	7	1
DIARRHEA (DIARRHEA)	981231	15	3
RASH (RASH ARMS)	990104	19	1
RASH (RASH LEGS)	990104	19	1
RHINITIS (SNIFFLES)	990104	19	1
EAR DISORDER (IRRITATED EAR)	990109	24	2

ABNORMAL DREAMS (BAD DREAMS)	990118	33	7
HYPERTONIA (MUSCLE CRAMP LOWER BACK)	990120	35	5
DIZZINESS (DIZZINESS)	990122	37	1
URINARY FREQUENCY (FREQUENT URINATION)	990125	40	1
THIRST (INCREASED THIRST)	990126	41	13
NERVOUSNESS (RESTLESSNESS)	990126	41	13
RASH (RASH ON INNER THIGHS)	990208	54	1
ANOREXIA (DECREASED APPETITE)	990210	56	12
RHINITIS (NASAL DRAINAGE)	990210	56	12
BACK PAIN (BACK PAIN)	990220	66	1
HEADACHE (HEADACHE)	990221	67	1
DIARRHEA (DIARRHEA INTERMITTENT)	990306	80	2
ABDOMINAL PAIN (STOMACHACHE INTERMITTENT)	990306	80	2
HEADACHE (HEADACHE)	990307	81	1
HYPERTONIA (MUSCLE CRAMP IN LOWER BACK)	990308	82	1
PHARYNGITIS (SORE THROAT INTERMITTENT)	990308	82	1
DRY MOUTH (CHAPPED LIPS)	990310	84	12
FEVER (FEVER)	990315	89	1
PERSONALITY DISORDER (DEMANDING)	990324	98	8
HOSTILITY (PHYSICALLY AGGRESSIVE)	990324	98	8
NERVOUSNESS (SKITTISH)	990324	98	8
PERSONALITY DISORDER (IMPATIENT)	990324	98	8
HOSTILITY (QUICK-TEMPERED)	990324	98	8

* denotes event was classified as serious.

Concomitant Medications

Drug	Start Date	Stop Date
DIPHENHYDRAMINE HYDROCHLORIDE	990102	990102
CALAMINE	990103	990108
CLEMASTINE FUMARATE	990103	990104
NEOMYCIN/POLYMYXIN B SULFATE/B	990109	990112
ACETYLSALICYLIC ACID	990315	990315

Summary Paragraph

Patient was randomized to fluoxetine treatment on 16-December-1998. On 22-February-1999 at visit 10 the patient was classified as a non-responder, as determined by the response rate on the CDRS-R, and was re-randomized to the treatment group that continued on fluoxetine 20 mg. The investigator noted at visit 13 on 1-April-1999 that the patient had physical aggressive behavior that had started on 24-March-1999. Patient discontinued from the study by TriaLine due to not tolerating medication at that dose. Patient had 106 days of study drug therapy at the time of discontinuation and in the investigator’s opinion the physical aggressiveness was possibly related to the study drug.

Protocol: B1Y-MC-HCJE Discontinued Due To Adverse Event
Patient : 016-1603

Study Medication: Therapy 1: 21 Jan 1999-Fluoxetine

Age: 11.47 years Sex: Male
Origin: Caucasian Weight: 43.54 kg

Event: Actual Term - AGITATION
Class Term - AGITATION
Severity - Severe
Serious? - No

Onset from initial therapy: 28

Historical Diagnoses
PNEUMONIA

Abnormal Labs

Analyte	Result		Units	Lo Limit	Hi Limit
MONOS	(H)	1.24	GI/L	0.12	0.92
EOSN	(H)	0.71	GI/L	0	0.57
CPK	(L)	46	U/L	150	489
CPK	(L)	80	U/L	150	489
CHOL	(L)	2.95	mmol/L	3.36	5.28

Adverse Events

Classification Term (Actual)	Onset	Relative Onset	Duration
ASTHMA (ASTHMA)	96----		
RHINITIS (NASAL CONGESTION)	96----		
NERVOUSNESS (IRRITABLE)	9807--		
ASTHENIA (FATIGUE)	9807--		
THINKING ABNORMAL (DECREASED CONCENTRATION)	9807--		
INSOMNIA (SLEEP-WAKES FREQUENTLY)	9807--		
ABDOMINAL PAIN (STOMACHACHES)	9809--		
DIARRHEA (DIARRHEA)	9809--		
INFECTION (EAR INFECTION (LEFT))	990103	-18	2
EAR DISORDER (RUPTURED EAR DRUM (LEFT))	990103	-18	2
EAR DISORDER (LEFT EAR DISCOMFORT)	990104	-17	1
CHILLS (COLD CHILLS)	990125	4	1
SWEATING (SWEATS)	990125	4	1
INSOMNIA (TROUBLE SLEEPING)	990218	28	4
AGITATION (AGITATION)	990218	28	4
HOSTILITY	990218	28	4

(ANGER)			
ASTHENIA (FATIGUE)	990222	32	1
HALLUCINATIONS (HEARING VOICES)	990222	32	1
THINKING ABNORMAL (RACING THOUGHTS)	990222	32	1
EMOTIONAL LABILITY (MOOD SWINGS)	990222	32	1
PERSONALITY DISORDER (TEMPER TANTRUMS)	990222	32	1

* denotes event was classified as serious.

Concomitant Medications

Drug	Start Date	Stop Date
ASCORBIC ACID	9812--	-
AMOXICILLIN	990104	990109
IBUPROFEN	990104	990106
BUDESONIDE	990129	-
SALBUTAMOL	990129	-

Summary Paragraph

Patient was randomized to fluoxetine treatment on 21-January-1999. Patient discontinued at visit 8 on 22-February-1999 from study for agitation that started on 18-February-1999. Additional events, which were reported included difficulty sleeping, anger, fatigue, hearing voices, racing thoughts, mood swings and temper tantrums. Patient had 31 days of study drug therapy at the time of discontinuation and in the investigator’s opinion the agitation was possibly related to the study drug.

Protocol: B1Y-MC-HCJE Serious Adverse Event
Patient : 016-1609

Study Medication: Therapy 1: 30 Jun 1999-Fluoxetine
Therapy 2: Fluoxetine Continued
Age: 9.63 years Sex: Female
Origin: Caucasian Weight: 44.91 kg

Event: Actual Term - SWOLLEN TONSILS
Class Term - PHARYNGITIS
Severity - Moderate
Serious? - Yes

Onset from initial therapy: 11

Abnormal Labs

Analyte	Result	Units	Lo Limit	Hi Limit
U-SPGR	(H) 1.035	No Units	1.01	1.034
ALKPH	(H) 341	U/L	69	325

Adverse Events

Classification Term (Actual)	Onset	Relative Onset	Duration
ALLERGIC REACTION (SEASONAL ALLERGIES)	98----		
HEADACHE (HEADACHES)	9806--		
INSOMNIA (INSOMNIA)	9809--		
NERVOUSNESS (IRRITABILITY)	9809--		
INFECTION (EAR INFECTION)	990608	-22	3
PAIN (INTERMITTENT SHOULDER PAIN)	990611	-19	1
* PHARYNGITIS (SWOLLEN TONSILS)	990711	11	3
FEVER (FEVER)	990713	13	1
DYSPHAGIA (DIFFICULTY SWALLOWING)	990714	14	1
INFECTION (VIRAL INFECTION)	990723	23	1
PHARYNGITIS (SORE THROAT)	990723	23	1
ASTHENIA (FATIGUE)	990723	23	1
NERVOUSNESS (IRRITABILITY)	990904	66	3
VOMITING (VOMITING)	990906	68	1
ANXIETY (ANXIETY)	990906	68	1
DYSPNEA (SHORTNESS OF BREATH)	990907	69	1
ACCIDENTAL INJURY (RIGHT SPRAINED WRIST)	990918	80	2
ASTHENIA (FATIGUE)	991002	94	2
ANOREXIA	991002	94	2

(LOSS OF APPETITE)			
FEVER	991113	136	1
(FEVER)			
MYALGIA	991113	136	1
(MUSCLE ACHES)			
CHILLS	991129	152	1
(CHILLS)			
DIZZINESS	991129	152	1
(DIZZINESS)			
NAUSEA	991129	152	1
(NAUSEA)			

* denotes event was classified as serious.
Patient:016-1609

Concomitant Medications

Drug	Start Date	Stop Date
AMOXICILLIN TRIHYDRATE	990608	990616
IBUPROFEN	990711	990713
IBUPROFEN	990719	990719
IBUPROFEN	990724	990930
PHENOL	990724	-
CETIRIZINE	990904	990918
CLAVULANATE/AMOXICILLIN	990907	990919
AMOXICILLIN	991001	991009
CODEINE/PARACETAMOL	991001	991002
IBUPROFEN	991129	991129

Summary Paragraph

Patient was randomized to fluoxetine treatment on 30-June-1999. On 7-September-1999 at visit 10 patient was classified as a responder, as determined by the response rate on the CDRS-R, and remained on fluoxetine 20 mg. The patient had reported swollen tonsils with a start date of 11-July-99. On 1-October-1999, the patient underwent a scheduled tonsillectomy and was hospitalized as a precaution to watch for any bleeding complications. No complications were noted or reported. The patient was prescribed amoxicillin 500mg TID to prevent infection and acetaminophen with codeine 300mg PRN. The patient was discharged on 2-October-1999 and continued in study. In the investigator’s opinion the swollen tonsils and resulting tonsillectomy were not related to the study drug.

Protocol: B1Y-MC-HCJE Discontinued Due To Adverse Event
Patient : 016-1652

Study Medication: Therapy 1: 06 Apr 1999-Fluoxetine
Therapy 2: 10 Jun 1999-Fluoxetine 20 mg

Age: 9.17 years Sex: Male
Origin: Caucasian Weight: 36.29 kg

Event: Actual Term - ELEVATED MOOD
Class Term - EUPHORIA
Severity - Moderate
Serious? - No

Onset from initial therapy: 65

Abnormal Labs

Analyte	Result	Units	Lo Limit	Hi Limit
U-SPGR	(H) 1.038	No Units	1.01	1.034
U-SPGR	(H) 1.036	No Units	1.01	1.034
AST	(H) 46	U/L	10	40
CHOL	(H) 5.09	mmol/L	3.26	4.94
CHOL	(H) 5.35	mmol/L	3.26	4.94

Adverse Events

Classification Term (Actual)	Onset	Relative Onset	Duration
HYPERKINESIA (ATTENTION DEFICIT HYPERACTIVITY DISORDER)	94----		
NERVOUSNESS (IRRITABILITY)	97----		
INSOMNIA (IRREGULAR SLEEP PATTERNS)	9808--		
ASTHENIA (FATIGUE)	9808--		
INCREASED APPETITE (INCREASED APPETITE)	9902--		
DEPRESSION (SUICIDAL IDEATION)	990310	-27	6
ABNORMAL DREAMS (BAD DREAMS)	990329	-8	1
DIARRHEA (DIARRHEA)	990330	-7	1
ABDOMINAL PAIN (STOMACHACHE)	990330	-7	7
NAUSEA (NAUSEA)	990330	-7	7
NERVOUSNESS (FIDGETING)	990407	1	6
DEPRESSION (CRYING)	990407	1	6
HEADACHE (HEADACHES)	990414	8	6
DRY MOUTH (DRY MOUTH)	990423	17	4
RASH (RED BUMPS ON RIGHT LEG)	990507	31	4
ACCIDENTAL INJURY (ABRASION ON RIGHT LEG)	990507	31	4
PRURITUS	990507	31	4

(ITCHINESS)			
ABNORMAL DREAMS (BAD DREAM)	990520	44	1
FUNGAL DERMATITIS (ATHLETE'S FOOT)	990525	49	1
INFECTION (CUTICLE INFECTION)	990525	49	1
DRY MOUTH (DRY LIPS)	990527	51	14
EUPHORIA (ELEVATED MOOD)	990610	65	11
SPEECH DISORDER (PRESSURED SPEECH)	990610	65	11
PERSONALITY DISORDER (TANGENTIALITY)	990610	65	11
THINKING ABNORMAL (FLIGHT OF IDEAS)	990610	65	11
HOSTILITY (BELLIGERENCE)	990610	65	11
THINKING ABNORMAL (LOOSENING OF ASSOCIATIONS)	990610	65	11
DRY MOUTH (CHAPPED LIPS)	990611	66	10

* denotes event was classified as serious.

Concomitant Medications

Drug	Start Date	Stop Date
CALCIUM/MAGNESIUM/MAGNESIUM TR	990330	990330
PETROLATUM/LANOLIN	990526	990530
TERBINAFINE HYDROCHLORIDE	990526	990621

Summary Paragraph

Patient was randomized to fluoxetine treatment on 6-April-1999. At 4 years of age the patient was reported to be hyperkinetic. On 10-June-1999, at visit 10, the patient was classified as a non-responder, determined by the response rate on the CDRS-R, and was re-randomized to the treatment group that continued on fluoxetine 20mg. The patient was discontinued from the study on 21-June-1999, visit 11, due to events of elevated mood, increased irritability, restlessness, increased hyperactivity and impulsivity, pressured speech, tangentiality, flight of ideas, belligerence, and mild looseness of associations. These events were reported as starting on 10-June-1999. The patient had 76 days of study drug therapy at the time of discontinuation and in the investigator's opinion the events were possibly related to the study drug.

Protocol: B1Y-MC-HCJE Discontinued Due To Adverse Event
Patient : 016-1653

Study Medication: Therapy 1: 06 Apr 1999-Placebo

Age: 12.09 years Sex: Male
Origin: Caucasian Weight: 77.11 kg

Event: Actual Term - DIZZY
Class Term - DIZZINESS
Severity - Severe
Serious? - No

Onset from initial therapy: 21

Abnormal Labs

Analyte	Result	Units	Lo Limit	Hi Limit
CPK	(L) 80	U/L	94	499
CHOL	(H) 6.00	mmol/L	3.36	5.28

Adverse Events

Classification Term (Actual)	Onset	Relative Onset	Duration
HYPERKINESIA (ATTENTION DEFICIT DISORDER)	95----		
NAUSEA (NAUSEA)	96----		
ABDOMINAL PAIN (STOMACHACHE)	96----		
NERVOUSNESS (IRRITABILITY)	9804--		
HEADACHE (HEADACHES)	9809--		
ANOREXIA (DECREASED APPETITE)	9902--		
ASTHENIA (FATIGUE)	990329	-8	1
THINKING ABNORMAL (DECREASED CONCENTRATION)	990406	0	1
ABDOMINAL PAIN (PAIN AT RIB + ABDOMEN)	990412	6	1
HYPOVENTILATION (EPISODE OF DIFFICULTY TAKING A BREATH)	990419	13	1
DIZZINESS (EPISODE OF FEELING DIZZY)	990419	13	1
HYPOVENTILATION (DIFFICULTY TAKING A DEEP BREATH)	990427	21	1
DIZZINESS (DIZZY)	990427	21	1
THIRST (INCREASED THIRST)	990504	28	14
VOMITING (VOMITING)	990506	30	1

* denotes event was classified as serious.

Concomitant Medications

Drug	Start Date	Stop Date

PARACETAMOL	9809--	980909
IBUPROFEN	990415	990415

Summary Paragraph

Patient was randomized to placebo treatment on 6-April-1999. The parent reported to the site on 28-April-1999 that the patient was having dizziness that started on 27-April-1999. The site reduced the dose of study drug from 3 capsules to 2 capsules and had the patient come in for an unscheduled visit evaluation on 3-May-1999. The study medication was discontinued on 5-May-1999. The dizziness ceased 5 days later. The patient was discontinued from study at on 18-May-1999 (visit 8). Patient had 31 days of study drug therapy at the time of discontinuation and in the investigator’s opinion the dizziness was possibly related to the study drug.

Protocol: B1Y-MC-HCJE Discontinued Due To Adverse Event

Patient : 016-1656 Serious Adverse Event

Study Medication: Therapy 1: 13 Apr 1999-Placebo
Therapy 2: Placebo Continued
Therapy 3: Placebo continued

Age: 9.84 years Sex: Male
Origin: African Descent Weight: 28.12 kg

Event: Actual Term - VIRAL INFECTION
Class Term - INFECTION
Severity - Moderate
Serious? - No

Onset from initial therapy: 143

Abnormal Labs

Analyte	Result		Units	Lo Limit	Hi Limit
ALKPH	(H)	349	U/L	86	315
ALKPH	(H)	370	U/L	86	315
UR AC	(L)	155	umol/L	161	393
CHOL	(H)	5.33	mmol/L	3.26	4.94
CHOL	(H)	5.79	mmol/L	3.26	4.94

Adverse Events

Classification Term (Actual)	Onset	Relative Onset	Duration
DEPRESSION (CRYING)	9809--		
THINKING ABNORMAL (DIFFICULTY CONCENTRATING)	9811--		
INSOMNIA (WAKES FREQUENTLY)	9902--		
FEVER (FEVER)	990330	-14	3
RHINITIS (COLD)	990330	-14	3
ASTHENIA (FATIGUE)	990407	-6	1
NERVOUSNESS (FIDGETY)	990413	0	1
PRURITUS (ITCHY SKIN)	990414	1	6
RASH (RASH ON RIGHT CALF)	990414	1	6
ABNORMAL DREAMS (BAD DREAMS)	990414	1	6
DRY MOUTH (CHAPPED LIPS)	990518	35	4
FEVER (FEVER)	990526	43	3
* ABDOMINAL SYNDROME ACUTE (ABDOMINAL PAIN/APPENDICITIS)	990526	43	2
ABDOMINAL PAIN (PAIN AT ABDOMINAL INCISION)	990527	44	5
NAUSEA (NAUSEA POST SURGERY)	990527	44	2

RHINITIS (SNIFFLES)	990629	77	14
DIZZINESS (DIZZINESS)	990705	83	8
RASH (RASH ON CHEST)	990813	122	1
RHINITIS (SNEEZING)	990814	123	16
HEADACHE (HEADACHE)	990824	133	2
INFECTION (VIRAL INFECTION)	990903	143	9
PHARYNGITIS (SORE THROAT)	990903	143	9
MOUTH ULCERATION (ORAL LEGIONS)	990903	143	27
RASH (RASH OF FACE)	990903	143	27
RASH (RASH OF SHOULDERS)	990903	143	27
FEVER (FEVER)	990905	145	2

* denotes event was classified as serious.

Concomitant Medications

Drug	Start Date	Stop Date
PARACETAMOL/CHLORPHENAMINE/DEX	990330	990401
MAGNESIUM/ALUMINIUM HYDROXIDE	990526	990527
PARACETAMOL	990526	990527
CEFOXITIN	990527	990528
MORPHINE	990528	990528
PROMETHAZINE HYDROCHLORIDE	990528	990528
PARACETAMOL/HYDROCODONE	990530	990531
PARACETAMOL	990723	990723
PARACETAMOL	990825	990825
IBUPROFEN	990905	990906
PARACETAMOL	990905	990906

Summary Paragraph

Patient was randomized to placebo treatment on 13-April-1999. Patient reported abdominal pain and fever starting on 26-May-1999. Patient was hospitalized on 27-May-1999 for appendicitis and had an appendectomy on the same day, without complications. Patient was discharged on 30-May-1999 with prescription for Lortab 250mg PRN, 1-2 teaspoons as needed for pain. Patient missed 5 consecutive days of study medication from 27-May-1999 through 31-May-1999. Patient was allowed to continue in study due to previous study medication compliance and the extenuating circumstances of hospitalization. In the investigator’s opinion the appendicitis was not related to the study drug.

Patient met criteria for entry into the relapse prevention phase of the study on 30-August-1999, visit 15, by having a CDRS-R score less than or equal to 28 (score was 19). Patient reported viral infection starting on 3-September-1999 and study medication was missed. Viral infection stopped on 11-September-1999 and patient did not restart medication. Patient was discontinued at visit 16 on 29-September-1999.

Protocol: B1Y-MC-HCJE Discontinued Due To Adverse Event

Patient : 022-2201 Serious Adverse Event

Study Medication: Therapy 1: 19 Mar 1999-Placebo

Age: 10.95 years Sex: Male
Origin: Caucasian Weight: 34.47 kg

Event: Actual Term - AGGRESSIVE BEHAVIOR
Class Term - HOSTILITY
Severity - Severe
Serious? - Yes

Onset from initial therapy: 0

Historical Diagnoses
HYPERKINESIA

Abnormal Labs

Analyte	Result	Units	Lo Limit	Hi Limit
EOSN	(H) 0.58	GI/L	0	0.57
PLTCT	(H) 433	GI/L	130	394
CPK	(L) 144	U/L	150	489

Adverse Events

Classification Term (Actual)	Onset	Relative Onset	Duration
* HOSTILITY (AGGRESSIVE BEHAVIOR)	93----		
HEADACHE (INTERMITTENT HEADACHES)	9901--		
ASTHENIA (INTERMITTENT FATIGUE)	990303	-16	1

* denotes event was classified as serious.

Concomitant Medications

Drug	Start Date	Stop Date
ACETYLSALICYLIC ACID	9901--	-
AMFEBUTAMONE HYDROCHLORIDE	990326	-

Summary Paragraph

Patient was randomized to placebo treatment on 19-March-1999. The patient was hospitalized for aggressive behavior 26-March-1999. The patient had previously reported a history of aggressive behavior starting in 1993. Patient was discharged on 29-March-1999 with a prescription for Wellbutrin (an excluded medication), the patient and the parent wanted to discontinue study. Patient had the discontinuation visit on 30-March-1999. Patient had 10 days of study drug therapy at the time of discontinuation and in the investigator’s opinion the aggressive behavior was not related to the study drug.

Protocol: B1Y-MC-HCJE Discontinued Due To Adverse Event

Patient : 022-2213 Serious Adverse Event

Study Medication: Therapy 1: 29 Jun 1999-Placebo
Therapy 2: Placebo Continued

Age: 10.56 years Sex: Female
Origin: Caucasian Weight: 68.95 kg

Event: Actual Term - KIDNEY INFECTION
Class Term - INFECTION
Severity - Severe
Serious? - Yes

Onset from initial therapy: 66

Historical Diagnoses
URINARY TRACT INFECTION

Abnormal Labs

Analyte	Result		Units	Lo Limit	Hi Limit
PLTCT	(H)	461	GI/L	130	394
M-WBC	(A)	-	No Units	-	-
M-WBC	(A)	-	No Units	-	-
M-BACT	(A)	-	No Units	-	-
CPK	(L)	74	U/L	91	391
CPK	(L)	27	U/L	91	391
PHOS	(H)	2.03	mmol/L	1	1.94
BICARB	(H)	31.1	mmol/L	17	30.6

Adverse Events

Classification Term (Actual)	Onset	Relative Onset	Duration
ASTHMA (ASTHMA)	881115	-3878	3858
DRY MOUTH (CHAPPED LIPS)	881115	-3878	3858
CONGENITAL ANOMALY (TRACHEOMALACIA (WEBBED VOCAL CHORDS))	881115	-3878	3858
ALLERGIC REACTION (INTERMITTENT ALLERGIES)	9801--		
DIARRHEA (INTERMITTENT DIARRHEA)	990609	-20	1
ABDOMINAL PAIN (INTERMITTENT STOMACHACHE)	990609	-20	1
CONSTIPATION (INTERMITTENT CONSTIPATION)	990609	-20	1
DYSPEPSIA (INTERMITTENT HEARTBURN)	990609	-20	1
SOMNOLENCE (LETHARGY IN THE MORNING)	990609	-20	1
NERVOUSNESS (INTERMITTENT IRRITABILITY)	990609	-20	1
ASTHMA (SCATTERED WHEEZES)	990609	-20	1
HEADACHE (INTERMITTENT HEADACHE)	990620	-9	2
COUGH INCREASED (COUGHING)	990620	-9	1

BACK PAIN (BACK PAIN)	990620	-9	2
FLU SYNDROME (FLU)	990624	-5	2
NERVOUSNESS (SHAKINESS)	990710	11	1
EAR PAIN (INTERMITTENT EARACHE)	990712	13	3
BRADYCARDIA (SLOWED HEART RATE)	990715	16	1
RHINITIS (RUNNY NOSE)	990719	20	3
NERVOUSNESS (SHAKINESS)	990722	23	1
MYALGIA (CRAMP IN RIGHT ARM)	990809	41	1
FEVER (FEVER)	990819	51	2
PHARYNGITIS (SORE THROAT)	990819	51	2
APHTHOUS STOMATITIS (MOUTH SORES)	990819	51	4
SKIN DISCOLORATION (WHITE SPOTS ON HANDS)	990819	51	4
FLU SYNDROME (HEADACHE RELATED FLU SYMPTOMS)	990819	51	2
PAIN (PAINFUL AREAS ON SPOTS)	990819	51	4
SKIN ULCER (SWEAT SORES)	990827	59	12
ANOREXIA (DECREASED APPETITE)	990828	60	11
VOMITING (VOMITING)	990828	60	11
PHARYNGITIS (SORE THROAT)	990828	60	5
ASTHENIA (INCREASED FATIGUE)	990828	60	11
* INFECTION (KIDNEY INFECTION)	990903	66	5
ABDOMINAL PAIN (ABDOMINAL TENDERNESS)	990903	66	5
PAIN (GENERAL BODY PAIN)	990903	66	5
BACK PAIN (LOWER BACK PAIN)	990903	66	5
DYSURIA (PAIN DURING URINATION)	990903	66	5
LEUKORRHEA (VAGINAL DISCHARGE)	990903	66	5
RHINITIS (RUNNY NOSE)	990903	66	5
DEHYDRATION (DEHYDRATION)	990903	66	5
VOMITING (EMESIS)	990903	66	5
FEVER (HIGH FEVER)	990903	66	5

* denotes event was classified as serious.

Concomitant Medications

Drug	Start Date	Stop Date
FLUTICASONE PROPIONATE	9801--	-
SALBUTAMOL	9801--	-
IBUPROFEN	990621	990621
IBUPROFEN	990624	990625
PARACETAMOL	990624	990625
IBUPROFEN	990716	990718
CEFIXIME	990819	990825
IBUPROFEN	990828	990905
AMPICILLIN	990906	-
GENTAMICIN SULFATE	990906	-
PARACETAMOL	990906	-
SENNA FRUIT	990906	-

Summary Paragraph

Patient was randomized to placebo treatment on 29-June-1999. The patient was hospitalized with a kidney infection on 6-September-1999 when. The patient reported fever, vomiting, back pain and pain during urination starting on 3-September-1999. Patient was hospitalized on 6-September-1999 and diagnosed with a kidney infection. Patient was discharged on 8-September-1999 and investigator discontinued patient from study because the patient had missed several days of medication prior to and during her hospitalization. Patient had missed doses from 5-September-1999 through 8-September-1999. Patient had 67 days of study drug therapy at the time of discontinuation and in the investigator’s opinion the kidney infection was not related to the study drug.

Protocol: B1Y-MC-HCJE Discontinued Due To Adverse Event
Patient : 022-2220

Study Medication: Therapy 1: 22 Jul 1999-Fluoxetine
Therapy 2: Fluoxetine Continued

Age: 10.1 years Sex: Female
Origin: Other Weight: 60.78 kg

Event: Actual Term - INTERMITTENT MIGRAINE
Class Term - MIGRAINE
Severity - Severe
Serious? - No

Onset from initial therapy: 0

Historical Diagnoses
INFECTION
SUICIDAL GESTURES

Abnormal Labs

Analyte	Result		Units	Lo Limit	Hi Limit
U-SPGR	(H)	1.036	No Units	1.01	1.034
CREAT	(H)	97	umol/L	35	88
CHOL	(H)	6.10	mmol/L	3.21	5.61
CHOL	(H)	5.72	mmol/L	3.21	5.61

Adverse Events

Classification Term (Actual)	Onset	Relative Onset	Duration
OBESITY (OBESITY)	890523	-3712	3690
SOMNOLENCE (INTERMITTENT INCREASED SLEEP)	93----		
ASTHENIA (INTERMITTENT FATIGUE)	93----		
HEADACHE (INTERMITTENT HEADACHES)	96----		
MIGRAINE (INTERMITTENT MIGRAINE)	97----		
DEPRESSION (TEARFULNESS (INTERMITTENT))	97----		
NERVOUSNESS (INTERMITTENT IRRITABILITY)	97----		
INSOMNIA (INTERMITTENT TERMINAL INSOMNIA)	97----		
INSOMNIA (INTERMITTENT INITIAL INSOMNIA)	97----		
INSOMNIA (INTERMITTENT MIDDLE INSOMNIA)	97----		
EMOTIONAL LABILITY (LABILE MOOD)	97----		
APATHY (WITHDRAWN BEHAVIOR)	97----		
AGITATION (AGITATION)	97----		
ANXIETY (EXCESSIVE WORRYING)	97----		
HOSTILITY	9707--		

(ANGER)			
DEPRESSION	9902--		
(SUICIDAL IDEATION INTERMITTENT)			
NAUSEA	990630	-22	1
(INTERMITTENT NAUSEA)			
ABDOMINAL PAIN	990630	-22	1
(INTERMITTENT STOMACHACHES)			
ANOREXIA	990630	-22	1
(DECREASED APPETITE (INTERMITTENT))			
THINKING ABNORMAL	990630	-22	1
(INTERMITTENT DIFFICULTY CONCENTRATING)			
DIARRHEA	990719	-3	4
(DIARRHEA)			
ABNORMAL DREAMS	990720	-2	1
(BAD DREAM)			
HOSTILITY	990721	-1	1
(AGGRESSION (INTERMITTENT))			
RASH	990730	8	8
(RASH ON LEFT LEG)			
PAIN	990805	14	1
(PAIN IN LEFT SIDE)			
RASH	990807	16	8
(HEAT RASH ON LEGS)			
SLEEP DISORDER	990807	16	9
(SLEEP DISTURBANCE)			
RASH	990807	16	8
(HEAT RASH ON ARMS)			
NECK PAIN	990811	20	1
(PAIN ON LEFT SIDE OF NECK)			
THIRST	990816	25	1
(INCREASED THIRST (INTERMITTENT))			
NERVOUSNESS	990826	35	1
(SHAKINESS)			
DIARRHEA	990906	46	4
(DIARRHEA)			
PAIN	990922	62	1
(PAIN IN RIGHT SIDE (TORSO))			
ABNORMAL DREAMS	991018	88	1
(BAD DREAM)			
AKATHISIA	991019	89	2
(RESTLESSNESS INTERMITTENT)			

* denotes event was classified as serious.

Concomitant Medications

Drug	Start Date	Stop Date
ST. JOHN’S WORT	9804--	9807--
FLUOXETINE HYDROCHLORIDE	9807--	981023
LIDOCAINE/PRILOCAINE	990630	990630
PARACETAMOL	990701	990701
PARACETAMOL	990811	990811
IBUPROFEN	990907	990909
LIDOCAINE/PRILOCAINE	990924	990924
IBUPROFEN	991006	991006
PARACETAMOL	991006	991006
IBUPROFEN	991102	991102
IBUPROFEN	991103	991103
PARACETAMOL	991107	991107

Summary Paragraph

Patient was randomized to fluoxetine treatment on 22-July-1999. At visit 10 on 24-September-1999 the patient was classified as a responder, as determined by the response rate on the CDRS-R, and remained in the fluoxetine 20 mg responder group. The patient had reported previous history of intermittent migraines starting in 1997 and on 27-August-1999 at visit 8 the patient reported an increase in severity of the intermittent migraines from moderate to severe. The patient was discontinued from study due to the increased severity of intermittent migraines on 19-November-1999 at visit 14. Patient had 120 days of study drug therapy at the time of discontinuation and in the investigator’s opinion the increase in severity of the migraines was possibly related to the study drug.

14.3.5. Vital Signs

14.3.5.1. Out of Range Vital Signs

Blood pressure reference ranges were established by the National Institutes of Health and are presented in Appendix 16.1.12. These reference ranges were used to determine the incidence of out of range blood pressure measurements. Tables 14.60, 14.61, and 14.62 present the incidence of out of range blood pressure measurements for the acute treatment phase, the subchronic treatment phase, and Study Period V, respectively. These results are discussed in Section 12.5.1.

Table 14.60. Vital Signs
Incidence of Out of Range Measurements
Acute Treatment Phase (Study Periods III-IV)
B1Y-MC-HCJE

Test	Incidence Group	Fluox (Total=109) N	n	(%)	Placebo (Total=110) N	n	(%)	p-value*
Sitting Systolic BP (mmHg)	HIGH	105	15	(14.3)	98	14	(14.3)	1.000
Sitting Diastolic BP (mmHg)	HIGH	104	11	(10.6)	101	8	(07.9)	0.632

* Frequencies are analyzed using a Fisher's Exact test.
Note: Total = Number of patients in the treatment group.
N = Number of patients Normal at Baseline.
n = Number of patients in the Incidence Group post Baseline.

RMP.B1YP.SASPGM(CUSTJEDA)
RMP.B1YO.HCJEREP(CUSTJEDA)

Table 14.61. Vital Signs
Incidence of Out of Range Measurements
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE

Test	Incidence Group	Fluox (Total=109) N	n	(%)	Placebo (Total=110) N	n	(%)	p-value*
Sitting Systolic BP (mmHg)	HIGH	105	20	(19.0)	98	18	(18.4)	1.000
Sitting Diastolic BP (mmHg)	HIGH	104	11	(10.6)	101	13	(12.9)	0.668

* Frequencies are analyzed using a Fisher's Exact test.
Note: Total = Number of patients in the treatment group.
N = Number of patients Normal at Baseline.
n = Number of patients in the Incidence Group post Baseline.

RMP.B1YP.SASPGM(CUSTJEDA)
RMP.B1YO.HCJEREP(CUSTJEDB)

Table 14.62. Vital Signs
Incidence of Out of Range Measurements
Study Period V, B1Y-MC-HCJE

Test	Incidence Group	Fluox (Total=90) N	n	(%)	Placebo (Total=68) N	n	(%)	p-value*
Sitting Systolic BP (mmHg)	HIGH	81	9	(11.1)	64	7	(10.9)	1.000
Sitting Diastolic BP (mmHg)	HIGH	78	1	(01.3)	66	7	(10.6)	0.024

* Frequencies are analyzed using a Fisher's Exact test.
Note: Total = Number of patients in the treatment group.
N = Number of patients Normal at Baseline.
n = Number of patients in the Incidence Group post Baseline.

RMP.B1YP.SASPGM(CUSTJEDA)
RMP.B1YO.HCJEREP(CUSTJEDC)

14.3.5.2. Change from Baseline to Endpoint for Study Period V

Table 14.63 summarizes the change in vital signs, height, and weight from baseline to endpoint for all randomized patients entering Study Period V. This analysis includes all randomized patients who did not discontinue prior to Visit 11.

On average, fluoxetine-treated patients gained less weight (mean increase of 1.3 kg) than placebo-treated patients (mean increase of 2.5 kg) over the 19-week treatment period (p=.010).

Fluoxetine-treated patients grew an average of 1.2 cm over the 19-week treatment period as compared with placebo-treated patients, who grew an average of 2.4 cm (p=.007).

Table 14.63. Vital Signs
Change from Baseline to Endpoint
All Patients Entering Study Period V
Study Period V, B1Y-MC-HCJE

Research Project Code: B1Y

Variables Analyzed	Therapy	n	Baseline Mean	Baseline SD	Change to Endpoint Mean	Change to Endpoint SD	p-Values Therapy (Int*1)
HEIGHT	Flx	75	156.0	14.6	1.2	2.4	.007
	Placebo	58	153.3	12.5	2.4	2.8	
WEIGHT	Flx	77	57.7	18.9	1.3	2.7	.010
	Placebo	60	54.7	19.6	2.5	2.6	
SI_HR	Flx	86	77.2	12.0	1.3	13.9	.732
	Placebo	67	78.3	10.7	0.5	13.9	
SI_SYSBP	Flx	86	109.8	11.4	0.2	10.3	.106
	Placebo	67	109.2	11.0	2.8	9.2	
SI_DIABP	Flx	86	67.0	9.7	0.1	9.6	.449
	Placebo	67	66.5	8.3	1.3	10.2	
TEMP	Flx	86	36.6	0.4	0.0	0.5	.498
	Placebo	67	36.5	0.5	-0.0	0.4	

RMP.B1YP.JCLLIB2(LAS6JEAD)
RMP.B1YO.HCJEREP(LAS6JEAD)
Note: n = Total number of patients in each treatment group having the variable in both baseline and postbaseline visits.

Note: Models:

FULL1 - *1 Type III Sums of Squares from an analysis of variance (ANOVA): PROC GLM model=treatment.
Least-squares mean option in PROC GLM from the ANOVA using the mean square for error.

XLAS0006

Table 14.63. Vital Signs
Change from Baseline to Endpoint
All Patients Entering Study Period V
Study Period V, B1Y-MC-HCJE (concluded)

```
Legend of Variable Abbreviations:
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Abbrev.     Description
-------     -----------

HEIGHT      Height/cm
SI_DIABP    Sitting Diastolic Blood Pressure/mmHg
SI_HR       Sitting Heart Rate/bpm
SI_SYSBP    Sitting Systolic Blood Pressure/mmHg
TEMP        Temperature
WEIGHT      Weight/kg
```

14.3.6. Electrocardiograms

Table 14.64 presents a summary of the ECG changes from baseline to endpoint for all randomized patients entering Study Period V. This analysis includes all patients who discontinued at Visit 11 or after and uses the [redacted] dataset. Fluoxetine-treated patients demonstrated a mean increase of 5.9 msec in Fridericia's QTc interval compared with a mean decrease of 0.3 msec observed in placebo-treated patients (p=.05).

Table 14.64. Electrocardiogram Measures [redacted]
Change from Baseline to Endpoint
All Patients Entering Study Period V
Study Period V, B1Y-MC-HCJE

Research Project Code: B1Y

Variables Analyzed	Therapy	n	Baseline Mean	Baseline SD	Change to Endpoint Mean	Change to Endpoint SD	p-Values Therapy
ECGHR	Flx	75	70.960	10.211	-0.067	10.507	.846
	Placebo	58	72.552	11.740	0.310	11.846	
RR_INT	Flx	75	862.667	123.007	-1.467	125.469	.762
	Placebo	58	851.207	150.974	-8.621	145.884	
PR_INT	Flx	75	139.067	16.618	0.800	13.230	.509
	Placebo	58	141.379	19.775	-0.690	12.406	
QRS_INT	Flx	75	81.733	6.652	-0.400	8.767	.676
	Placebo	58	81.207	7.511	0.172	6.350	
QT_INT	Flx	75	369.080	25.716	5.453	26.815	.124
	Placebo	58	368.103	22.041	-1.207	21.446	
QTC_INT	Flx	75	398.854	18.630	6.140	23.796	.118
	Placebo	58	401.572	18.178	0.121	19.100	
QTC_FRID	Flx	75	388.453	16.973	5.924	20.955	.050
	Placebo	58	389.792	12.497	-0.295	13.196	

RMP.B1YP.JCLLIB2(LAS6JEAJ)
RMP.B1YO.HCJEREP(LAS6JEAJ)
Note: n = Total number of patients in each treatment group having the variable in both baseline and postbaseline visits.

Note: Models:

FULL1 - Type III Sums of Squares from an analysis of variance (ANOVA): PROC GLM model=treatment.
Least-squares mean option in PROC GLM from the ANOVA using the mean square for error.

XLAS0006

Table 14.64. Electrocardiogram Measures[redacted]
Change from Baseline to Endpoint
All Patients Entering Study Period V
Study Period V, B1Y-MC-HCJE (concluded)

```
Legend of Variable Abbreviations:
---------------------------------

Abbrev.     Description
-------     -----------

ECGHR       ECG Heart Rate
PR_INT      PR Interval
QRS_INT     QRS Interval
QT_INT      QT Interval
QTC_FRID    QTC Interval Fridericia Method
QTC_INT     QTC Interval Bazett Method
RR_INT      RR Interval
```

ECG reference ranges are presented in Appendix 16.1.12. These reference ranges were used to determine out of range ECG intervals.

Out of range ECG measurements for the 10 weeks of treatment during Study Period V are presented in Table 14.65. The [redacted] dataset was used for this analysis. Using Bazett's correction, 2 fluoxetine-treated and 1 placebo-treated patient had QTc intervals that exceeded the high range (defined as an interval >440 msec). Using Fridericia's correction, 1 fluoxetine-treated and 0 placebo-treated patients had QTc intervals that met this criterion. There were no statistically significant differences between treatment groups in the incidence of any out of range ECG changes.

Table 14.65. Electrocardiogram Measures [redacted]
Incidence of Out of Range Measurements
Study Period V, B1Y-MC-HCJE

Test	Incidence Group	Fluox (Total=90) N	n	(%)	Placebo (Total=68) N	n	(%)	p-value*
Heart Rate (beats/min)	LOW	59	7	(11.9)	49	6	(12.2)	1.000
	HIGH	75	0	(0.0)	58	0	(0.0)	
PR Interval (msec)	LOW	75	0	(0.0)	58	0	(0.0)	
	HIGH	72	1	(1.4)	54	0	(0.0)	1.000
QRS Interval (msec)	LOW	75	0	(0.0)	58	0	(0.0)	
	HIGH	67	7	(10.4)	52	2	(3.8)	0.296
Bazett's QTC (msec)	HIGH	75	2	(2.7)	58	1	(1.7)	1.000
Fridericia's QTC (msec)	HIGH	75	1	(1.3)	58	0	(0.0)	1.000

* Frequencies are analyzed using a Fisher's Exact test.
Note: Total = Number of patients in the treatment group.
N = Number of patients at risk.
n = Number of patients in the Incidence Group Post Baseline.

RMP.B1YP.SASPGM(CUSTJEEA)
RMP.B1YO.HCJEREP(CUSTJEEB)

14.3.7. Abnormal Laboratory Values

14.3.7.1. Out of Range Laboratory Values

The laboratory reference ranges used in this study were established by [redacted] and are presented in Appendix 16.2.8. These reference ranges were used to determine if a laboratory value was abnormal or became abnormal during the study. Table 14.66 presents the proportion of patients with treatment-emergent abnormal laboratory values for the subchronic treatment phase. Discussion of these analyses is presented in Section 12.4.2.

Table 14.66. Laboratory Analysis
Treatment-Emergent Abnormal Values
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE

Lab Result Type: Numeric
Laboratory Test Group: Complete Blood Count

Incidence Group	Flx (1) (Total=109) N	n	(%)	Placebo(2) (Total=109) N	n	(%)	- p-Value *1 - Overall
Lab Test: HEMATOCRIT							
LOW	82	6	(7.3)	66	2	(3.0)	.299
HIGH	88	0		70	0		
Lab Test: HEMOGLOBIN							
LOW	84	1	(1.2)	70	4	(5.7)	.178
HIGH	88	0		73	0		
Lab Test: ERYTHROCYTE COUNT							
LOW	86	2	(2.3)	72	1	(1.4)	1.00
HIGH	88	0		73	0		

RMP.B1YP.JCLLIB2(LAS4JEAA)
RMP.B1YO.HCJEREP(LAS4JEAA)
* Frequencies are analyzed using a Fisher's Exact test.
Note:Total = Total number of patients in the treatment group having both baseline and endpoint visits.
N = Total number of at risk patients with the lab test.
n = Total number of at risk patients with the specific lab result (e.g. HIGH).
XLAS0004

Table 14.66. Laboratory Analysis
Treatment-Emergent Abnormal Values
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE (continued)

Lab Result Type: Numeric
Laboratory Test Group: Complete Blood Count

Incidence Group	Flx (1) (Total=109) N	n	(%)	Placebo(2) (Total=109) N	n	(%)	- p-Value *1 - Overall
Lab Test: MEAN CELL HEMOGLOBIN CONCENTRATION (MCHC) ---							
LOW	87	0		70	1	(1.4)	.446
HIGH	88	0		71	0		
Lab Test: MEAN CELL HEMOGLOBIN (MCH) ---							
LOW	87	0		70	0		
HIGH	88	0		73	0		
Lab Test: LEUKOCYTE COUNT ---							
LOW	84	3	(3.6)	70	1	(1.4)	.626
HIGH	88	0		73	0		

RMP.B1YP.JCLLIB2(LAS4JEAA)
RMP.B1YO.HCJEREP(LAS4JEAA)
* Frequencies are analyzed using a Fisher's Exact test.
Note:Total = Total number of patients in the treatment group having both baseline and endpoint visits.
N = Total number of at risk patients with the lab test.
n = Total number of at risk patients with the specific lab result (e.g. HIGH).
XLAS0004

Table 14.66. Laboratory Analysis
Treatment-Emergent Abnormal Values
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE (continued)

Lab Result Type: Numeric
Laboratory Test Group: Complete Blood Count

Incidence Group	Flx (1) (Total=109) N	n	(%)	Placebo(2) (Total=109) N	n	(%)	- p-Value *1 - Overall
Lab Test: BANDS							
LOW	88	0		73	0		
HIGH	88	0		73	1	(1.4)	.453
Lab Test: NEUTROPHILS, SEGMENTED							
LOW	87	1	(1.1)	73	1	(1.4)	1.00
HIGH	87	0		73	3	(4.1)	.093
Lab Test: LYMPHOCYTES							
LOW	87	1	(1.1)	73	0		1.00
HIGH	88	0		73	0		

RMP.B1YP.JCLLIB2(LAS4JEAA)
RMP.B1YO.HCJEREP(LAS4JEAA)
* Frequencies are analyzed using a Fisher's Exact test.
Note:Total = Total number of patients in the treatment group having both baseline and endpoint visits.
N = Total number of at risk patients with the lab test.
n = Total number of at risk patients with the specific lab result (e.g. HIGH).
XLAS0004

Table 14.66. Laboratory Analysis
Treatment-Emergent Abnormal Values
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE (continued)

Lab Result Type: Numeric
Laboratory Test Group: Complete Blood Count

Incidence Group	Flx (1) (Total=109) N	n	(%)	Placebo(2) (Total=109) N	n	(%)	- p-Value *1 - Overall
Lab Test: MONOCYTES							
LOW	87	1	(1.1)	73	1	(1.4)	1.00
HIGH	87	0		72	2	(2.8)	.203
Lab Test: EOSINOPHILS							
LOW	88	0		73	0		
HIGH	81	4	(4.9)	73	2	(2.7)	.684
Lab Test: BASOPHILS							
LOW	88	0		73	0		
HIGH	88	0		73	0		

RMP.B1YP.JCLLIB2(LAS4JEAA)
RMP.B1YO.HCJEREP(LAS4JEAA)
* Frequencies are analyzed using a Fisher's Exact test.
Note:Total = Total number of patients in the treatment group having both baseline and endpoint visits.
N = Total number of at risk patients with the lab test.
n = Total number of at risk patients with the specific lab result (e.g. HIGH).
XLAS0004

Table 14.66. Laboratory Analysis
Treatment-Emergent Abnormal Values
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE (continued)

Lab Result Type: Numeric
Laboratory Test Group: Complete Blood Count

Incidence Group	Flx (1) (Total=109) N	n	(%)	Placebo(2) (Total=109) N	n	(%)	- p-Value *1 - Overall
Lab Test: MEAN CELL VOLUME (MCV)							
LOW	84	4	(4.8)	68	2	(2.9)	.692
HIGH	88	3	(3.4)	70	0		.255
Lab Test: PLATELET COUNT							
LOW	86	0		73	0		
HIGH	84	2	(2.4)	69	2	(2.9)	1.00
Lab Test: LYMPHOCYTES, ATYPICAL							
LOW	88	0		73	0		
HIGH	88	0		73	1	(1.4)	.453

RMP.B1YP.JCLLIB2(LAS4JEAA)
RMP.B1YO.HCJEREP(LAS4JEAA)
* Frequencies are analyzed using a Fisher's Exact test.
Note:Total = Total number of patients in the treatment group having both baseline and endpoint visits.
N = Total number of at risk patients with the lab test.
n = Total number of at risk patients with the specific lab result (e.g. HIGH).
XLAS0004

Table 14.66. Laboratory Analysis
Treatment-Emergent Abnormal Values
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE (continued)

Lab Result Type: Numeric
Laboratory Test Group: Blood Chemistry

Incidence Group	Flx (1) (Total=109) N	n	(%)	Placebo(2) (Total=109) N	n	(%)	- p-Value *1 - Overall
Lab Test: AST/SGOT							
LOW	86	0		75	0		
HIGH	84	1	(1.2)	74	3	(4.1)	.341
Lab Test: ALT/SGPT							
LOW	86	0		75	2	(2.7)	.215
HIGH	83	2	(2.4)	72	4	(5.6)	.417
Lab Test: CREATINE PHOSPHOKINASE							
LOW	53	5	(9.4)	42	4	(9.5)	1.00
HIGH	85	1	(1.2)	75	2	(2.7)	.600

RMP.B1YP.JCLLIB2(LAS4JEAA)
RMP.B1YO.HCJEREP(LAS4JEAA)
* Frequencies are analyzed using a Fisher's Exact test.
Note:Total = Total number of patients in the treatment group having both baseline and endpoint visits.
N = Total number of at risk patients with the lab test.
n = Total number of at risk patients with the specific lab result (e.g. HIGH).
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Table 14.66. Laboratory Analysis
Treatment-Emergent Abnormal Values
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE (continued)

Lab Result Type: Numeric
Laboratory Test Group: Blood Chemistry

Incidence Group	Flx (1) (Total=109) N	n	(%)	Placebo(2) (Total=109) N	n	(%)	- p-Value *1 - Overall
Lab Test: ALKALINE PHOSPHATASE							
LOW	84	0		74	1	(1.4)	.468
HIGH	74	0		60	2	(3.3)	.199
Lab Test: GGT (GGPT/SGGT/YGGT)							
LOW	86	0		75	0		
HIGH	84	1	(1.2)	73	1	(1.4)	1.00
Lab Test: UREA NITROGEN							
LOW	86	0		75	0		
HIGH	86	0		75	0		

RMP.B1YP.JCLLIB2(LAS4JEAA)
RMP.B1YO.HCJEREP(LAS4JEAA)
* Frequencies are analyzed using a Fisher's Exact test.
Note:Total = Total number of patients in the treatment group having both baseline and endpoint visits.
N = Total number of at risk patients with the lab test.
n = Total number of at risk patients with the specific lab result (e.g. HIGH).
XLAS0004

Table 14.66. Laboratory Analysis
Treatment-Emergent Abnormal Values
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE (continued)

Lab Result Type: Numeric
Laboratory Test Group: Blood Chemistry

Incidence Group	Flx (1) (Total=109) N	n	(%)	Placebo(2) (Total=109) N	n	(%)	- p-Value *1 - Overall
Lab Test: CREATININE							
LOW	86	0		75	0		
HIGH	84	0		74	1	(1.4)	.468
Lab Test: CALCIUM							
LOW	86	0		75	0		
HIGH	86	0		75	0		
Lab Test: INORGANIC PHOSPHORUS							
LOW	83	0		74	0		
HIGH	81	1	(1.2)	72	2	(2.8)	.601

RMP.B1YP.JCLLIB2(LAS4JEAA)
RMP.B1YO.HCJEREP(LAS4JEAA)
* Frequencies are analyzed using a Fisher's Exact test.
Note:Total = Total number of patients in the treatment group having both baseline and endpoint visits.
N = Total number of at risk patients with the lab test.
n = Total number of at risk patients with the specific lab result (e.g. HIGH).
XLAS0004

Table 14.66. Laboratory Analysis
Treatment-Emergent Abnormal Values
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE (continued)

Lab Result Type: Numeric
Laboratory Test Group: Blood Chemistry

Incidence Group	Flx (1) (Total=109) N	n	(%)	Placebo(2) (Total=109) N	n	(%)	- p-Value *1 - Overall
Lab Test: TOTAL PROTEIN							
LOW	86	0		75	0		
HIGH	84	0		75	0		
Lab Test: ALBUMIN							
LOW	86	0		75	0		
HIGH	82	1	(1.2)	72	1	(1.4)	1.00
Lab Test: GLUCOSE, NON-FASTING							
LOW	84	0		75	0		
HIGH	84	0		75	0		

RMP.B1YP.JCLLIB2(LAS4JEAA)
RMP.B1YO.HCJEREP(LAS4JEAA)
* Frequencies are analyzed using a Fisher's Exact test.
Note:Total = Total number of patients in the treatment group having both baseline and endpoint visits.
N = Total number of at risk patients with the lab test.
n = Total number of at risk patients with the specific lab result (e.g. HIGH).
XLAS0004

Table 14.66. Laboratory Analysis
Treatment-Emergent Abnormal Values
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE (continued)

Lab Result Type: Numeric
Laboratory Test Group: Blood Chemistry

Incidence Group	Flx (1) (Total=109) N	n	(%)	Placebo(2) (Total=109) N	n	(%)	- p-Value *1 - Overall
Lab Test: URIC ACID							
LOW	82	1	(1.2)	70	1	(1.4)	1.00
HIGH	84	0		73	0		
Lab Test: CHOLESTEROL							
LOW	79	1	(1.3)	66	4	(6.1)	.177
HIGH	78	8	(10.3)	63	4	(6.3)	.548
Lab Test: BILIRUBIN, TOTAL							
LOW	85	1	(1.2)	74	3	(4.1)	.339
HIGH	85	0		74	1	(1.4)	.465

RMP.B1YP.JCLLIB2(LAS4JEAA)
RMP.B1YO.HCJEREP(LAS4JEAA)
* Frequencies are analyzed using a Fisher's Exact test.
Note:Total = Total number of patients in the treatment group having both baseline and endpoint visits.
N = Total number of at risk patients with the lab test.
n = Total number of at risk patients with the specific lab result (e.g. HIGH).
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Table 14.66. Laboratory Analysis
Treatment-Emergent Abnormal Values
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE (continued)

Lab Result Type: Numeric
Laboratory Test Group: Electrolytes

Incidence Group	Flx (1) (Total=109) N	n	(%)	Placebo(2) (Total=109) N	n	(%)	- p-Value *1 - Overall
Lab Test: SODIUM							
LOW	86	0		75	0		
HIGH	86	0		75	0		
Lab Test: POTASSIUM							
LOW	83	0		73	0		
HIGH	83	0		74	0		
Lab Test: CHLORIDE							
LOW	86	0		75	0		
HIGH	86	0		75	0		

RMP.B1YP.JCLLIB2(LAS4JEAA)
RMP.B1YO.HCJEREP(LAS4JEAA)
* Frequencies are analyzed using a Fisher's Exact test.
Note:Total = Total number of patients in the treatment group having both baseline and endpoint visits.
N = Total number of at risk patients with the lab test.
n = Total number of at risk patients with the specific lab result (e.g. HIGH).
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Table 14.66. Laboratory Analysis
Treatment-Emergent Abnormal Values
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE (continued)

Lab Result Type: Numeric
Laboratory Test Group: Electrolytes

Incidence Group	Flx (1) (Total=109) N	n	(%)	Placebo(2) (Total=109) N	n	(%)	- p-Value *1 - Overall
Lab Test: BICARBONATE, HCO3							
LOW	86	0		74	0		
HIGH	84	1	(1.2)	74	5	(6.8)	.099

RMP.B1YP.JCLLIB2(LAS4JEAA)
RMP.B1YO.HCJEREP(LAS4JEAA)
* Frequencies are analyzed using a Fisher's Exact test.
Note:Total = Total number of patients in the treatment group having both baseline and endpoint visits.
N = Total number of at risk patients with the lab test.
n = Total number of at risk patients with the specific lab result (e.g. HIGH).
XLAS0004

Table 14.66. Laboratory Analysis
Treatment-Emergent Abnormal Values
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE (continued)

Lab Result Type: Numeric
Laboratory Test Group: Thyroids

Incidence Group	Flx (1) (Total=109) N	n	(%)	Placebo(2) (Total=109) N	n	(%)	- p-Value *1 - Overall
Lab Test: THYROXINE, TOTAL-T4							
LOW	37	0		33	1	(3.0)	.471
HIGH	37	0		33	0		
Lab Test: THYROID STIM. HORMONE							
LOW	37	1	(2.7)	33	0		1.00
HIGH	36	0		33	0		
Lab Test: T3, TOTAL (TRIIODOTHYRONINE)							
LOW	36	0		33	0		
HIGH	37	0		33	0		

RMP.B1YP.JCLLIB2(LAS4JEAA)
RMP.B1YO.HCJEREP(LAS4JEAA)
* Frequencies are analyzed using a Fisher's Exact test.
Note:Total = Total number of patients in the treatment group having both baseline and endpoint visits.
N = Total number of at risk patients with the lab test.
n = Total number of at risk patients with the specific lab result (e.g. HIGH).
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Table 14.66. Laboratory Analysis
Treatment-Emergent Abnormal Values
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE (continued)

Lab Result Type: Numeric
Laboratory Test Group: Thyroids

Incidence Group	Flx (1) (Total=109) N	n	(%)	Placebo(2) (Total=109) N	n	(%)	- p-Value *1 - Overall
Lab Test: FREE THYROXINE INDEX							
LOW	37	0		33	0		
HIGH	37	0		33	0		
Lab Test: T3 % UPTAKE							
LOW	37	0		33	0		
HIGH	37	0		33	0		

RMP.B1YP.JCLLIB2(LAS4JEAA)
RMP.B1YO.HCJEREP(LAS4JEAA)
* Frequencies are analyzed using a Fisher's Exact test.
Note:Total = Total number of patients in the treatment group having both baseline and endpoint visits.
N = Total number of at risk patients with the lab test.
n = Total number of at risk patients with the specific lab result (e.g. HIGH).
XLAS0004

Table 14.66. Laboratory Analysis
Treatment-Emergent Abnormal Values
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE (continued)

Lab Result Type: Numeric
Laboratory Test Group: Urinalysis

Incidence Group	Flx (1) (Total=109) N	n	(%)	Placebo(2) (Total=109) N	n	(%)	- p-Value *1 - Overall
Lab Test: UA-SPECIFIC GRAVITY							
LOW	74	3	(4.1)	73	3	(4.1)	1.00
HIGH	81	6	(7.4)	74	6	(8.1)	1.00
Lab Test: UA-PH							
LOW	85	0		75	0		
HIGH	85	0		75	0		

RMP.B1YP.JCLLIB2(LAS4JEAA)
RMP.B1YO.HCJEREP(LAS4JEAA)
* Frequencies are analyzed using a Fisher's Exact test.
Note:Total = Total number of patients in the treatment group having both baseline and endpoint visits.
N = Total number of at risk patients with the lab test.
n = Total number of at risk patients with the specific lab result (e.g. HIGH).
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Table 14.66. Laboratory Analysis
Treatment-Emergent Abnormal Values
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE (continued)

Lab Result Type: Ordinal
Laboratory Test Group: Complete Blood Count

Incidence Group	Flx (1) (Total=109) N	n	(%)	Placebo(2) (Total=109) N	n	(%)	- p-Value *1 - Overall
Lab Test: ANISOCYTOSIS							
ABNORMAL	83	4	(4.8)	67	2	(3.0)	.692
Lab Test: MICROCYTOSIS							
ABNORMAL	87	1	(1.1)	67	2	(3.0)	.580
Lab Test: MACROCYTOSIS							
ABNORMAL	88	0		73	0		
Lab Test: POIKILOCYTOSIS							
ABNORMAL	88	0		73	0		
Lab Test: HYPOCHROMIA							
ABNORMAL	88	0		73	1	(1.4)	.453

RMP.B1YP.JCLLIB2(LAS4JEAA)
RMP.B1YO.HCJEREP(LAS4JEAA)
* Frequencies are analyzed using a Fisher's Exact test.
Note:Total = Total number of patients in the treatment group having both baseline and endpoint visits.
N = Total number of at risk patients with the lab test.
n = Total number of at risk patients with the specific lab result (e.g. HIGH).
XLAS0004

Table 14.66. Laboratory Analysis
Treatment-Emergent Abnormal Values
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE (continued)

Lab Result Type: Ordinal
Laboratory Test Group: Complete Blood Count

Incidence Group	Flx (1) (Total=109) N	n	(%)	Placebo(2) (Total=109) N	n	(%)	- p-Value *1 - Overall
Lab Test: POLYCHROMIA							
ABNORMAL	88	1	(1.1)	71	0		1.00
Lab Test: SPHEROCYTES							
ABNORMAL	88	0		73	0		
Lab Test: STOMATOCYTES							
ABNORMAL	88	0		73	0		
Lab Test: HYPERCHROMIA							
ABNORMAL	88	0		73	0		

RMP.B1YP.JCLLIB2(LAS4JEAA)
RMP.B1YO.HCJEREP(LAS4JEAA)
* Frequencies are analyzed using a Fisher's Exact test.
Note:Total = Total number of patients in the treatment group having both baseline and endpoint visits.
N = Total number of at risk patients with the lab test.
n = Total number of at risk patients with the specific lab result (e.g. HIGH).
XLAS0004

Table 14.66. Laboratory Analysis
Treatment-Emergent Abnormal Values
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE (continued)

Lab Result Type: Ordinal
Laboratory Test Group: Urinalysis

Incidence Group	Flx (1) (Total=109) N	n	(%)	Placebo(2) (Total=109) N	n	(%)	- p-Value *1 - Overall
Lab Test: UA-GLUCOSE							
ABNORMAL	85	0		75	1	(1.3)	.469
Lab Test: UA-RBC							
ABNORMAL	80	2	(2.5)	73	1	(1.4)	1.00
Lab Test: UA-WBC							
ABNORMAL	81	1	(1.2)	73	2	(2.7)	.604
Lab Test: UA-CASTS							
ABNORMAL	84	0		75	0		
Lab Test: UA-PROTEIN							
ABNORMAL	82	5	(6.1)	71	7	(9.9)	.548

RMP.B1YP.JCLLIB2(LAS4JEAA)
RMP.B1YO.HCJEREP(LAS4JEAA)
* Frequencies are analyzed using a Fisher's Exact test.
Note:Total = Total number of patients in the treatment group having both baseline and endpoint visits.
N = Total number of at risk patients with the lab test.
n = Total number of at risk patients with the specific lab result (e.g. HIGH).
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Table 14.66. Laboratory Analysis
Treatment-Emergent Abnormal Values
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE (continued)

```
Lab Result Type: Ordinal
Laboratory Test Group: Urinalysis

                                                - p-Value *1 -
            Flx    (1)      Placebo(2)
Incidence   (Total=109)     (Total=109)
Group       N   n   (%)     N   n   (%)       Overall
----------  --------------  --------------  --------------

Lab Test: UA-BILIRUBIN
          ---

ABNORMAL    85  0           75  0

Lab Test: UA-UROBILINOGEN
          ---

ABNORMAL    85  0           75  0

Lab Test: UA-KETONES
          ---

ABNORMAL    83  4  (4.8)    71  4  (5.6)    1.00

Lab Test: UA-OCCULT BLOOD
          ---

ABNORMAL    77  4  (5.2)    74  2  (2.7)    .682


RMP.B1YP.JCLLIB2(LAS4JEAA)
RMP.B1YO.HCJEREP(LAS4JEAA)
*  Frequencies are analyzed using a Fisher's Exact test.
Note:Total = Total number of patients in the treatment group having
             both baseline and endpoint visits.
          N = Total number of at risk patients with the lab test.
          n = Total number of at risk patients with the specific lab result
              (e.g. HIGH).
XLAS0004
```

Table 14.66. Laboratory Analysis
Treatment-Emergent Abnormal Values
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE (continued)

```
Lab Result Type: Subjective
Laboratory Test Group: Complete Blood Count

                                                - p-Value *1 -
            Flx    (1)      Placebo(2)
Incidence   (Total=109)     (Total=109)
Group       N   n   (%)     N   n   (%)       Overall
----------  --------------  --------------  --------------

Lab Test: RBC MORPHOLOGY
          ---

ABNORMAL    82  3  (3.7)    65  2  (3.1)    1.00

Lab Test: BASOPHILIC STIPPLING
          ---

ABNORMAL    88  0           73  0

Lab Test: HOWELL-JOLLY BODIES
          ---

ABNORMAL    88  0           73  0

Lab Test: TARGET CELLS
          ---

ABNORMAL    88  0           73  0

Lab Test: ELLIPTOCYTES
          ---

ABNORMAL    88  0           73  0


RMP.B1YP.JCLLIB2(LAS4JEAA)
RMP.B1YO.HCJEREP(LAS4JEAA)
*  Frequencies are analyzed using a Fisher's Exact test.
Note:Total = Total number of patients in the treatment group having
             both baseline and endpoint visits.
          N = Total number of at risk patients with the lab test.
          n = Total number of at risk patients with the specific lab result
              (e.g. HIGH).
XLAS0004
```

Table 14.66. Laboratory Analysis
Treatment-Emergent Abnormal Values
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE (continued)

Lab Result Type: Subjective
Laboratory Test Group: Complete Blood Count

Incidence Group	Flx (1) (Total=109) N	n	(%)	Placebo(2) (Total=109) N	n	(%)	- p-Value *1 - Overall
Lab Test: SCHISTOCYTES							
ABNORMAL	88	0		73	0		
Lab Test: ACANTHOCYTES							
ABNORMAL	88	0		73	0		
Lab Test: BURR CELLS							
ABNORMAL	88	0		73	0		
Lab Test: HELMET CELLS							
ABNORMAL	88	0		73	0		
Lab Test: ROULEAUX							
ABNORMAL	88	0		73	0		

RMP.B1YP.JCLLIB2(LAS4JEAA)
RMP.B1YO.HCJEREP(LAS4JEAA)
* Frequencies are analyzed using a Fisher's Exact test.
Note:Total = Total number of patients in the treatment group having both baseline and endpoint visits.
N = Total number of at risk patients with the lab test.
n = Total number of at risk patients with the specific lab result (e.g. HIGH).
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Table 14.66. Laboratory Analysis
Treatment-Emergent Abnormal Values
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE (continued)

```
Lab Result Type: Subjective
Laboratory Test Group: Urinalysis

                                                - p-Value *1 -
            Flx    (1)      Placebo(2)
Incidence   (Total=109)     (Total=109)
Group       N   n   (%)     N   n   (%)       Overall
----------  --------------  --------------  --------------

Lab Test: URINE COLOR
          ---

ABNORMAL    85  0           75  0

Lab Test: UA-MICROSCOPIC EXAM
          ---

ABNORMAL    72  4  (5.6)    64  8 (12.5)    .226

Lab Test: UA-NITRITES
          ---

ABNORMAL    85  0           75  2  (2.7)    .218


RMP.B1YP.JCLLIB2(LAS4JEAA)
RMP.B1YO.HCJEREP(LAS4JEAA)
*  Frequencies are analyzed using a Fisher's Exact test.
Note:Total = Total number of patients in the treatment group having
             both baseline and endpoint visits.
          N = Total number of at risk patients with the lab test.
          n = Total number of at risk patients with the specific lab result
              (e.g. HIGH).
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```

Table 14.66. Laboratory Analysis
Treatment-Emergent Abnormal Values
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE (continued)

```
Lab Result Type: Subjective
Laboratory Test Group: UDS

                                            - p-Value *1 -
            Flx    (1)      Placebo(2)
Incidence   (Total=109)     (Total=109)
Group       N   n   (%)     N   n   (%)       Overall
----------  --------------  --------------  --------------

Lab Test: DRUG SCREEN, URINE
          ---

ABNORMAL     4  0            1  0


RMP.B1YP.JCLLIB2(LAS4JEAA)
RMP.B1YO.HCJEREP(LAS4JEAA)
*  Frequencies are analyzed using a Fisher's Exact test.
Note:Total = Total number of patients in the treatment group having
             both baseline and endpoint visits.
          N = Total number of at risk patients with the lab test.
          n = Total number of at risk patients with the specific lab result
              (e.g. HIGH).
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```

Table 14.66. Laboratory Analysis
Treatment-Emergent Abnormal Values
All Randomized Patients
Subchronic Treatment Phase (Study Periods III-V)
B1Y-MC-HCJE (concluded)

OBS	Test Name	Test Code	Treatment Group	No. of Patients Excluded
1	UA-EPI.CELLS, RENAL TUBULAR	C12	Flx	1
2	UA-BACTERIA	C24	Flx	5
3	UA-BACTERIA	C24	Placebo	7
4	SQUAMOUS EPITHELIAL CELLS	D51	Flx	1
5	ALKALINE PHOSPHATASE	E13	Placebo	1
6	INORGANIC PHOSPHORUS	F06	Placebo	1
7	POTASSIUM	F08	Placebo	1
8	BICARBONATE, HCO3	F65	Placebo	1
9	LAST MEDICATION DOSE DATE	H13	Flx	104
10	LAST MEDICATION DOSE DATE	H13	Placebo	83
11	LAST MEDICATION DOSE TIME	H14	Flx	103
12	LAST MEDICATION DOSE TIME	H14	Placebo	83
13	NEXT TO LAST MEDICATION DOSE DATE	H15	Flx	104
14	NEXT TO LAST MEDICATION DOSE DATE	H15	Placebo	83
15	NEXT TO LAST MEDICATION DOSE TIME	H16	Flx	102
16	NEXT TO LAST MEDICATION DOSE TIME	H16	Placebo	83

Table 14.67 presents the proportion of patients with treatment-emergent abnormal laboratory values for all patients entering Study Period V. Zero fluoxetine-treated patients experienced an out of range alkaline phosphatase level, while 1 (2%) placebo-treated patient experienced an abnormally high alkaline phosphatase level and 1 (2%) placebo-treated patient experienced an abnormally low alkaline phosphatase level.

One (1%) fluoxetine-treated patient experienced an abnormally low cholesterol level and 8 (12%) fluoxetine-treated patients experienced an abnormally high cholesterol level. Two (4%) placebo-treated patients experienced an abnormally low cholesterol level and 4 (9%) placebo-treated patients experienced an abnormally high cholesterol level.

Table 14.67. Laboratory Analysis
Treatment-Emergent Abnormal Values
All Patients Entering Study Period V
Study Period V, B1Y-MC-HCJE

Lab Result Type: Numeric
Laboratory Test Group: Complete Blood Count

Incidence Group	Flx (1) (Total=90) N	n	(%)	Placebo(2) (Total=68) N	n	(%)	- p-Value *1 - Overall
Lab Test: HEMATOCRIT							
LOW	72	6	(8.3)	51	1	(2.0)	.237
HIGH	75	0		55	0		
Lab Test: HEMOGLOBIN							
LOW	75	2	(2.7)	55	1	(1.8)	1.00
HIGH	75	0		57	0		
Lab Test: ERYTHROCYTE COUNT							
LOW	74	2	(2.7)	56	1	(1.8)	1.00
HIGH	75	0		57	0		

RMP.B1YP.JCLLIB2(LAS4JEAB)
RMP.B1YO.HCJEREP(LAS4JEAB)
* Frequencies are analyzed using a Fisher's Exact test.
Note:Total = Total number of patients in the treatment group having both baseline and endpoint visits.
N = Total number of at risk patients with the lab test.
n = Total number of at risk patients with the specific lab result (e.g. HIGH).
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Table 14.67. Laboratory Analysis
Treatment-Emergent Abnormal Values
All Patients Entering Study Period V
Study Period V, B1Y-MC-HCJE (continued)

Lab Result Type: Numeric
Laboratory Test Group: Complete Blood Count

Incidence Group	Flx (1) (Total=90) N	n	(%)	Placebo(2) (Total=68) N	n	(%)	- p-Value *1 - Overall
Lab Test: MEAN CELL HEMOGLOBIN CONCENTRATION (MCHC)							
LOW	74	0		56	1	(1.8)	.431
HIGH	75	0		56	0		
Lab Test: MEAN CELL HEMOGLOBIN (MCH)							
LOW	74	0		56	0		
HIGH	75	0		57	0		
Lab Test: LEUKOCYTE COUNT							
LOW	72	2	(2.8)	54	1	(1.9)	1.00
HIGH	75	0		57	0		

RMP.B1YP.JCLLIB2(LAS4JEAB)
RMP.B1YO.HCJEREP(LAS4JEAB)
* Frequencies are analyzed using a Fisher's Exact test.
Note:Total = Total number of patients in the treatment group having both baseline and endpoint visits.
N = Total number of at risk patients with the lab test.
n = Total number of at risk patients with the specific lab result (e.g. HIGH).
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Table 14.67. Laboratory Analysis
Treatment-Emergent Abnormal Values
All Patients Entering Study Period V
Study Period V, B1Y-MC-HCJE (continued)

```
Lab Result Type: Numeric
Laboratory Test Group: Complete Blood Count

                                                - p-Value *1 -
            Flx    (1)      Placebo(2)
Incidence   (Total=90)      (Total=68)
Group       N   n   (%)     N   n   (%)       Overall
----------  --------------  --------------  --------------

Lab Test: BANDS
          ---

LOW         75  0           57  0

HIGH        75  0           57  0

Lab Test: NEUTROPHILS, SEGMENTED
          ---

LOW         74  0           57  1  (1.8)    .435

HIGH        74  0           57  2  (3.5)    .187

Lab Test: LYMPHOCYTES
          ---

LOW         75  0           57  0

HIGH        75  0           57  0


RMP.B1YP.JCLLIB2(LAS4JEAB)
RMP.B1YO.HCJEREP(LAS4JEAB)
*  Frequencies are analyzed using a Fisher's Exact test.
Note:Total = Total number of patients in the treatment group having
             both baseline and endpoint visits.
          N = Total number of at risk patients with the lab test.
          n = Total number of at risk patients with the specific lab result
              (e.g. HIGH).
XLAS0004
```

Table 14.67. Laboratory Analysis
Treatment-Emergent Abnormal Values
All Patients Entering Study Period V
Study Period V, B1Y-MC-HCJE (continued)

```
Lab Result Type: Numeric
Laboratory Test Group: Complete Blood Count

                                                - p-Value *1 -
            Flx    (1)      Placebo(2)
Incidence   (Total=90)      (Total=68)
Group       N   n   (%)     N   n   (%)       Overall
----------  --------------  --------------  --------------

Lab Test: MONOCYTES
          ---

LOW         74  1  (1.4)    57  0           1.00

HIGH        75  0           56  2  (3.6)    .181

Lab Test: EOSINOPHILS
          ---

LOW         75  0           57  0

HIGH        69  4  (5.8)    57  2  (3.5)    .689

Lab Test: BASOPHILS
          ---

LOW         75  0           57  0

HIGH        75  0           57  0


RMP.B1YP.JCLLIB2(LAS4JEAB)
RMP.B1YO.HCJEREP(LAS4JEAB)
*  Frequencies are analyzed using a Fisher's Exact test.
Note:Total = Total number of patients in the treatment group having
             both baseline and endpoint visits.
          N = Total number of at risk patients with the lab test.
          n = Total number of at risk patients with the specific lab result
              (e.g. HIGH).
XLAS0004
```

Table 14.67. Laboratory Analysis
Treatment-Emergent Abnormal Values
All Patients Entering Study Period V
Study Period V, B1Y-MC-HCJE (continued)

Lab Result Type: Numeric
Laboratory Test Group: Complete Blood Count

Incidence Group	Flx (1) (Total=90) N	n	(%)	Placebo(2) (Total=68) N	n	(%)	- p-Value *1 - Overall
Lab Test: MEAN CELL VOLUME (MCV)							
LOW	72	4	(5.6)	54	1	(1.9)	.391
HIGH	75	3	(4.0)	56	0		.260
Lab Test: PLATELET COUNT							
LOW	74	0		57	0		
HIGH	72	2	(2.8)	54	1	(1.9)	1.00

RMP.B1YP.JCLLIB2(LAS4JEAB)
RMP.B1YO.HCJEREP(LAS4JEAB)
* Frequencies are analyzed using a Fisher's Exact test.
Note:Total = Total number of patients in the treatment group having both baseline and endpoint visits.
N = Total number of at risk patients with the lab test.
n = Total number of at risk patients with the specific lab result (e.g. HIGH).
XLAS0004

Table 14.67. Laboratory Analysis
Treatment-Emergent Abnormal Values
All Patients Entering Study Period V
Study Period V, B1Y-MC-HCJE (continued)

Lab Result Type: Numeric
Laboratory Test Group: Blood Chemistry

Incidence Group	Flx (1) (Total=90) N	n	(%)	Placebo(2) (Total=68) N	n	(%)	- p-Value *1 - Overall
Lab Test: AST/SGOT							
LOW	75	0		58	0		
HIGH	72	1	(1.4)	56	2	(3.6)	.581
Lab Test: ALT/SGPT							
LOW	75	0		58	2	(3.4)	.188
HIGH	71	1	(1.4)	55	4	(7.3)	.167
Lab Test: CREATINE PHOSPHOKINASE							
LOW	46	5	(10.9)	34	4	(11.8)	1.00
HIGH	74	1	(1.4)	58	0		1.00

RMP.B1YP.JCLLIB2(LAS4JEAB)
RMP.B1YO.HCJEREP(LAS4JEAB)
* Frequencies are analyzed using a Fisher's Exact test.
Note:Total = Total number of patients in the treatment group having both baseline and endpoint visits.
N = Total number of at risk patients with the lab test.
n = Total number of at risk patients with the specific lab result (e.g. HIGH).
XLAS0004

Table 14.67. Laboratory Analysis
Treatment-Emergent Abnormal Values
All Patients Entering Study Period V
Study Period V, B1Y-MC-HCJE (continued)

Lab Result Type: Numeric
Laboratory Test Group: Blood Chemistry

Incidence Group	Flx (1) (Total=90) N	n	(%)	Placebo(2) (Total=68) N	n	(%)	- p-Value *1 - Overall
Lab Test: ALKALINE PHOSPHATASE							
LOW	73	0		57	1	(1.8)	.438
HIGH	64	0		46	1	(2.2)	.418
Lab Test: GGT (GGPT/SGGT/YGGT)							
LOW	75	0		58	0		
HIGH	73	1	(1.4)	56	1	(1.8)	1.00
Lab Test: UREA NITROGEN							
LOW	75	0		58	0		
HIGH	75	0		58	0		

RMP.B1YP.JCLLIB2(LAS4JEAB)
RMP.B1YO.HCJEREP(LAS4JEAB)
* Frequencies are analyzed using a Fisher's Exact test.
Note:Total = Total number of patients in the treatment group having both baseline and endpoint visits.
N = Total number of at risk patients with the lab test.
n = Total number of at risk patients with the specific lab result (e.g. HIGH).
XLAS0004

Table 14.67. Laboratory Analysis
Treatment-Emergent Abnormal Values
All Patients Entering Study Period V
Study Period V, B1Y-MC-HCJE (continued)

Lab Result Type: Numeric
Laboratory Test Group: Blood Chemistry

Incidence Group	Flx (1) (Total=90) N	n	(%)	Placebo(2) (Total=68) N	n	(%)	- p-Value *1 - Overall
Lab Test: CREATININE							
LOW	75	0		58	0		
HIGH	73	1	(1.4)	58	1	(1.7)	1.00
Lab Test: CALCIUM							
LOW	75	0		58	0		
HIGH	75	0		58	0		
Lab Test: INORGANIC PHOSPHORUS							
LOW	72	0		57	0		
HIGH	70	1	(1.4)	56	1	(1.8)	1.00

RMP.B1YP.JCLLIB2(LAS4JEAB)
RMP.B1YO.HCJEREP(LAS4JEAB)
* Frequencies are analyzed using a Fisher's Exact test.
Note:Total = Total number of patients in the treatment group having both baseline and endpoint visits.
N = Total number of at risk patients with the lab test.
n = Total number of at risk patients with the specific lab result (e.g. HIGH).
XLAS0004

Table 14.67. Laboratory Analysis
Treatment-Emergent Abnormal Values
All Patients Entering Study Period V
Study Period V, B1Y-MC-HCJE (continued)

Lab Result Type: Numeric
Laboratory Test Group: Blood Chemistry

Incidence Group	Flx (1) (Total=90) N	n	(%)	Placebo(2) (Total=68) N	n	(%)	- p-Value *1 - Overall
Lab Test: TOTAL PROTEIN							
LOW	75	0		58	0		
HIGH	75	0		58	0		
Lab Test: ALBUMIN							
LOW	73	7	(9.6)	55	3	(5.5)	.514
HIGH	75	0		58	0		
Lab Test: GLUCOSE, NON-FASTING							
LOW	73	0		58	0		
HIGH	73	0		58	0		

RMP.B1YP.JCLLIB2(LAS4JEAB)
RMP.B1YO.HCJEREP(LAS4JEAB)
* Frequencies are analyzed using a Fisher's Exact test.
Note:Total = Total number of patients in the treatment group having both baseline and endpoint visits.
N = Total number of at risk patients with the lab test.
n = Total number of at risk patients with the specific lab result (e.g. HIGH).
XLAS0004

Table 14.67. Laboratory Analysis
Treatment-Emergent Abnormal Values
All Patients Entering Study Period V
Study Period V, B1Y-MC-HCJE (continued)

Lab Result Type: Numeric
Laboratory Test Group: Blood Chemistry

Incidence Group	Flx (1) (Total=90) N	n	(%)	Placebo(2) (Total=68) N	n	(%)	- p-Value *1 - Overall
Lab Test: URIC ACID							
LOW	71	0		53	1	(1.9)	.427
HIGH	73	0		56	0		
Lab Test: CHOLESTEROL							
LOW	69	1	(1.4)	52	2	(3.8)	.576
HIGH	68	8	(11.8)	47	4	(8.5)	.759
Lab Test: BILIRUBIN, TOTAL							
LOW	74	1	(1.4)	57	3	(5.3)	.317
HIGH	74	0		57	1	(1.8)	.435

RMP.B1YP.JCLLIB2(LAS4JEAB)
RMP.B1YO.HCJEREP(LAS4JEAB)
* Frequencies are analyzed using a Fisher's Exact test.
Note:Total = Total number of patients in the treatment group having both baseline and endpoint visits.
N = Total number of at risk patients with the lab test.
n = Total number of at risk patients with the specific lab result (e.g. HIGH).
XLAS0004

Table 14.67. Laboratory Analysis
Treatment-Emergent Abnormal Values
All Patients Entering Study Period V
Study Period V, B1Y-MC-HCJE (continued)

Lab Result Type: Numeric
Laboratory Test Group: Electrolytes

Incidence Group	Flx (1) (Total=90) N	n	(%)	Placebo(2) (Total=68) N	n	(%)	- p-Value *1 - Overall
Lab Test: SODIUM							
LOW	75	0		58	0		
HIGH	75	0		58	0		
Lab Test: POTASSIUM							
LOW	72	0		56	0		
HIGH	72	0		57	0		
Lab Test: CHLORIDE							
LOW	75	0		58	0		
HIGH	75	0		58	0		

RMP.B1YP.JCLLIB2(LAS4JEAB)
RMP.B1YO.HCJEREP(LAS4JEAB)
* Frequencies are analyzed using a Fisher's Exact test.
Note:Total = Total number of patients in the treatment group having both baseline and endpoint visits.
N = Total number of at risk patients with the lab test.
n = Total number of at risk patients with the specific lab result (e.g. HIGH).
XLAS0004

Table 14.67. Laboratory Analysis
Treatment-Emergent Abnormal Values
All Patients Entering Study Period V
Study Period V, B1Y-MC-HCJE (continued)

```
Lab Result Type: Numeric
Laboratory Test Group: Electrolytes

                                                - p-Value *1 -
            Flx    (1)      Placebo(2)
Incidence   (Total=90)      (Total=68)
Group       N   n   (%)     N   n   (%)       Overall
----------  --------------  --------------  --------------

Lab Test: BICARBONATE, HCO3
          ---

LOW         75  0           57  0

HIGH        73  1  (1.4)    57  4  (7.0)    .168


RMP.B1YP.JCLLIB2(LAS4JEAB)
RMP.B1YO.HCJEREP(LAS4JEAB)
*  Frequencies are analyzed using a Fisher's Exact test.
Note:Total = Total number of patients in the treatment group having
             both baseline and endpoint visits.
          N = Total number of at risk patients with the lab test.
          n = Total number of at risk patients with the specific lab result
              (e.g. HIGH).
XLAS0004
```

Table 14.67. Laboratory Analysis
Treatment-Emergent Abnormal Values
All Patients Entering Study Period V
Study Period V, B1Y-MC-HCJE (continued)

Lab Result Type: Numeric
Laboratory Test Group: Thyroids

Incidence Group	Flx (1) (Total=90) N	n	(%)	Placebo(2) (Total=68) N	n	(%)	- p-Value *1 - Overall
Lab Test: THYROXINE, TOTAL-T4							
LOW	26	0		16	0		
HIGH	26	0		16	0		
Lab Test: THYROID STIM. HORMONE							
LOW	26	1	(3.8)	16	0		1.00
HIGH	25	0		16	0		
Lab Test: T3, TOTAL (TRIIODOTHYRONINE)							
LOW	26	0		16	1	(6.3)	.381
HIGH	26	0		16	0		

RMP.B1YP.JCLLIB2(LAS4JEAB)
RMP.B1YO.HCJEREP(LAS4JEAB)
* Frequencies are analyzed using a Fisher's Exact test.
Note:Total = Total number of patients in the treatment group having both baseline and endpoint visits.
N = Total number of at risk patients with the lab test.
n = Total number of at risk patients with the specific lab result (e.g. HIGH).
XLAS0004

Table 14.67. Laboratory Analysis
Treatment-Emergent Abnormal Values
All Patients Entering Study Period V
Study Period V, B1Y-MC-HCJE (continued)

Lab Result Type: Numeric
Laboratory Test Group: Thyroids

Incidence Group	Flx (1) (Total=90) N	n	(%)	Placebo(2) (Total=68) N	n	(%)	- p-Value *1 - Overall
Lab Test: FREE THYROXINE INDEX							
LOW	26	0		16	0		
HIGH	26	0		16	0		
Lab Test: T3 % UPTAKE							
LOW	26	0		16	0		
HIGH	26	0		16	0		

RMP.B1YP.JCLLIB2(LAS4JEAB)
RMP.B1YO.HCJEREP(LAS4JEAB)
* Frequencies are analyzed using a Fisher's Exact test.
Note:Total = Total number of patients in the treatment group having both baseline and endpoint visits.
N = Total number of at risk patients with the lab test.
n = Total number of at risk patients with the specific lab result (e.g. HIGH).
XLAS0004

Table 14.67. Laboratory Analysis
Treatment-Emergent Abnormal Values
All Patients Entering Study Period V
Study Period V, B1Y-MC-HCJE (continued)

Lab Result Type: Numeric
Laboratory Test Group: Urinalysis

Incidence Group	Flx (1) (Total=90) N	n	(%)	Placebo(2) (Total=68) N	n	(%)	- p-Value *1 - Overall
Lab Test: UA-SPECIFIC GRAVITY							
LOW	63	3	(4.8)	56	3	(5.4)	1.00
HIGH	68	6	(8.8)	57	4	(7.0)	.754
Lab Test: UA-PH							
LOW	72	0		58	0		
HIGH	72	0		58	0		

RMP.B1YP.JCLLIB2(LAS4JEAB)
RMP.B1YO.HCJEREP(LAS4JEAB)
* Frequencies are analyzed using a Fisher's Exact test.
Note:Total = Total number of patients in the treatment group having both baseline and endpoint visits.
N = Total number of at risk patients with the lab test.
n = Total number of at risk patients with the specific lab result (e.g. HIGH).
XLAS0004

Table 14.67. Laboratory Analysis
Treatment-Emergent Abnormal Values
All Patients Entering Study Period V
Study Period V, B1Y-MC-HCJE (continued)

Lab Result Type: Ordinal
Laboratory Test Group: Urinalysis

Incidence Group	Flx (1) (Total=90) N	n	(%)	Placebo(2) (Total=68) N	n	(%)	- p-Value *1 - Overall
Lab Test: UA-GLUCOSE							
ABNORMAL	72	0		58	1	(1.7)	.446
Lab Test: UA-PROTEIN							
ABNORMAL	70	5	(7.1)	54	7	(13.0)	.362
Lab Test: UA-BILIRUBIN							
ABNORMAL	72	0		58	0		
Lab Test: UA-UROBILINOGEN							
ABNORMAL	72	0		58	0		
Lab Test: UA-KETONES							
ABNORMAL	70	4	(5.7)	54	4	(7.4)	.727

RMP.B1YP.JCLLIB2(LAS4JEAB)
RMP.B1YO.HCJEREP(LAS4JEAB)
* Frequencies are analyzed using a Fisher's Exact test.
Note:Total = Total number of patients in the treatment group having both baseline and endpoint visits.
N = Total number of at risk patients with the lab test.
n = Total number of at risk patients with the specific lab result (e.g. HIGH).
XLAS0004

Table 14.67. Laboratory Analysis
Treatment-Emergent Abnormal Values
All Patients Entering Study Period V
Study Period V, B1Y-MC-HCJE (continued)

```
Lab Result Type: Ordinal
Laboratory Test Group: Urinalysis

                                                - p-Value *1 -
            Flx    (1)      Placebo(2)
Incidence   (Total=90)      (Total=68)
Group       N   n   (%)     N   n   (%)       Overall
----------  --------------  --------------  --------------

Lab Test: UA-OCCULT BLOOD
          ---

ABNORMAL    65  3  (4.6)    58  2  (3.4)    1.00


RMP.B1YP.JCLLIB2(LAS4JEAB)
RMP.B1YO.HCJEREP(LAS4JEAB)
*  Frequencies are analyzed using a Fisher's Exact test.
Note:Total = Total number of patients in the treatment group having
             both baseline and endpoint visits.
          N = Total number of at risk patients with the lab test.
          n = Total number of at risk patients with the specific lab result
              (e.g. HIGH).
XLAS0004
```

Table 14.67. Laboratory Analysis
Treatment-Emergent Abnormal Values
All Patients Entering Study Period V
Study Period V, B1Y-MC-HCJE (continued)

```
Lab Result Type: Subjective
Laboratory Test Group: Complete Blood Count

                                                - p-Value *1 -
            Flx    (1)      Placebo(2)
Incidence   (Total=90)      (Total=68)
Group       N   n   (%)     N   n   (%)       Overall
----------  --------------  --------------  --------------

Lab Test: RBC MORPHOLOGY
          ---

ABNORMAL    68  0           50  0


RMP.B1YP.JCLLIB2(LAS4JEAB)
RMP.B1YO.HCJEREP(LAS4JEAB)
*  Frequencies are analyzed using a Fisher's Exact test.
Note:Total = Total number of patients in the treatment group having
             both baseline and endpoint visits.
          N = Total number of at risk patients with the lab test.
          n = Total number of at risk patients with the specific lab result
              (e.g. HIGH).
XLAS0004
```

Table 14.67. Laboratory Analysis
Treatment-Emergent Abnormal Values
All Patients Entering Study Period V
Study Period V, B1Y-MC-HCJE (continued)

```
Lab Result Type: Subjective
Laboratory Test Group: Urinalysis

                                                - p-Value *1 -
            Flx    (1)      Placebo(2)
Incidence   (Total=90)      (Total=68)
Group       N   n   (%)     N   n   (%)       Overall
----------  --------------  --------------  --------------

Lab Test: URINE COLOR
          ---

ABNORMAL    72  0           58  0

Lab Test: UA-MICROSCOPIC EXAM
          ---

ABNORMAL    46  0           36  0

Lab Test: UA-NITRITES
          ---

ABNORMAL    72  0           58  2  (3.4)    .197


RMP.B1YP.JCLLIB2(LAS4JEAB)
RMP.B1YO.HCJEREP(LAS4JEAB)
*  Frequencies are analyzed using a Fisher's Exact test.
Note:Total = Total number of patients in the treatment group having
             both baseline and endpoint visits.
          N = Total number of at risk patients with the lab test.
          n = Total number of at risk patients with the specific lab result
              (e.g. HIGH).
XLAS0004
```

Table 14.67. Laboratory Analysis
Treatment-Emergent Abnormal Values
All Patients Entering Study Period V
Study Period V, B1Y-MC-HCJE (continued)

```
Lab Result Type: Subjective
Laboratory Test Group: UDS

                                                - p-Value *1 -
            Flx    (1)      Placebo(2)
Incidence   (Total=90)      (Total=68)
Group       N   n   (%)     N   n   (%)       Overall
----------  --------------  --------------  --------------

Lab Test: DRUG SCREEN, URINE
          ---

ABNORMAL     2  0


RMP.B1YP.JCLLIB2(LAS4JEAB)
RMP.B1YO.HCJEREP(LAS4JEAB)
*  Frequencies are analyzed using a Fisher's Exact test.
Note:Total = Total number of patients in the treatment group having
             both baseline and endpoint visits.
          N = Total number of at risk patients with the lab test.
          n = Total number of at risk patients with the specific lab result
              (e.g. HIGH).
XLAS0004
```

Table 14.67. Laboratory Analysis
Treatment-Emergent Abnormal Values
All Patients Entering Study Period V
Study Period V, B1Y-MC-HCJE (concluded)

, March 22, 2000

OBS	Test Name	Test Code	Treatment Group	No. of Patients Excluded
1	RBC MORPHOLOGY	A60	Flx	2
2	RBC MORPHOLOGY	A60	Placebo	2
3	ANISOCYTOSIS	A61	Flx	4
4	ANISOCYTOSIS	A61	Placebo	2
5	MICROCYTOSIS	A62	Flx	1
6	MICROCYTOSIS	A62	Placebo	2
7	HYPOCHROMIA	A65	Placebo	1
8	POLYCHROMIA	A66	Flx	1
9	LYMPHOCYTES, ATYPICAL	A87	Placebo	1
10	UA-RBC	C11	Flx	6
11	UA-RBC	C11	Placebo	4
12	UA-EPI.CELLS, RENAL TUBULAR	C12	Flx	1
13	UA-MICROSCOPIC EXAM	C14	Flx	9
14	UA-MICROSCOPIC EXAM	C14	Placebo	5
15	UA-WBC	C15	Flx	6
16	UA-WBC	C15	Placebo	8
17	UA-BACTERIA	C24	Flx	4
18	UA-BACTERIA	C24	Placebo	6
19	ALKALINE PHOSPHATASE	E13	Placebo	1
20	INORGANIC PHOSPHORUS	F06	Placebo	1
21	POTASSIUM	F08	Placebo	1
22	BICARBONATE, HCO3	F65	Placebo	1
23	LAST MEDICATION DOSE DATE	H13	Flx	76
24	LAST MEDICATION DOSE DATE	H13	Placebo	57
25	LAST MEDICATION DOSE TIME	H14	Flx	74
26	LAST MEDICATION DOSE TIME	H14	Placebo	56
27	NEXT TO LAST MEDICATION DOSE DATE	H15	Flx	76
28	NEXT TO LAST MEDICATION DOSE DATE	H15	Placebo	58
29	NEXT TO LAST MEDICATION DOSE TIME	H16	Flx	74
30	NEXT TO LAST MEDICATION DOSE TIME	H16	Placebo	57

14.3.7.2. Change from Baseline to Endpoint for Study Period V

Table 14.68 summarizes the changes in laboratory values from baseline to endpoint for all randomized patients entering Study Period V. This analysis includes all patients who did not discontinue prior to Visit 11.

As seen in the subchronic treatment phase, there were statistically significant differences between treatment groups for the change in alkaline phosphatase and cholesterol levels. Fluoxetine-treated patients experienced a mean decrease of 37.4 U/L (SD 29.0) in alkaline phosphatase compared with a mean decrease of 1.1 (SD 37.5) for placebo-treated patients ($p<.001$). The clinical relevance of this finding is unknown. Additional analyses are presented in Section 12.4.3. Fluoxetine-treated patients experienced a mean increase of 0.1 mmol/L (SD 0.5) in cholesterol compared with a mean decrease of 0.1 (SD 0.6) for placebo-treated patients ($p=.024$). The variability in cholesterol levels is not considered clinically significant. The pattern observed in the mean change from baseline to endpoint for cholesterol levels is similar to what has been reported in adult patients (Clinical Investigator's Brochure 1999).

Table 14.68. Laboratory Analysis
Change from Baseline to Endpoint
All Patients Entering Study Period V
Study Period V, B1Y-MC-HCJE

Laboratory Test Group: Complete Blood Count

Lab Test	Lab Unit	Therapy	n	Baseline Mean	Baseline SD	Change to Endpoint Mean	Change to Endpoint SD	p-Values Therapy
HCT	1	Flx	75	0.403	0.027	-0.014	0.029	.515
		Placebo	56	0.403	0.032	-0.011	0.024	
HGB	mml/L-Fe	Flx	75	8.422	0.513	-0.215	0.384	.932
		Placebo	57	8.448	0.637	-0.209	0.427	
RBC	TI/L	Flx	75	4.736	0.295	-0.123	0.249	.673
		Placebo	57	4.753	0.346	-0.105	0.212	
MCHC	mml/L-Fe	Flx	75	21.051	0.961	0.132	1.234	.961
		Placebo	56	21.034	0.764	0.122	1.192	
MCH	fmol(Fe)	Flx	75	1.786	0.105	0.004	0.063	.682
		Placebo	57	1.779	0.100	0.000	0.048	
WBC	GI/L	Flx	75	6.818	1.933	0.266	1.860	.672
		Placebo	57	6.860	1.827	0.112	2.308	
BANDS	GI/L	Flx	75	0.000	0.000	0.003	0.029	.385
		Placebo	57	0.000	0.000	0.000	0.000	
POLYS	GI/L	Flx	75	3.810	1.538	0.229	1.548	.691
		Placebo	57	3.733	1.415	0.105	2.041	
LYMPHS	GI/L	Flx	75	2.351	0.531	-0.008	0.552	.820
		Placebo	57	2.476	0.680	-0.032	0.665	
MONOS	GI/L	Flx	75	0.432	0.158	0.023	0.169	.970
		Placebo	57	0.454	0.153	0.022	0.203	
EOSN	GI/L	Flx	75	0.183	0.205	0.015	0.171	.938
		Placebo	57	0.151	0.120	0.016	0.095	
BASO	GI/L	Flx	75	0.043	0.018	0.003	0.027	.580
		Placebo	57	0.046	0.019	0.001	0.026	

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Table 14.68. Laboratory Analysis
Change from Baseline to Endpoint
All Patients Entering Study Period V
Study Period V, B1Y-MC-HCJE (continued)

Laboratory Test Group: Complete Blood Count

Lab Test	Lab Unit	Therapy	n	Baseline Mean	Baseline SD	Change to Endpoint Mean	Change to Endpoint SD	p-Values Therapy
MCV	fL	Flx	75	84.947	4.020	-0.467	4.114	.731
		Placebo	56	84.589	4.713	-0.214	4.181	
PLTCT	GI/L	Flx	75	281.933	62.283	-0.080	44.769	.744
		Placebo	57	270.351	58.392	2.351	38.575	
ATLYMP	GI/L	Flx	75	0.000	0.000	0.000	0.000	.253
		Placebo	57	0.000	0.000	0.002	0.016	

XLAS0006

Table 14.68. Laboratory Analysis
Change from Baseline to Endpoint
All Patients Entering Study Period V
Study Period V, B1Y-MC-HCJE (continued)

Laboratory Test Group: Blood Chemistry

Lab Test	Lab Unit	Therapy	n	Baseline Mean	Baseline SD	Change to Endpoint Mean	Change to Endpoint SD	p-Values Therapy
AST	U/L	Flx	75	24.987	9.159	-0.373	7.949	.691
		Placebo	58	25.741	7.100	-0.931	8.109	
ALT	U/L	Flx	75	19.640	15.704	-0.480	13.768	.820
		Placebo	58	20.638	9.429	0.052	12.845	
CPK	U/L	Flx	75	126.640	77.922	14.213	76.523	.446
		Placebo	58	125.603	67.049	5.379	49.396	
ALKPH	U/L	Flx	73	220.918	93.433	-37.370	28.940	<.001
		Placebo	57	219.263	97.049	-1.070	37.476	
GGT	U/L	Flx	75	15.520	7.089	-0.867	4.657	.493
		Placebo	58	14.983	6.517	-0.190	6.687	
BUN	mmol/L	Flx	75	3.946	1.037	0.447	1.093	.586
		Placebo	58	4.216	0.933	0.345	1.051	
CREAT	umol/L	Flx	75	77.085	11.403	1.414	9.196	.507
		Placebo	58	74.683	11.005	2.439	8.245	
CALC	mmol/L	Flx	75	2.362	0.079	-0.032	0.095	.577
		Placebo	58	2.356	0.088	-0.022	0.093	
PHOS	mmol/L	Flx	72	1.487	0.207	0.009	0.180	.119
		Placebo	57	1.544	0.159	-0.042	0.188	
TPROT	g/L	Flx	75	73.347	3.961	-1.333	4.058	.411
		Placebo	58	72.672	4.666	-0.776	3.594	
ALBUM	g/L	Flx	75	42.907	2.467	-1.640	2.425	.510
		Placebo	58	42.741	2.844	-1.345	2.718	
NFGLU	mmol/L	Flx	73	4.959	0.575	0.051	0.947	.539
		Placebo	58	4.971	0.841	0.160	1.075	

XLAS0006

Table 14.68. Laboratory Analysis
Change from Baseline to Endpoint
All Patients Entering Study Period V
Study Period V, B1Y-MC-HCJE (continued)

Laboratory Test Group: Blood Chemistry

Lab Test	Lab Unit	Therapy	n	Baseline Mean	Baseline SD	Change to Endpoint Mean	Change to Endpoint SD	p-Values Therapy
UR AC	umol/L	Flx	75	271.625	72.211	8.565	42.130	.308
		Placebo	58	261.199	74.276	16.101	41.985	
CHOL	mmol/L	Flx	75	4.386	0.858	0.109	0.521	.024
		Placebo	58	4.352	0.933	-0.104	0.550	
T.BILI	umol/L	Flx	73	8.058	3.496	-0.468	2.767	.463
		Placebo	54	8.202	4.019	0.000	4.382	

XLAS0006

Table 14.68. Laboratory Analysis
Change from Baseline to Endpoint
All Patients Entering Study Period V
Study Period V, B1Y-MC-HCJE (continued)

Laboratory Test Group: Electrolytes

Lab Test	Lab Unit	Therapy	n	Baseline Mean	Baseline SD	Change to Endpoint Mean	Change to Endpoint SD	p-Values Therapy
SODIUM	mmol/L	Flx	75	139.733	2.042	-0.240	2.842	.534
		Placebo	58	139.310	2.437	0.069	2.821	
POTAS	mmol/L	Flx	72	4.192	0.329	-0.064	0.367	.594
		Placebo	57	4.193	0.296	-0.028	0.391	
CHLOR	mmol/L	Flx	75	102.773	2.299	0.413	2.973	.230
		Placebo	58	102.276	2.533	1.052	3.092	
BICARB	mmol/L	Flx	75	25.653	2.189	0.520	2.367	.421
		Placebo	57	25.840	1.895	0.851	2.286	

XLAS0006

Table 14.68. Laboratory Analysis
Change from Baseline to Endpoint
All Patients Entering Study Period V
Study Period V, B1Y-MC-HCJE (continued)

Laboratory Test Group: Thyroids

Lab Test	Lab Unit	Therapy	n	Baseline Mean	Baseline SD	Change to Endpoint Mean	Change to Endpoint SD	p-Values Therapy
T4-RIA	nmol/L	Flx	26	100.881	13.962	-3.069	13.070	.363
		Placebo	16	102.880	17.984	1.689	20.537	
TSH	mU/L	Flx	26	1.950	1.221	-0.498	0.978	.202
		Placebo	16	1.781	0.866	-0.116	0.841	
T3-TOT	nmol/L	Flx	26	1.929	0.306	-0.027	0.360	.611
		Placebo	16	1.880	0.410	0.039	0.470	
FTI	INDEX	Flx	26	2.658	0.283	-0.081	0.343	.369
		Placebo	16	2.700	0.386	0.031	0.453	
RT3U	1	Flx	26	0.341	0.023	0.004	0.014	.584
		Placebo	16	0.340	0.020	0.001	0.024	

XLAS0006

Table 14.68. Laboratory Analysis
Change from Baseline to Endpoint
All Patients Entering Study Period V
Study Period V, B1Y-MC-HCJE (continued)

Laboratory Test Group: Urinalysis

Lab Test	Lab Unit	Therapy	n	Baseline Mean	Baseline SD	Change to Endpoint Mean	Change to Endpoint SD	p-Values Therapy
U-SPGR	NO UNITS	Flx	72	1.021	0.009	0.003	0.010	.970
		Placebo	58	1.024	0.008	0.003	0.008	
U-PH	U	Flx	72	5.917	0.884	0.083	1.110	.654
		Placebo	58	5.707	0.773	0.000	0.973	

RMP.B1YP.JCLLIB2(LAS6JEAE)
RMP.B1Y0.HCJEREP(LAS6JEAE)
Note: n = Total number of patients in each treatment group having the variable in both baseline and postbaseline visits.

Note: Models:

FULL1 - Type III Sums of Squares from an analysis of variance (ANOVA): PROC GLM model=treatment.
Least-squares mean option in PROC GLM from the ANOVA using the mean square for error.

XLAS0006

Table 14.68. Laboratory Analysis
Change from Baseline to Endpoint
All Patients Entering Study Period V
Study Period V, B1Y-MC-HCJE (concluded)

Legend of Lab Test Code Abbreviations:

Abbrev.	Description
HCT	HEMATOCRIT
HGB	HEMOGLOBIN
RBC	ERYTHROCYTE COUNT
MCHC	MEAN CELL HEMOGLOBIN CONCENTRATION (MCHC)
MCH	MEAN CELL HEMOGLOBIN (MCH)
WBC	LEUKOCYTE COUNT
BANDS	BANDS
POLYS	NEUTROPHILS, SEGMENTED
LYMPHS	LYMPHOCYTES
MONOS	MONOCYTES
EOSN	EOSINOPHILS
BASO	BASOPHILS
MCV	MEAN CELL VOLUME (MCV)
PLTCT	PLATELET COUNT
ATLYMP	LYMPHOCYTES, ATYPICAL
U-SPGR	UA-SPECIFIC GRAVITY
U-PH	UA-PH
AST	AST/SGOT
ALT	ALT/SGPT
CPK	CREATINE PHOSPHOKINASE
ALKPH	ALKALINE PHOSPHATASE
GGT	GGT (GGPT/SGGT/YGGT)
T4-RIA	THYROXINE, TOTAL-T4
TSH	THYROID STIM. HORMONE
T3-TOT	T3, TOTAL (TRIIODOTHYRONINE)
FTI	FREE THYROXINE INDEX
RT3U	T3 % UPTAKE
BUN	UREA NITROGEN
CREAT	CREATININE
CALC	CALCIUM
PHOS	INORGANIC PHOSPHORUS
SODIUM	SODIUM
POTAS	POTASSIUM
CHLOR	CHLORIDE
TPROT	TOTAL PROTEIN
ALBUM	ALBUMIN
NFGLU	GLUCOSE, NON-FASTING
UR AC	URIC ACID
CHOL	CHOLESTEROL
BICARB	BICARBONATE, HCO3
T.BILI	BILIRUBIN, TOTAL

14.3.7.3. Abnormal Laboratory Values Listing

Table 14.69 provides a by-patient listing of all abnormal laboratory values that occurred during the study with their associated reference ranges. Clinically relevant laboratory abnormalities are discussed in Section 12.4.

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE

Protocol: B1Y-MC-HCJE
Investigator Number: 1
Patient Number: 101
Treatment Group: NON-RAND

Lab Test	Units	Low/High Reference	VISIT 1
Complete Blood Count			
LEUKOCYTE COUNT	GI/L	6.000/11.000	5.7L
NEUTROPHILS, SEGMENTED	GI/L	4.000/13.500	2.11L
LYMPHOCYTES	GI/L	4.000/12.000	2.38L
EOSINOPHILS	GI/L	0.000/0.570	0.78H

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 1
Patient Number: 102
Treatment Group: NON-RAND

Lab Test	Units	Low/High Reference	VISIT 1
Complete Blood Count			
LEUKOCYTE COUNT	GI/L	6.000/11.000	4.9L
NEUTROPHILS, SEGMENTED	GI/L	4.000/13.500	2.04L
LYMPHOCYTES	GI/L	4.000/12.000	2.55L
MEAN CELL VOLUME (MCV)	fL	70.000/90.000	96H
Blood Chemistry			
TOTAL PROTEIN	g/L	55.000/71.000	77H
Thyroids			
THYROXINE, TOTAL-T4	nmol/L	93.000/201.000	88L

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 1
Patient Number: 102
Treatment Group: NON-RAND

Lab Test	Units	Low/High Reference	VISIT 2
Complete Blood Count			
LEUKOCYTE COUNT	GI/L	6.000/11.000	
NEUTROPHILS, SEGMENTED	GI/L	4.000/13.500	
LYMPHOCYTES	GI/L	4.000/12.000	
MEAN CELL VOLUME (MCV)	fL	70.000/90.000	
Blood Chemistry			
TOTAL PROTEIN	g/L	55.000/71.000	
Thyroids			
THYROXINE, TOTAL-T4	nmol/L	93.000/201.000	80L

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 1
Patient Number: 103
Treatment Group: Placebo

Lab Test	Units	Low/High Reference	VISIT 1
Complete Blood Count			
MEAN CELL VOLUME (MCV)	fL	76.000/93.000	96H
Blood Chemistry			
ALKALINE PHOSPHATASE	U/L	51.000/300.000	

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 1
Patient Number: 103
Treatment Group: Placebo

Lab Test	Units	Low/High Reference	VISIT 8
Complete Blood Count			
MEAN CELL VOLUME (MCV)	fL	76.000/93.000	
Blood Chemistry			
ALKALINE PHOSPHATASE	U/L	51.000/300.000	322H

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 1
Patient Number: 104
Treatment Group: Flx

Lab Test	Units	Low/High Reference	VISIT 1
Complete Blood Count			
HEMATOCRIT	1	0.340/0.440	
HEMOGLOBIN	mml/L-Fe	7.000/9.600	6.95L
MEAN CELL HEMOGLOBIN CONCENTRATION (MCHC	mml/L-Fe	19.000/24.000	17L
MEAN CELL HEMOGLOBIN (MCH)	fmol(Fe)	1.500/2.100	1.30L
MEAN CELL VOLUME (MCV)	fL	76.000/93.000	75L
ANISOCYTOSIS	NO UNITS		1 A
MICROCYTOSIS	NO UNITS		
Urinalysis			
UA-OCCULT BLOOD	NO UNITS		

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 1
Patient Number: 104
Treatment Group: Flx

Lab Test	Units	Low/High Reference	VISIT 13
Complete Blood Count			
HEMATOCRIT	1	0.340/0.440	0.320L
HEMOGLOBIN	mml/L-Fe	7.000/9.600	6.27L
MEAN CELL HEMOGLOBIN CONCENTRATION (MCHC	mml/L-Fe	19.000/24.000	
MEAN CELL HEMOGLOBIN (MCH)	fmol(Fe)	1.500/2.100	1.37L
MEAN CELL VOLUME (MCV)	fL	76.000/93.000	69L
ANISOCYTOSIS	NO UNITS		1 A
MICROCYTOSIS	NO UNITS		1 A
Urinalysis			
UA-OCCULT BLOOD	NO UNITS		1 A

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 1
Patient Number: 105
Treatment Group: NON-RAND

Lab Test	Units	Low/High Reference	VISIT 1
Complete Blood Count			
LYMPHOCYTES	GI/L	4.000/12.000	2.89L
EOSINOPHILS	GI/L	0.000/0.570	1.24H
BASOPHILS	GI/L	0.000/0.200	0.24H
MEAN CELL VOLUME (MCV)	fL	70.000/90.000	91H

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 1
Patient Number: 107
Treatment Group: Placebo

Lab Test	Units	Low/High Reference	VISIT 1
Complete Blood Count			
HEMATOCRIT	1	0.390/0.540	
HEMOGLOBIN	mml/L-Fe	7.880/11.230	
Blood Chemistry			
CHOLESTEROL	mmol/L	3.360/5.280	5.82H

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 1
Patient Number: 107
Treatment Group: Placebo

Lab Test	Units	Low/High Reference	VISIT 9
Complete Blood Count			
HEMATOCRIT	1	0.390/0.540	0.360L
HEMOGLOBIN	mml/L-Fe	7.880/11.230	7.57L
Blood Chemistry			
CHOLESTEROL	mmol/L	3.360/5.280	

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 1
Patient Number: 108
Treatment Group: NON-RAND

Lab Test	Units	Low/High Reference	VISIT 1
Complete Blood Count			
HEMOGLOBIN	mml/L-Fe	6.520/8.380	8.81H
NEUTROPHILS, SEGMENTED	GI/L	4.000/13.500	3.72L
LYMPHOCYTES	GI/L	4.000/12.000	2.59L
Blood Chemistry			
TOTAL PROTEIN	g/L	55.000/71.000	78H
Electrolytes			
BICARBONATE, HCO3	mmol/L	12.000/28.000	29.1H

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 1
Patient Number: 109
Treatment Group: NON-RAND

Lab Test	Units	Low/High Reference	VISIT 1
Complete Blood Count			
HEMOGLOBIN	mml/L-Fe	6.520/8.380	8.50H
LEUKOCYTE COUNT	GI/L	6.000/11.000	5.2L
NEUTROPHILS, SEGMENTED	GI/L	4.000/13.500	2.78L
LYMPHOCYTES	GI/L	4.000/12.000	1.92L
Blood Chemistry			
TOTAL PROTEIN	g/L	55.000/71.000	76H

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 1
Patient Number: 110
Treatment Group: Flx

Lab Test	Units	Low/High Reference	VISIT 1
Blood Chemistry			
CREATINE PHOSPHOKINASE	U/L	150.000/489.000	141L

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 1
Patient Number: 111
Treatment Group: NON-RAND

Lab Test	Units	Low/High Reference	VISIT 1
Complete Blood Count			
HEMOGLOBIN	mml/L-Fe	6.520/8.380	9.56H
LEUKOCYTE COUNT	GI/L	6.000/11.000	4.8L
NEUTROPHILS, SEGMENTED	GI/L	4.000/13.500	2.40L
LYMPHOCYTES	GI/L	4.000/12.000	1.92L
PLATELET COUNT	GI/L	200.000/400.000	199L
Blood Chemistry			
TOTAL PROTEIN	g/L	55.000/71.000	73H
Electrolytes			
BICARBONATE, HCO3	mmol/L	12.000/28.000	28.1H
Thyroids			
THYROXINE, TOTAL-T4	nmol/L	93.000/201.000	88L

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 1
Patient Number: 112
Treatment Group: Placebo

Lab Test	Units	Low/High Reference	VISIT 1
Blood Chemistry			
CREATINE PHOSPHOKINASE	U/L	91.000/391.000	83L
CHOLESTEROL	mmol/L	3.210/5.610	

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Listing of Abnormal Laboratory Values
All Patients
Study Periods I-V,B1Y-MC-HCJE

Protocol: B1Y-MC-HCJE
Investigator Number: 1
Patient Number: 112
Treatment Group: Placebo

Lab Test	Units	Low/High Reference	VISIT 10
Blood Chemistry			
CREATINE PHOSPHOKINASE	U/L	91.000/391.000	83L
CHOLESTEROL	mmol/L	3.210/5.610	2.95L

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 1
Patient Number: 113
Treatment Group: Placebo

Lab Test	Units	Low/High Reference	VISIT 1
Complete Blood Count			
ANISOCYTOSIS	NO UNITS		
MICROCYTOSIS	NO UNITS		
Blood Chemistry			
CREATINE PHOSPHOKINASE	U/L	150.000/489.000	88L
			114L
CHOLESTEROL	mmol/L	3.360/5.280	6.08H
Electrolytes			
BICARBONATE, HCO3	mmol/L	17.000/30.600	
Thyroids			
THYROXINE, TOTAL-T4	nmol/L	82.000/171.000	79L
			76L
Urinalysis			
UA-SPECIFIC GRAVITY	NO UNITS	1.010/1.034	

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 1
Patient Number: 113
Treatment Group: Placebo

Lab Test	Units	Low/High Reference	VISIT 15
Complete Blood Count			
ANISOCYTOSIS	NO UNITS		1 A
MICROCYTOSIS	NO UNITS		1 A
Blood Chemistry			
CREATINE PHOSPHOKINASE	U/L	150.000/489.000	102L
CHOLESTEROL	mmol/L	3.360/5.280	5.30H
Electrolytes			
BICARBONATE, HCO3	mmol/L	17.000/30.600	31.2H
Thyroids			
THYROXINE, TOTAL-T4	nmol/L	82.000/171.000	
Urinalysis			
UA-SPECIFIC GRAVITY	NO UNITS	1.010/1.034	1.036H

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 1
Patient Number: 114
Treatment Group: Flx

Lab Test	Units	Low/High Reference	VISIT 1
Complete Blood Count			
EOSINOPHILS	GI/L	0.000/0.570	
Blood Chemistry			
CREATINE PHOSPHOKINASE	U/L	91.000/391.000	82L
ALKALINE PHOSPHATASE	U/L	51.000/300.000	327H
URIC ACID	umol/L	202.000/535.000	178L
CHOLESTEROL	mmol/L	3.210/5.610	3.13L
Urinalysis			
UA-RBC	NO UNITS		
UA-BACTERIA	NO UNITS		
UA-OCCULT BLOOD	NO UNITS		

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 1
Patient Number: 114
Treatment Group: Flx

Lab Test	Units	Low/High Reference	VISIT 12
Complete Blood Count			
EOSINOPHILS	GI/L	0.000/0.570	0.66H
Blood Chemistry			
CREATINE PHOSPHOKINASE	U/L	91.000/391.000	83L
ALKALINE PHOSPHATASE	U/L	51.000/300.000	
URIC ACID	umol/L	202.000/535.000	161L
CHOLESTEROL	mmol/L	3.210/5.610	2.59L
Urinalysis			
UA-RBC	NO UNITS		1 A
UA-BACTERIA	NO UNITS		1 A
UA-OCCULT BLOOD	NO UNITS		1 A

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 1
Patient Number: 115
Treatment Group: NON-RAND

Lab Test	Units	Low/High Reference	VISIT 1
Complete Blood Count			
LYMPHOCYTES	GI/L	4.000/12.000	2.18L

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 1
Patient Number: 116
Treatment Group: NON-RAND

Lab Test	Units	Low/High Reference	VISIT 1
Complete Blood Count			
LEUKOCYTE COUNT	GI/L	6.000/11.000	4.7L
NEUTROPHILS, SEGMENTED	GI/L	4.000/13.500	2.40L
LYMPHOCYTES	GI/L	4.000/12.000	1.93L
Blood Chemistry			
TOTAL PROTEIN	g/L	55.000/71.000	80H
Urinalysis			
UA-PROTEIN	NO UNITS		2 A
UA-BACTERIA	NO UNITS		1 A
UDS			
BUTALBITAL	NO UNITS		POS A

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 1
Patient Number: 118
Treatment Group: Flx

Lab Test	Units	Low/High Reference	VISIT 1
Blood Chemistry			
CREATINE PHOSPHOKINASE	U/L	150.000/489.000	139L
ALKALINE PHOSPHATASE	U/L	95.000/385.000	400H
CHOLESTEROL	mmol/L	3.360/5.280	7.63H
Thyroids			
THYROID STIM. HORMONE	mU/L	0.320/5.000	5.99H
Urinalysis			
UA-SPECIFIC GRAVITY	NO UNITS	1.010/1.034	1.007L
UA-BACTERIA	NO UNITS		

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 1
Patient Number: 118
Treatment Group: Flx

Lab Test	Units	Low/High Reference	VISIT 11
Blood Chemistry			
CREATINE PHOSPHOKINASE	U/L	150.000/489.000	
ALKALINE PHOSPHATASE	U/L	95.000/385.000	
CHOLESTEROL	mmol/L	3.360/5.280	7.71H
Thyroids			
THYROID STIM. HORMONE	mU/L	0.320/5.000	
Urinalysis			
UA-SPECIFIC GRAVITY	NO UNITS	1.010/1.034	1.008L
UA-BACTERIA	NO UNITS	1	A

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 1
Patient Number: 119
Treatment Group: Placebo

Lab Test	Units	Low/High Reference	VISIT 1	
Complete Blood Count				
ANISOCYTOSIS	NO UNITS		1	A
MICROCYTOSIS	NO UNITS		1	A
Blood Chemistry				
CREATINE PHOSPHOKINASE	U/L	150.000/489.000		
URIC ACID	umol/L	161.000/393.000	125	L
CHOLESTEROL	mmol/L	3.260/4.940	3.21	L
Urinalysis				
UA-SPECIFIC GRAVITY	NO UNITS	1.010/1.034		

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 1
Patient Number: 119
Treatment Group: Placebo

Lab Test	Units	Low/High Reference	VISIT 15
Complete Blood Count			
ANISOCYTOSIS	NO UNITS		
MICROCYTOSIS	NO UNITS		1 A
Blood Chemistry			
CREATINE PHOSPHOKINASE	U/L	150.000/489.000	129L
URIC ACID	umol/L	161.000/393.000	95L
CHOLESTEROL	mmol/L	3.260/4.940	3.05L
Urinalysis			
UA-SPECIFIC GRAVITY	NO UNITS	1.010/1.034	1.037H

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 1
Patient Number: 120
Treatment Group: NON-RAND

Lab Test	Units	Low/High Reference	VISIT 1
Complete Blood Count			
HEMOGLOBIN	mml/L-Fe	6.520/8.380	8.63H
LEUKOCYTE COUNT	GI/L	6.000/11.000	5.1L
NEUTROPHILS, SEGMENTED	GI/L	4.000/13.500	2.71L
LYMPHOCYTES	GI/L	4.000/12.000	1.71L
Blood Chemistry			
TOTAL PROTEIN	g/L	55.000/71.000	80H
Urinalysis			
UA-RBC	NO UNITS		1 A
UA-BACTERIA	NO UNITS		1 A
UA-OCCULT BLOOD	NO UNITS		1 A

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 1
Patient Number: 121
Treatment Group: NON-RAND

Lab Test	Units	Low/High Reference	VISIT 1
Complete Blood Count			
HEMOGLOBIN	mml/L-Fe	6.520/8.380	8.75H
LEUKOCYTE COUNT	GI/L	6.000/11.000	5.6L
NEUTROPHILS, SEGMENTED	GI/L	4.000/13.500	2.78L
LYMPHOCYTES	GI/L	4.000/12.000	2.04L

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 1
Patient Number: 122
Treatment Group: NON-RAND

Lab Test	Units	Low/High Reference	VISIT 1
Complete Blood Count			
LEUKOCYTE COUNT	GI/L	6.000/11.000	3.4L
NEUTROPHILS, SEGMENTED	GI/L	4.000/13.500	1.33L
LYMPHOCYTES	GI/L	4.000/12.000	1.73L
ANISOCYTOSIS	NO UNITS		1 A
MICROCYTOSIS	NO UNITS		1 A
Blood Chemistry			
TOTAL PROTEIN	g/L	55.000/71.000	

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 1
Patient Number: 122
Treatment Group: NON-RAND

Lab Test	Units	Low/High Reference	VISIT 3
Complete Blood Count			
LEUKOCYTE COUNT	GI/L	6.000/11.000	4.3L
NEUTROPHILS, SEGMENTED	GI/L	4.000/13.500	1.31L
LYMPHOCYTES	GI/L	4.000/12.000	2.46L
ANISOCYTOSIS	NO UNITS		1 A
MICROCYTOSIS	NO UNITS		1 A
Blood Chemistry			
TOTAL PROTEIN	g/L	55.000/71.000	72H

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 1
Patient Number: 123
Treatment Group: NON-RAND

Lab Test	Units	Low/High Reference	VISIT 1
Complete Blood Count			
HEMOGLOBIN	mml/L-Fe	6.520/8.380	8.56H
LEUKOCYTE COUNT	GI/L	6.000/11.000	5.6L
NEUTROPHILS, SEGMENTED	GI/L	4.000/13.500	3.63L
LYMPHOCYTES	GI/L	4.000/12.000	1.52L
PLATELET COUNT	GI/L	200.000/400.000	196L
Blood Chemistry			
TOTAL PROTEIN	g/L	55.000/71.000	74H
Thyroids			
THYROXINE, TOTAL-T4	nmol/L	93.000/201.000	77L

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 1
Patient Number: 125
Treatment Group: NON-RAND

Lab Test	Units	Low/High Reference	VISIT 1
Complete Blood Count			
HEMOGLOBIN	mml/L-Fe	6.520/8.380	9.50H
LEUKOCYTE COUNT	GI/L	6.000/11.000	4.7L
NEUTROPHILS, SEGMENTED	GI/L	4.000/13.500	2.96L
LYMPHOCYTES	GI/L	4.000/12.000	1.46L
Blood Chemistry			
TOTAL PROTEIN	g/L	55.000/71.000	80H
Thyroids			
THYROXINE, TOTAL-T4	nmol/L	93.000/201.000	89L

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 1
Patient Number: 127
Treatment Group: Flx

Lab Test	Units	Low/High Reference	VISIT 1
Complete Blood Count			
EOSINOPHILS	GI/L	0.000/0.570	1.24H
PLATELET COUNT	GI/L	130.000/394.000	409H
Blood Chemistry			
CREATINE PHOSPHOKINASE	U/L	91.000/391.000	67L
CHOLESTEROL	mmol/L	3.150/5.400	

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 1
Patient Number: 127
Treatment Group: Flx

Lab Test	Units	Low/High Reference	VISIT 11
Complete Blood Count			
EOSINOPHILS	GI/L	0.000/0.570	0.77H
PLATELET COUNT	GI/L	130.000/394.000	
Blood Chemistry			
CREATINE PHOSPHOKINASE	U/L	91.000/391.000	
CHOLESTEROL	mmol/L	3.150/5.400	5.87H

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 1
Patient Number: 128
Treatment Group: NON-RAND

Lab Test	Units	Low/High Reference	VISIT 1
Complete Blood Count			
HEMOGLOBIN	mml/L-Fe	6.520/8.380	8.75H
NEUTROPHILS, SEGMENTED	GI/L	4.000/13.500	3.33L
LYMPHOCYTES	GI/L	4.000/12.000	2.54L
Electrolytes			
BICARBONATE, HCO3	mmol/L	12.000/28.000	31.5H

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 1
Patient Number: 129
Treatment Group: NON-RAND

Lab Test	Units	Low/High Reference	VISIT 1
Complete Blood Count			
HEMOGLOBIN	mml/L-Fe	6.520/8.380	9.12H
			8.50H
LEUKOCYTE COUNT	GI/L	6.000/11.000	4.2L
			5.2L
NEUTROPHILS, SEGMENTED	GI/L	4.000/13.500	0.97L
			2.69L
LYMPHOCYTES	GI/L	4.000/12.000	2.88L
			2.20L
PLATELET COUNT	GI/L	200.000/400.000	179L
			186L
Blood Chemistry			
TOTAL PROTEIN	g/L	55.000/71.000	74H
Urinalysis			
UA-PROTEIN	NO UNITS	1	A

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 1
Patient Number: 130
Treatment Group: NON-RAND

Lab Test	Units	Low/High Reference	VISIT 1
Complete Blood Count			
HEMOGLOBIN	mml/L-Fe	6.520/8.380	8.75H
NEUTROPHILS, SEGMENTED	GI/L	4.000/13.500	2.52L
LYMPHOCYTES	GI/L	4.000/12.000	3.22L
Electrolytes			
BICARBONATE, HCO3	mmol/L	12.000/28.000	28.4H
Thyroids			
THYROXINE, TOTAL-T4	nmol/L	93.000/201.000	80L

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 1
Patient Number: 131
Treatment Group: Placebo

Lab Test	Units	Low/High Reference	VISIT 1
Blood Chemistry			
CREATINE PHOSPHOKINASE	U/L	91.000/391.000	
ALKALINE PHOSPHATASE	U/L	51.000/300.000	316H
Urinalysis			
UA-BACTERIA	NO UNITS		1 A

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 1
Patient Number: 131
Treatment Group: Placebo

Lab Test	Units	Low/High Reference	VISIT 12
Blood Chemistry			
CREATINE PHOSPHOKINASE	U/L	91.000/391.000	88L
ALKALINE PHOSPHATASE	U/L	51.000/300.000	
Urinalysis			
UA-BACTERIA	NO UNITS		

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 1
Patient Number: 132
Treatment Group: NON-RAND

Lab Test	Units	Low/High Reference	VISIT 1
Complete Blood Count			
LEUKOCYTE COUNT	GI/L	6.000/11.000	5.5L
NEUTROPHILS, SEGMENTED	GI/L	4.000/13.500	2.82L
LYMPHOCYTES	GI/L	4.000/12.000	2.32L
Blood Chemistry			
CALCIUM	mmol/L	2.250/2.740	2.22L

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 1
Patient Number: 133
Treatment Group: Flx

Lab Test	Units	Low/High Reference	VISIT 1
Blood Chemistry			
CREATINE PHOSPHOKINASE	U/L	91.000/391.000	
ALKALINE PHOSPHATASE	U/L	51.000/300.000	344H
Urinalysis			
UA-PROTEIN	NO UNITS		

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 1
Patient Number: 133
Treatment Group: Flx

Lab Test	Units	Low/High Reference	VISIT 11
Blood Chemistry			
CREATINE PHOSPHOKINASE	U/L	91.000/391.000	84L
ALKALINE PHOSPHATASE	U/L	51.000/300.000	334H
Urinalysis			
UA-PROTEIN	NO UNITS	1	A

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 1
Patient Number: 134
Treatment Group: NON-RAND

Lab Test	Units	Low/High Reference	VISIT 1
Complete Blood Count			
LEUKOCYTE COUNT	GI/L	6.000/11.000	5.1L
NEUTROPHILS, SEGMENTED	GI/L	4.000/13.500	2.64L
LYMPHOCYTES	GI/L	4.000/12.000	1.98L
Thyroids			
THYROXINE, TOTAL-T4	nmol/L	93.000/201.000	86L

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 1
Patient Number: 135
Treatment Group: Placebo

Lab Test	Units	Low/High Reference	VISIT 1
Blood Chemistry			
CREATINE PHOSPHOKINASE	U/L	94.000/499.000	62L

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 1
Patient Number: 136
Treatment Group: NON-RAND

Lab Test	Units	Low/High Reference	VISIT 1
Complete Blood Count			
HEMOGLOBIN	mml/L-Fe	6.520/8.380	8.44H
LEUKOCYTE COUNT	GI/L	6.000/11.000	5.6L
NEUTROPHILS, SEGMENTED	GI/L	4.000/13.500	3.01L
LYMPHOCYTES	GI/L	4.000/12.000	2.18L
Blood Chemistry			
TOTAL PROTEIN	g/L	55.000/71.000	72H
Thyroids			
THYROXINE, TOTAL-T4	nmol/L	93.000/201.000	89L

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 1
Patient Number: 137
Treatment Group: Flx

Lab Test	Units	Low/High Reference	VISIT 1
Complete Blood Count			
ERYTHROCYTE COUNT	TI/L	4.500/6.400	4.40L
LEUKOCYTE COUNT	GI/L	4.350/13.150	4.2L
Blood Chemistry			
CREATINE PHOSPHOKINASE	U/L	94.000/499.000	92L

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 1
Patient Number: 138
Treatment Group: NON-RAND

Lab Test	Units	Low/High Reference	VISIT 1
Complete Blood Count			
LEUKOCYTE COUNT	GI/L	6.000/11.000	5.0L
NEUTROPHILS, SEGMENTED	GI/L	4.000/13.500	2.62L
LYMPHOCYTES	GI/L	4.000/12.000	2.03L
Blood Chemistry			
TOTAL PROTEIN	g/L	55.000/71.000	77H
Urinalysis			
UA-PROTEIN	NO UNITS	1	A

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 1
Patient Number: 139
Treatment Group: Flx

Lab Test	Units	Low/High Reference	VISIT 1
Complete Blood Count			
MEAN CELL VOLUME (MCV)	fL	76.000/93.000	
Blood Chemistry			
AST/SGOT	U/L	10.000/40.000	72.0H
			86.0H
ALT/SGPT	U/L	6.000/43.000	107.0H
			136.0H
CREATINE PHOSPHOKINASE	U/L	150.000/489.000	91L
			120L
GGT (GGPT/SGGT/YGGT)	U/L	0.000/24.000	34.0H
			42.0H
Thyroids			
T3, TOTAL (TRIIODOTHYRONINE)	nmol/L	1.200/3.100	3.1H
T3 % UPTAKE	1	0.270/0.410	0.26L
			0.26L

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 1
Patient Number: 139
Treatment Group: Flx

Lab Test	Units	Low/High Reference	VISIT 15
Complete Blood Count			
MEAN CELL VOLUME (MCV)	fL	76.000/93.000	95H
Blood Chemistry			
AST/SGOT	U/L	10.000/40.000	
ALT/SGPT	U/L	6.000/43.000	
CREATINE PHOSPHOKINASE	U/L	150.000/489.000	116L
GGT (GGPT/SGGT/YGGT)	U/L	0.000/24.000	
Thyroids			
T3, TOTAL (TRIIODOTHYRONINE)	nmol/L	1.200/3.100	
T3 % UPTAKE	1	0.270/0.410	

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 1
Patient Number: 140
Treatment Group: Placebo

Lab Test	Units	Low/High Reference	VISIT 1	
Blood Chemistry				
CREATINE PHOSPHOKINASE	U/L	94.000/499.000	69L	
Urinalysis				
UA-KETONES	NO UNITS		1	A

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 1
Patient Number: 141
Treatment Group: Flx

Lab Test	Units	Low/High Reference	VISIT 1	
Blood Chemistry				
ALKALINE PHOSPHATASE	U/L	95.000/385.000	417H	
Urinalysis				
UA-PROTEIN	NO UNITS		1	A

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 1
Patient Number: 142
Treatment Group: Flx

Lab Test	Units	Low/High Reference	VISIT 1
Blood Chemistry			
CREATINE PHOSPHOKINASE	U/L	150.000/489.000	86L
CHOLESTEROL	mmol/L	3.360/5.280	2.92L

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 1
Patient Number: 142
Treatment Group: Flx

Lab Test	Units	Low/High Reference	VISIT 15
Blood Chemistry			
CREATINE PHOSPHOKINASE	U/L	150.000/489.000	110L
CHOLESTEROL	mmol/L	3.360/5.280	2.95L

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 1
Patient Number: 143
Treatment Group: Placebo

Lab Test	Units	Low/High Reference	VISIT 1
Blood Chemistry			
ALKALINE PHOSPHATASE	U/L	51.000/300.000	397H

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 1
Patient Number: 144
Treatment Group: NON-RAND

Lab Test	Units	Low/High Reference	VISIT 1
Complete Blood Count			
LEUKOCYTE COUNT	GI/L	6.000/11.000	4.7L
NEUTROPHILS, SEGMENTED	GI/L	4.000/13.500	2.99L
LYMPHOCYTES	GI/L	4.000/12.000	1.32L
MEAN CELL VOLUME (MCV)	fL	70.000/90.000	93H
Blood Chemistry			
TOTAL PROTEIN	g/L	55.000/71.000	77H

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 1
Patient Number: 145
Treatment Group: NON-RAND

Lab Test	Units	Low/High Reference	VISIT 1
Complete Blood Count			
HEMOGLOBIN	mml/L-Fe	6.520/8.380	8.69H
NEUTROPHILS, SEGMENTED	GI/L	4.000/13.500	3.94L
LYMPHOCYTES	GI/L	4.000/12.000	2.15L
Blood Chemistry			
TOTAL PROTEIN	g/L	55.000/71.000	73H

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 1
Patient Number: 146
Treatment Group: NON-RAND

Lab Test	Units	Low/High Reference	VISIT 1
Blood Chemistry			
TOTAL PROTEIN	g/L	55.000/71.000	74H

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 1
Patient Number: 147
Treatment Group: NON-RAND

Lab Test	Units	Low/High Reference	VISIT 1
Complete Blood Count			
LEUKOCYTE COUNT	GI/L	6.000/11.000	5.6L
NEUTROPHILS, SEGMENTED	GI/L	4.000/13.500	2.91L
LYMPHOCYTES	GI/L	4.000/12.000	2.25L
Blood Chemistry			
TOTAL PROTEIN	g/L	55.000/71.000	73H
Urinalysis			
UA-SPECIFIC GRAVITY	NO UNITS	1.010/1.034	1.035H

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 1
Patient Number: 148
Treatment Group: NON-RAND

Lab Test	Units	Low/High Reference	VISIT 1
Complete Blood Count			
HEMOGLOBIN	mml/L-Fe	6.520/8.380	8.81H
LYMPHOCYTES	GI/L	4.000/12.000	2.17L
Blood Chemistry			
TOTAL PROTEIN	g/L	55.000/71.000	77H

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 1
Patient Number: 149
Treatment Group: Placebo

Lab Test	Units	Low/High Reference	VISIT 1
Blood Chemistry			
CREATINE PHOSPHOKINASE	U/L	150.000/489.000	113L
ALKALINE PHOSPHATASE	U/L	86.000/315.000	369H
ALBUMIN	g/L	29.000/47.000	49H

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 1
Patient Number: 149
Treatment Group: Placebo

Lab Test	Units	Low/High Reference	VISIT 11
Blood Chemistry			
CREATINE PHOSPHOKINASE	U/L	150.000/489.000	105L
ALKALINE PHOSPHATASE	U/L	86.000/315.000	395H
ALBUMIN	g/L	29.000/47.000	48H

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 1
Patient Number: 150
Treatment Group: Flx

Lab Test	Units	Low/High Reference	VISIT 15
Complete Blood Count			
MEAN CELL VOLUME (MCV)	fL	76.000/93.000	94H

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 1
Patient Number: 151
Treatment Group: Flx

Lab Test	Units	Low/High Reference	VISIT 1
Blood Chemistry			
CREATINE PHOSPHOKINASE	U/L	150.000/489.000	123L
CHOLESTEROL	mmol/L	3.360/5.280	
Electrolytes			
BICARBONATE, HCO3	mmol/L	17.000/30.600	31.4H

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 1
Patient Number: 151
Treatment Group: Flx

Lab Test	Units	Low/High Reference	VISIT 11
Blood Chemistry			
CREATINE PHOSPHOKINASE	U/L	150.000/489.000	127L
CHOLESTEROL	mmol/L	3.360/5.280	5.30H
Electrolytes			
BICARBONATE, HCO3	mmol/L	17.000/30.600	

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 1
Patient Number: 153
Treatment Group: Placebo

Lab Test	Units	Low/High Reference	VISIT 1
Complete Blood Count			
HEMOGLOBIN	mml/L-Fe	7.880/11.230	
Blood Chemistry			
CREATINE PHOSPHOKINASE	U/L	94.000/499.000	88L
ALKALINE PHOSPHATASE	U/L	95.000/385.000	388H
CHOLESTEROL	mmol/L	3.360/5.280	2.84L

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 1
Patient Number: 153
Treatment Group: Placebo

Lab Test	Units	Low/High Reference	VISIT 10
Complete Blood Count			
HEMOGLOBIN	mml/L-Fe	7.880/11.230	7.63L
Blood Chemistry			
CREATINE PHOSPHOKINASE	U/L	94.000/499.000	37L
ALKALINE PHOSPHATASE	U/L	95.000/385.000	
CHOLESTEROL	mmol/L	3.360/5.280	2.28L

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 1
Patient Number: 154
Treatment Group: NON-RAND

Lab Test	Units	Low/High Reference	VISIT 1
Complete Blood Count			
NEUTROPHILS, SEGMENTED	GI/L	4.000/13.500	3.17L
LYMPHOCYTES	GI/L	4.000/12.000	2.56L
Blood Chemistry			
TOTAL PROTEIN	g/L	55.000/71.000	72H
Urinalysis			
UA-BACTERIA	NO UNITS		1 A

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 1
Patient Number: 155
Treatment Group: NON-RAND

Lab Test	Units	Low/High Reference	VISIT 1
Complete Blood Count			
LEUKOCYTE COUNT	GI/L	6.000/11.000	5.0L
NEUTROPHILS, SEGMENTED	GI/L	4.000/13.500	2.68L
LYMPHOCYTES	GI/L	4.000/12.000	1.78L
Blood Chemistry			
GGT (GGPT/SGGT/YGGT)	U/L	0.000/24.000	33.0H
			30.0H
TOTAL PROTEIN	g/L	55.000/71.000	81H
			75H
Thyroids			
THYROXINE, TOTAL-T4	nmol/L	93.000/201.000	69L
			63L
THYROID STIM. HORMONE	mU/L	0.320/5.000	31.94H
			30.49H
FREE THYROXINE INDEX	INDEX	1.940/5.620	1.70L
			1.50L
Urinalysis			
UA-BACTERIA	NO UNITS	1	A

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 1
Patient Number: 156
Treatment Group: NON-RAND

Lab Test	Units	Low/High Reference	VISIT 1
Complete Blood Count			
LEUKOCYTE COUNT	GI/L	6.000/11.000	3.8L
NEUTROPHILS, SEGMENTED	GI/L	4.000/13.500	1.49L
LYMPHOCYTES	GI/L	4.000/12.000	1.70L
MEAN CELL VOLUME (MCV)	fL	70.000/90.000	91H
Blood Chemistry			
TOTAL PROTEIN	g/L	55.000/71.000	73H
Urinalysis			
UA-PROTEIN	NO UNITS		1 A

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 1
Patient Number: 157
Treatment Group: NON-RAND

Lab Test	Units	Low/High Reference	VISIT 1
Complete Blood Count			
NEUTROPHILS, SEGMENTED	GI/L	4.000/13.500	3.24L
LYMPHOCYTES	GI/L	4.000/12.000	2.22L
PLATELET COUNT	GI/L	200.000/400.000	415H
Blood Chemistry			
TOTAL PROTEIN	g/L	55.000/71.000	75H
Electrolytes			
POTASSIUM	mmol/L	3.400/5.400	3.3L

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 2
Patient Number: 201
Treatment Group: Placebo

Lab Test	Units	Low/High Reference	VISIT 5
Blood Chemistry			
CREATINE PHOSPHOKINASE	U/L	94.000/499.000	549H
ALBUMIN	g/L	29.000/47.000	48H
CHOLESTEROL	mmol/L	2.950/5.120	2.92L

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 2
Patient Number: 202
Treatment Group: Flx

Lab Test	Units	Low/High Reference	VISIT 1
Blood Chemistry			
TOTAL PROTEIN	g/L	61.000/84.000	87H
ALBUMIN	g/L	29.000/47.000	51H

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 2
Patient Number: 203
Treatment Group: Placebo

Lab Test	Units	Low/High Reference	VISIT 1
Blood Chemistry			
INORGANIC PHOSPHORUS	mmol/L	0.710/1.650	1.71H
Urinalysis			
UA-BACTERIA	NO UNITS		

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 2
Patient Number: 203
Treatment Group: Placebo

Lab Test	Units	Low/High Reference	VISIT 10	
Blood Chemistry				
INORGANIC PHOSPHORUS	mmol/L	0.710/1.650		
Urinalysis				
UA-BACTERIA	NO UNITS		1	A

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 2
Patient Number: 204
Treatment Group: Flx

Lab Test	Units	Low/High Reference	VISIT 1
Complete Blood Count			
HEMATOCRIT	1	0.390/0.540	
ERYTHROCYTE COUNT	TI/L	4.500/6.400	
LEUKOCYTE COUNT	GI/L	4.350/13.150	
MONOCYTES	GI/L	0.120/0.920	0.05L
Urinalysis			
UA-SPECIFIC GRAVITY	NO UNITS	1.010/1.034	

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 2
Patient Number: 204
Treatment Group: Flx

Lab Test	Units	Low/High Reference	VISIT 14
Complete Blood Count			
HEMATOCRIT	1	0.390/0.540	0.380L
ERYTHROCYTE COUNT	TI/L	4.500/6.400	4.30L
LEUKOCYTE COUNT	GI/L	4.350/13.150	4.2L
MONOCYTES	GI/L	0.120/0.920	
Urinalysis			
UA-SPECIFIC GRAVITY	NO UNITS	1.010/1.034	1.035H

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 2
Patient Number: 205
Treatment Group: Placebo

Lab Test	Units	Low/High Reference	VISIT 1
Complete Blood Count			
BANDS	GI/L	0.000/0.270	
NEUTROPHILS, SEGMENTED	GI/L	1.350/8.150	
MONOCYTES	GI/L	0.120/0.920	
MEAN CELL VOLUME (MCV)	fL	76.000/93.000	
PLATELET COUNT	GI/L	130.000/394.000	429H
MICROCYTOSIS	NO UNITS		1 A
Blood Chemistry			
CREATINE PHOSPHOKINASE	U/L	150.000/489.000	137L
Urinalysis			
UA-SPECIFIC GRAVITY	NO UNITS	1.010/1.034	

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 2
Patient Number: 205
Treatment Group: Placebo

Lab Test	Units	Low/High Reference	VISIT 8
Complete Blood Count			
BANDS	GI/L	0.000/0.270	0.63H
NEUTROPHILS, SEGMENTED	GI/L	1.350/8.150	8.48H
MONOCYTES	GI/L	0.120/0.920	0.00L
MEAN CELL VOLUME (MCV)	fL	76.000/93.000	75L
PLATELET COUNT	GI/L	130.000/394.000	438H
MICROCYTOSIS	NO UNITS		1 A
Blood Chemistry			
CREATINE PHOSPHOKINASE	U/L	150.000/489.000	98L
Urinalysis			
UA-SPECIFIC GRAVITY	NO UNITS	1.010/1.034	1.035H

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 2
Patient Number: 206
Treatment Group: Placebo

Lab Test	Units	Low/High Reference	VISIT 1
Blood Chemistry			
ALT/SGPT	U/L	6.000/34.000	
Thyroids			
THYROID STIM. HORMONE	mU/L	0.320/5.000	5.92H

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 2
Patient Number: 206
Treatment Group: Placebo

Lab Test	Units	Low/High Reference	VISIT 15
Blood Chemistry			
ALT/SGPT	U/L	6.000/34.000	59.0H
Thyroids			
THYROID STIM. HORMONE	mU/L	0.320/5.000	

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 2
Patient Number: 208
Treatment Group: Flx

Lab Test	Units	Low/High Reference	VISIT 1
Complete Blood Count			
HEMATOCRIT	1	0.390/0.540	0.360L
HEMOGLOBIN	mml/L-Fe	7.880/11.230	7.26L
LEUKOCYTE COUNT	GI/L	4.350/13.150	2.8L
			4.1L
NEUTROPHILS, SEGMENTED	GI/L	1.650/8.150	1.18L
LYMPHOCYTES	GI/L	0.950/5.250	0.73L
ANISOCYTOSIS	NO UNITS		1 A
Urinalysis			
UA-SPECIFIC GRAVITY	NO UNITS	1.010/1.034	1.008L

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 2
Patient Number: 208
Treatment Group: Flx

Lab Test	Units	Low/High Reference	VISIT 8
Complete Blood Count			
HEMATOCRIT	1	0.390/0.540	0.370L
HEMOGLOBIN	mml/L-Fe	7.880/11.230	7.70L
LEUKOCYTE COUNT	GI/L	4.350/13.150	3.1L
NEUTROPHILS, SEGMENTED	GI/L	1.650/8.150	1.38L
LYMPHOCYTES	GI/L	0.950/5.250	
ANISOCYTOSIS	NO UNITS		
Urinalysis			
UA-SPECIFIC GRAVITY	NO UNITS	1.010/1.034	1.007L

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 2
Patient Number: 209
Treatment Group: Placebo

Lab Test	Units	Low/High Reference	VISIT 1
Complete Blood Count			
HEMATOCRIT	1	0.390/0.540	0.370L
LEUKOCYTE COUNT	GI/L	4.350/13.150	4.3L
MEAN CELL VOLUME (MCV)	fL	79.000/96.000	
Blood Chemistry			
URIC ACID	umol/L	202.000/535.000	149L
Electrolytes			
POTASSIUM	mmol/L	3.400/5.400	3.3L

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 2
Patient Number: 209
Treatment Group: Placebo

Lab Test	Units	Low/High Reference	VISIT 15
Complete Blood Count			
HEMATOCRIT	1	0.390/0.540	0.360L
LEUKOCYTE COUNT	GI/L	4.350/13.150	4.1L
MEAN CELL VOLUME (MCV)	fL	79.000/96.000	78L
Blood Chemistry			
URIC ACID	umol/L	202.000/535.000	190L
Electrolytes			
POTASSIUM	mmol/L	3.400/5.400	

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 2
Patient Number: 210
Treatment Group: Placebo

Lab Test	Units	Low/High Reference	VISIT 1
Blood Chemistry			
CREATINE PHOSPHOKINASE	U/L	150.000/489.000	90L
Thyroids			
THYROXINE, TOTAL-T4	nmol/L	82.000/171.000	73L

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 2
Patient Number: 211
Treatment Group: NON-RAND

Lab Test	Units	Low/High Reference	VISIT 1
Complete Blood Count			
HEMOGLOBIN	mml/L-Fe	6.520/8.380	8.56H
NEUTROPHILS, SEGMENTED	GI/L	4.000/13.500	3.93L
LYMPHOCYTES	GI/L	4.000/12.000	2.00L
EOSINOPHILS	GI/L	0.000/0.570	0.62H
Blood Chemistry			
TOTAL PROTEIN	g/L	55.000/71.000	79H
Electrolytes			
BICARBONATE, HCO3	mmol/L	12.000/28.000	29.5H
Urinalysis			
UA-SPECIFIC GRAVITY	NO UNITS	1.010/1.034	1.036H
UA-PROTEIN	NO UNITS		2 A
UA-NITRITES	NO UNITS		POS A
UA-KETONES	NO UNITS		1 A
UA-OCCULT BLOOD	NO UNITS		3 A

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 2
Patient Number: 212
Treatment Group: NON-RAND

Lab Test	Units	Low/High Reference	VISIT 1
Complete Blood Count			
LEUKOCYTE COUNT	GI/L	6.000/11.000	5.8L
NEUTROPHILS, SEGMENTED	GI/L	4.000/13.500	2.58L
LYMPHOCYTES	GI/L	4.000/12.000	2.72L
Electrolytes			
BICARBONATE, HCO3	mmol/L	12.000/28.000	29.8H

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 2
Patient Number: 213
Treatment Group: NON-RAND

Lab Test	Units	Low/High Reference	VISIT 1
Complete Blood Count			
LEUKOCYTE COUNT	GI/L	6.000/11.000	5.1L
NEUTROPHILS, SEGMENTED	GI/L	4.000/13.500	1.57L
LYMPHOCYTES	GI/L	4.000/12.000	3.25L
Blood Chemistry			
TOTAL PROTEIN	g/L	55.000/71.000	83H
Electrolytes			
BICARBONATE, HCO3	mmol/L	12.000/28.000	29.5H
Thyroids			
THYROXINE, TOTAL-T4	nmol/L	93.000/201.000	91L
Urinalysis			
UA-PROTEIN	NO UNITS		1 A
UA-KETONES	NO UNITS		1 A

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 2
Patient Number: 214
Treatment Group: NON-RAND

Lab Test	Units	Low/High Reference	VISIT 1
Complete Blood Count			
LEUKOCYTE COUNT	GI/L	6.000/11.000	5.8L
NEUTROPHILS, SEGMENTED	GI/L	4.000/13.500	3.68L
LYMPHOCYTES	GI/L	4.000/12.000	1.60L
Blood Chemistry			
TOTAL PROTEIN	g/L	55.000/71.000	74H

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 3
Patient Number: 301
Treatment Group: Placebo

Lab Test	Units	Low/High Reference	VISIT 1
Complete Blood Count			
MEAN CELL HEMOGLOBIN CONCENTRATION (MCHC	mml/L-Fe	19.000/24.000	18L
Blood Chemistry			
CREATINE PHOSPHOKINASE	U/L	91.000/391.000	
ALKALINE PHOSPHATASE	U/L	51.000/300.000	351H
			340H
GGT (GGPT/SGGT/YGGT)	U/L	0.000/33.000	47.0H
			51.0H
CREATININE	umol/L	35.000/88.000	97H
			106H
Urinalysis			
UA-SPECIFIC GRAVITY	NO UNITS	1.010/1.034	
UA-WBC	NO UNITS		
UA-BACTERIA	NO UNITS		1 A
UA-NITRITES	NO UNITS		POS A

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 3
Patient Number: 301
Treatment Group: Placebo

Lab Test	Units	Low/High Reference	VISIT 8
Complete Blood Count			
MEAN CELL HEMOGLOBIN CONCENTRATION (MCHC	mml/L-Fe	19.000/24.000	
Blood Chemistry			
CREATINE PHOSPHOKINASE	U/L	91.000/391.000	838H
ALKALINE PHOSPHATASE	U/L	51.000/300.000	353H
GGT (GGPT/SGGT/YGGT)	U/L	0.000/33.000	56.0H
CREATININE	umol/L	35.000/88.000	97H
Urinalysis			
UA-SPECIFIC GRAVITY	NO UNITS	1.010/1.034	1.035H
UA-WBC	NO UNITS		2 A
UA-BACTERIA	NO UNITS		
UA-NITRITES	NO UNITS		

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 3
Patient Number: 302
Treatment Group: Flx

Lab Test	Units	Low/High Reference	VISIT 1
Complete Blood Count			
LEUKOCYTE COUNT	GI/L	4.350/13.150	
LYMPHOCYTES	GI/L	0.950/5.250	
PLATELET COUNT	GI/L	140.000/400.000	136L
Blood Chemistry			
CREATINE PHOSPHOKINASE	U/L	53.000/269.000	38L
TOTAL PROTEIN	g/L	61.000/84.000	85H
Thyroids			
T3, TOTAL (TRIIODOTHYRONINE)	nmol/L	1.200/3.100	1.1L
Urinalysis			
UA-SPECIFIC GRAVITY	NO UNITS	1.010/1.034	1.006L
UA-BACTERIA	NO UNITS		
UA-OCCULT BLOOD	NO UNITS		

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 3
Patient Number: 302
Treatment Group: Flx

Lab Test	Units	Low/High Reference	VISIT 9
Complete Blood Count			
LEUKOCYTE COUNT	GI/L	4.350/13.150	3.9L
LYMPHOCYTES	GI/L	0.950/5.250	0.82L
PLATELET COUNT	GI/L	140.000/400.000	44L
Blood Chemistry			
CREATINE PHOSPHOKINASE	U/L	53.000/269.000	49L
TOTAL PROTEIN	g/L	61.000/84.000	
Thyroids			
T3, TOTAL (TRIIODOTHYRONINE)	nmol/L	1.200/3.100	1.2L
Urinalysis			
UA-SPECIFIC GRAVITY	NO UNITS	1.010/1.034	1.007L
UA-BACTERIA	NO UNITS		1 A
UA-OCCULT BLOOD	NO UNITS		2 A

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 3
Patient Number: 303
Treatment Group: Placebo

Lab Test	Units	Low/High Reference	VISIT 1
Complete Blood Count			
NEUTROPHILS, SEGMENTED	GI/L	1.350/8.150	
Blood Chemistry			
AST/SGOT	U/L	10.000/40.000	
ALT/SGPT	U/L	6.000/34.000	
CREATINE PHOSPHOKINASE	U/L	91.000/391.000	90L
ALKALINE PHOSPHATASE	U/L	51.000/300.000	302H
GGT (GGPT/SGGT/YGGT)	U/L	0.000/33.000	
BILIRUBIN, TOTAL	umol/L	3.000/21.000	
Urinalysis			
UA-SPECIFIC GRAVITY	NO UNITS	1.010/1.034	1.008L

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 3
Patient Number: 303
Treatment Group: Placebo

Lab Test	Units	Low/High Reference	VISIT 14
Complete Blood Count			
NEUTROPHILS, SEGMENTED	GI/L	1.350/8.150	1.11L
Blood Chemistry			
AST/SGOT	U/L	10.000/40.000	58.0H
ALT/SGPT	U/L	6.000/34.000	80.0H
CREATINE PHOSPHOKINASE	U/L	91.000/391.000	50L
ALKALINE PHOSPHATASE	U/L	51.000/300.000	356H
GGT (GGPT/SGGT/YGGT)	U/L	0.000/33.000	52.0H
BILIRUBIN, TOTAL	umol/L	3.000/21.000	27H
Urinalysis			
UA-SPECIFIC GRAVITY	NO UNITS	1.010/1.034	

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 3
Patient Number: 305
Treatment Group: Flx

Lab Test	Units	Low/High Reference	VISIT 1
Complete Blood Count			
HEMATOCRIT	1	0.340/0.440	0.450H
Blood Chemistry			
CREATINE PHOSPHOKINASE	U/L	150.000/489.000	82L
ALBUMIN	g/L	29.000/47.000	48H
CHOLESTEROL	mmol/L	3.360/5.280	6.31H

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 3
Patient Number: 305
Treatment Group: Flx

Lab Test	Units	Low/High Reference	VISIT 15
Complete Blood Count			
HEMATOCRIT	1	0.340/0.440	
Blood Chemistry			
CREATINE PHOSPHOKINASE	U/L	150.000/489.000	121L
ALBUMIN	g/L	29.000/47.000	
CHOLESTEROL	mmol/L	3.360/5.280	5.90H

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 3
Patient Number: 306
Treatment Group: Placebo

Lab Test	Units	Low/High Reference	VISIT 1
Complete Blood Count			
LEUKOCYTE COUNT	GI/L	4.350/13.650	
MEAN CELL VOLUME (MCV)	fL	76.000/93.000	96H
PLATELET COUNT	GI/L	130.000/394.000	407H
Blood Chemistry			
CREATINE PHOSPHOKINASE	U/L	150.000/489.000	96L
CHOLESTEROL	mmol/L	3.360/5.280	5.66H
Urinalysis			
UA-PROTEIN	NO UNITS		1 A
UA-KETONES	NO UNITS		1 A

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 3
Patient Number: 306
Treatment Group: Placebo

Lab Test	Units	Low/High Reference	VISIT 11
Complete Blood Count			
LEUKOCYTE COUNT	GI/L	4.350/13.650	4.2L
MEAN CELL VOLUME (MCV)	fL	76.000/93.000	
PLATELET COUNT	GI/L	130.000/394.000	
Blood Chemistry			
CREATINE PHOSPHOKINASE	U/L	150.000/489.000	99L
CHOLESTEROL	mmol/L	3.360/5.280	5.72H
Urinalysis			
UA-PROTEIN	NO UNITS		
UA-KETONES	NO UNITS		

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 3
Patient Number: 307
Treatment Group: Flx

Lab Test	Units	Low/High Reference	VISIT 1
Complete Blood Count			
HEMATOCRIT	1	0.390/0.540	
Blood Chemistry			
CREATINE PHOSPHOKINASE	U/L	94.000/499.000	86L
ALKALINE PHOSPHATASE	U/L	50.000/250.000	258H
INORGANIC PHOSPHORUS	mmol/L	0.710/1.650	1.74H
Urinalysis			
UA-PROTEIN	NO UNITS		2 A
UA-OCCULT BLOOD	NO UNITS		1 A

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 3
Patient Number: 307
Treatment Group: Flx

Lab Test	Units	Low/High Reference	VISIT 12
Complete Blood Count			
HEMATOCRIT	1	0.390/0.540	0.380L
Blood Chemistry			
CREATINE PHOSPHOKINASE	U/L	94.000/499.000	
ALKALINE PHOSPHATASE	U/L	50.000/250.000	
INORGANIC PHOSPHORUS	mmol/L	0.710/1.650	1.74H
Urinalysis			
UA-PROTEIN	NO UNITS		
UA-OCCULT BLOOD	NO UNITS		

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 3
Patient Number: 308
Treatment Group: NON-RAND

Lab Test	Units	Low/High Reference	VISIT 1
Complete Blood Count			
HEMOGLOBIN	mml/L-Fe	6.520/8.380	8.87H
LEUKOCYTE COUNT	GI/L	6.000/11.000	5.6L
NEUTROPHILS, SEGMENTED	GI/L	4.000/13.500	3.15L
LYMPHOCYTES	GI/L	4.000/12.000	1.99L
Blood Chemistry			
TOTAL PROTEIN	g/L	55.000/71.000	73H
Thyroids			
THYROXINE, TOTAL-T4	nmol/L	93.000/201.000	64L
Urinalysis			
UA-KETONES	NO UNITS		1 A

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 3
Patient Number: 309
Treatment Group: Placebo

Lab Test	Units	Low/High Reference	VISIT 1
Complete Blood Count			
LEUKOCYTE COUNT	GI/L	4.350/13.150	4.3L
Blood Chemistry			
INORGANIC PHOSPHORUS	mmol/L	1.000/1.940	
Urinalysis			
UA-KETONES	NO UNITS		

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 3
Patient Number: 309
Treatment Group: Placebo

Lab Test	Units	Low/High Reference	VISIT 15	
Complete Blood Count				
LEUKOCYTE COUNT	GI/L	4.350/13.150		
Blood Chemistry				
INORGANIC PHOSPHORUS	mmol/L	1.000/1.940	1.97H	
Urinalysis				
UA-KETONES	NO UNITS		1	A

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 3
Patient Number: 311
Treatment Group: NON-RAND

Lab Test	Units	Low/High Reference	VISIT 1
Complete Blood Count			
HEMOGLOBIN	mml/L-Fe	6.520/8.380	9.18H
LEUKOCYTE COUNT	GI/L	6.000/11.000	6.0L
NEUTROPHILS, SEGMENTED	GI/L	4.000/13.500	3.73L
LYMPHOCYTES	GI/L	4.000/12.000	1.64L
Blood Chemistry			
TOTAL PROTEIN	g/L	55.000/71.000	77H
UDS			
MARIJUANA (THC)	NO UNITS		POS A

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 3
Patient Number: 313
Treatment Group: Flx

Lab Test	Units	Low/High Reference	VISIT 1
Blood Chemistry			
CREATINE PHOSPHOKINASE	U/L	91.000/391.000	63L

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 3
Patient Number: 314
Treatment Group: NON-RAND

Lab Test	Units	Low/High Reference	VISIT 1
Complete Blood Count			
LEUKOCYTE COUNT	GI/L	6.000/11.000	5.1L
NEUTROPHILS, SEGMENTED	GI/L	4.000/13.500	3.06L
LYMPHOCYTES	GI/L	4.000/12.000	1.52L
PLATELET COUNT	GI/L	200.000/400.000	199L
Blood Chemistry			
TOTAL PROTEIN	g/L	55.000/71.000	73H
Thyroids			
THYROXINE, TOTAL-T4	nmol/L	93.000/201.000	82L
T3, TOTAL (TRIIODOTHYRONINE)	nmol/L	1.200/3.100	1.1L
Urinalysis			
UA-BACTERIA	NO UNITS		1 A

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 3
Patient Number: 315
Treatment Group: Placebo

Lab Test	Units	Low/High Reference	VISIT 15
Blood Chemistry			
ALT/SGPT	U/L	6.000/34.000	4.0L
CREATINE PHOSPHOKINASE	U/L	53.000/269.000	48L
Urinalysis			
UA-SPECIFIC GRAVITY	NO UNITS	1.010/1.034	1.009L
UA-BACTERIA	NO UNITS		1 A

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 3
Patient Number: 316
Treatment Group: NON-RAND

Lab Test	Units	Low/High Reference	VISIT 1
Complete Blood Count			
MEAN CELL HEMOGLOBIN (MCH)	fmol(Fe)	1.430/1.920	1.99H
LYMPHOCYTES	GI/L	4.000/12.000	2.20L
MEAN CELL VOLUME (MCV)	fL	70.000/90.000	94H
Blood Chemistry			
TOTAL PROTEIN	g/L	55.000/71.000	75H

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 3
Patient Number: 317
Treatment Group: NON-RAND

Lab Test	Units	Low/High Reference	VISIT 1
Complete Blood Count			
LYMPHOCYTES	GI/L	4.000/12.000	2.73L
MEAN CELL VOLUME (MCV)	fL	70.000/90.000	95H
PLATELET COUNT	GI/L	200.000/400.000	192L
Blood Chemistry			
TOTAL PROTEIN	g/L	55.000/71.000	77H
Thyroids			
THYROXINE, TOTAL-T4	nmol/L	93.000/201.000	68L
THYROID STIM. HORMONE	mU/L	0.320/5.000	6.05H
FREE THYROXINE INDEX	INDEX	1.940/5.620	1.70L

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 3
Patient Number: 318
Treatment Group: Flx

Lab Test	Units	Low/High Reference	VISIT 1
Blood Chemistry			
CREATINE PHOSPHOKINASE	U/L	150.000/489.000	129L
Urinalysis			
UA-SPECIFIC GRAVITY	NO UNITS	1.010/1.034	1.039H

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 3
Patient Number: 320
Treatment Group: NON-RAND

Lab Test	Units	Low/High Reference	VISIT 1
Complete Blood Count			
HEMOGLOBIN	mml/L-Fe	6.520/8.380	8.75H
LYMPHOCYTES	GI/L	4.000/12.000	2.83L
Blood Chemistry			
TOTAL PROTEIN	g/L	55.000/71.000	75H

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 3
Patient Number: 321
Treatment Group: NON-RAND

Lab Test	Units	Low/High Reference	VISIT 1
Complete Blood Count			
HEMOGLOBIN	mml/L-Fe	6.520/8.380	9.06H
LYMPHOCYTES	GI/L	4.000/12.000	1.75L
Blood Chemistry			
BILIRUBIN, TOTAL	umol/L	3.000/21.000	24H
Electrolytes			
BICARBONATE, HCO3	mmol/L	12.000/28.000	30.9H

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 3
Patient Number: 322
Treatment Group: NON-RAND

Lab Test	Units	Low/High Reference	VISIT 1
Complete Blood Count			
LEUKOCYTE COUNT	GI/L	6.000/11.000	5.8L
NEUTROPHILS, SEGMENTED	GI/L	4.000/13.500	3.33L
LYMPHOCYTES	GI/L	4.000/12.000	1.96L
Blood Chemistry			
TOTAL PROTEIN	g/L	55.000/71.000	72H
Thyroids			
THYROXINE, TOTAL-T4	nmol/L	93.000/201.000	88L
Urinalysis			
UA-OCCULT BLOOD	NO UNITS		3 A

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 3
Patient Number: 326
Treatment Group: Flx

Lab Test	Units	Low/High Reference	VISIT 1	
Complete Blood Count				
NEUTROPHILS, SEGMENTED	GI/L	1.650/8.150	8.70	H
Urinalysis				
UA-RBC	NO UNITS		4	A
UA-KETONES	NO UNITS		1	A
UA-OCCULT BLOOD	NO UNITS		3	A

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 3
Patient Number: 326
Treatment Group: Flx

Lab Test	Units	Low/High Reference	VISIT 15	
Complete Blood Count				
NEUTROPHILS, SEGMENTED	GI/L	1.650/8.150		
Urinalysis				
UA-RBC	NO UNITS		1	A
UA-KETONES	NO UNITS			
UA-OCCULT BLOOD	NO UNITS		3	A

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 3
Patient Number: 327
Treatment Group: NON-RAND

Lab Test	Units	Low/High Reference	VISIT 1
Complete Blood Count			
LEUKOCYTE COUNT	GI/L	6.000/11.000	4.9L
NEUTROPHILS, SEGMENTED	GI/L	4.000/13.500	2.70L
LYMPHOCYTES	GI/L	4.000/12.000	1.68L
Thyroids			
THYROXINE, TOTAL-T4	nmol/L	93.000/201.000	81L

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 3
Patient Number: 328
Treatment Group: NON-RAND

Lab Test	Units	Low/High Reference	VISIT 1
Complete Blood Count			
HEMOGLOBIN	mml/L-Fe	6.520/8.380	8.87H
Blood Chemistry			
TOTAL PROTEIN	g/L	55.000/71.000	79H
Urinalysis			
UA-KETONES	NO UNITS	1	A

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 3
Patient Number: 330
Treatment Group: Placebo

Lab Test	Units	Low/High Reference	VISIT 1
Blood Chemistry			
CREATININE	umol/L	35.000/88.000	97H
BILIRUBIN, TOTAL	umol/L	3.000/21.000	26H

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 3
Patient Number: 332
Treatment Group: Flx

Lab Test	Units	Low/High Reference	VISIT 1
Blood Chemistry			
CREATINE PHOSPHOKINASE	U/L	150.000/489.000	60L
CHOLESTEROL	mmol/L	3.260/4.940	6.65H

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 3
Patient Number: 332
Treatment Group: Flx

Lab Test	Units	Low/High Reference	VISIT 9
Blood Chemistry			
CREATINE PHOSPHOKINASE	U/L	150.000/489.000	80L
CHOLESTEROL	mmol/L	3.260/4.940	6.88H

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 3
Patient Number: 334
Treatment Group: Flx

Lab Test	Units	Low/High Reference	VISIT 1
Complete Blood Count			
HEMATOCRIT	1	0.390/0.540	
ERYTHROCYTE COUNT	TI/L	4.500/6.400	
Blood Chemistry			
CHOLESTEROL	mmol/L	3.360/5.280	2.84L
Urinalysis			
UA-KETONES	NO UNITS		

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 3
Patient Number: 334
Treatment Group: Flx

Lab Test	Units	Low/High Reference	VISIT 15
Complete Blood Count			
HEMATOCRIT	1	0.390/0.540	0.380L
ERYTHROCYTE COUNT	TI/L	4.500/6.400	4.40L
Blood Chemistry			
CHOLESTEROL	mmol/L	3.360/5.280	2.82L
Urinalysis			
UA-KETONES	NO UNITS		1 A

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 3
Patient Number: 335
Treatment Group: Placebo

Lab Test	Units	Low/High Reference	VISIT 1
Blood Chemistry			
ALT/SGPT	U/L	6.000/43.000	
CREATINE PHOSPHOKINASE	U/L	150.000/489.000	143L
INORGANIC PHOSPHORUS	mmol/L	1.000/1.940	1.97H

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 3
Patient Number: 335
Treatment Group: Placebo

Lab Test	Units	Low/High Reference	VISIT 15
Blood Chemistry			
ALT/SGPT	U/L	6.000/43.000	45.0H
CREATINE PHOSPHOKINASE	U/L	150.000/489.000	
INORGANIC PHOSPHORUS	mmol/L	1.000/1.940	

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 3
Patient Number: 336
Treatment Group: Placebo

Lab Test	Units	Low/High Reference	VISIT 1
Blood Chemistry			
CHOLESTEROL	mmol/L	3.360/5.280	5.69H
Urinalysis			
UA-PROTEIN	NO UNITS		
UA-KETONES	NO UNITS		

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 3
Patient Number: 336
Treatment Group: Placebo

Lab Test	Units	Low/High Reference	VISIT 15	
Blood Chemistry				
CHOLESTEROL	mmol/L	3.360/5.280		
Urinalysis				
UA-PROTEIN	NO UNITS		1	A
UA-KETONES	NO UNITS		1	A

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 3
Patient Number: 337
Treatment Group: NON-RAND

Lab Test	Units	Low/High Reference	VISIT 1
Complete Blood Count			
LEUKOCYTE COUNT	GI/L	6.000/11.000	3.6L
NEUTROPHILS, SEGMENTED	GI/L	4.000/13.500	1.81L
LYMPHOCYTES	GI/L	4.000/12.000	1.40L
PLATELET COUNT	GI/L	200.000/400.000	165L

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 3
Patient Number: 339
Treatment Group: Placebo

Lab Test	Units	Low/High Reference	VISIT 1
Blood Chemistry			
CREATINE PHOSPHOKINASE	U/L	150.000/489.000	136L

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 3
Patient Number: 340
Treatment Group: NON-RAND

Lab Test	Units	Low/High Reference	VISIT 1
Complete Blood Count			
LEUKOCYTE COUNT	GI/L	6.000/11.000	5.7L
NEUTROPHILS, SEGMENTED	GI/L	4.000/13.500	2.55L
LYMPHOCYTES	GI/L	4.000/12.000	2.55L
Electrolytes			
BICARBONATE, HCO3	mmol/L	12.000/28.000	28.3H
Urinalysis			
UA-SPECIFIC GRAVITY	NO UNITS	1.010/1.034	1.038H

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 3
Patient Number: 343
Treatment Group: Placebo

Lab Test	Units	Low/High Reference	VISIT 1
Complete Blood Count			
HEMATOCRIT	1	0.390/0.540	0.370L
HEMOGLOBIN	mml/L-Fe	7.880/11.230	7.82L
Urinalysis			
UA-SPECIFIC GRAVITY	NO UNITS	1.010/1.034	1.035H

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 3
Patient Number: 343
Treatment Group: Placebo

Lab Test	Units	Low/High Reference	VISIT 12
Complete Blood Count			
HEMATOCRIT	1	0.390/0.540	0.380L
HEMOGLOBIN	mml/L-Fe	7.880/11.230	7.76L
Urinalysis			
UA-SPECIFIC GRAVITY	NO UNITS	1.010/1.034	

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 3
Patient Number: 346
Treatment Group: Flx

Lab Test	Units	Low/High Reference	VISIT 1
Complete Blood Count			
MONOCYTES	GI/L	0.120/0.920	
MEAN CELL VOLUME (MCV)	fL	76.000/93.000	
Blood Chemistry			
CREATINE PHOSPHOKINASE	U/L	91.000/391.000	68L
Urinalysis			
UA-OCCULT BLOOD	NO UNITS		1 A

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 3
Patient Number: 346
Treatment Group: Flx

Lab Test	Units	Low/High Reference	VISIT 15
Complete Blood Count			
MONOCYTES	GI/L	0.120/0.920	0.06L
MEAN CELL VOLUME (MCV)	fL	76.000/93.000	98H
Blood Chemistry			
CREATINE PHOSPHOKINASE	U/L	91.000/391.000	89L
Urinalysis			
UA-OCCULT BLOOD	NO UNITS		

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 3
Patient Number: 348
Treatment Group: NON-RAND

Lab Test	Units	Low/High Reference	VISIT 1
Complete Blood Count			
LEUKOCYTE COUNT	GI/L	6.000/11.000	4.5L
NEUTROPHILS, SEGMENTED	GI/L	4.000/13.500	2.26L
LYMPHOCYTES	GI/L	4.000/12.000	1.80L
MICROCYTOSIS	NO UNITS	1	A

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 3
Patient Number: 350
Treatment Group: Placebo

Lab Test	Units	Low/High Reference	VISIT 1
Complete Blood Count			
HEMATOCRIT	1	0.340/0.440	0.320L
			0.310L
			0.310L
			0.310L
HEMOGLOBIN	mml/L-Fe	7.000/9.600	6.95L
			6.70L
			6.45L
			6.70L
MEAN CELL VOLUME (MCV)	fL	76.000/93.000	74L
			75L
			75L
			75L
ANISOCYTOSIS	NO UNITS		1 A
			1 A
			1 A
MICROCYTOSIS	NO UNITS		1 A
			1 A
			1 A
POLYCHROMIA	NO UNITS		1 A
Blood Chemistry			
AST/SGOT	U/L	10.000/40.000	72.0H
			41.0H
ALT/SGPT	U/L	6.000/34.000	50.0H
			117.0H
			87.0H
			49.0H
GGT (GGPT/SGGT/YGGT)	U/L	0.000/33.000	43.0H
			39.0H
URIC ACID	umol/L	161.000/393.000	399H
			404H

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 3
Patient Number: 350
Treatment Group: Placebo

Lab Test	Units	Low/High Reference	VISIT 15
Complete Blood Count			
HEMATOCRIT	1	0.340/0.440	0.320L
HEMOGLOBIN	mml/L-Fe	7.000/9.600	6.39L
MEAN CELL VOLUME (MCV)	fL	76.000/93.000	
ANISOCYTOSIS	NO UNITS		
MICROCYTOSIS	NO UNITS		
POLYCHROMIA	NO UNITS		
Blood Chemistry			
AST/SGOT	U/L	10.000/40.000	
ALT/SGPT	U/L	6.000/34.000	35.0H
GGT (GGPT/SGGT/YGGT)	U/L	0.000/33.000	
URIC ACID	umol/L	161.000/393.000	458H

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 3
Patient Number: 351
Treatment Group: NON-RAND

Lab Test	Units	Low/High Reference	VISIT 1
Complete Blood Count			
HEMOGLOBIN	mml/L-Fe	6.520/8.380	9.12H
LEUKOCYTE COUNT	GI/L	6.000/11.000	4.8L
NEUTROPHILS, SEGMENTED	GI/L	4.000/13.500	0.48L
LYMPHOCYTES	GI/L	4.000/12.000	2.75L
EOSINOPHILS	GI/L	0.000/0.570	1.11H
PLATELET COUNT	GI/L	200.000/400.000	191L
Blood Chemistry			
TOTAL PROTEIN	g/L	55.000/71.000	78H
Thyroids			
THYROXINE, TOTAL-T4	nmol/L	93.000/201.000	59L
FREE THYROXINE INDEX	INDEX	1.940/5.620	1.90L

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 3
Patient Number: 352
Treatment Group: Placebo

Lab Test	Units	Low/High Reference	VISIT 1
Blood Chemistry			
ALKALINE PHOSPHATASE	U/L	51.000/300.000	307H

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 3
Patient Number: 353
Treatment Group: Flx

Lab Test	Units	Low/High Reference	VISIT 1
Complete Blood Count			
HEMATOCRIT	1	0.390/0.540	0.380L
HEMOGLOBIN	mml/L-Fe	7.880/11.230	
ERYTHROCYTE COUNT	TI/L	4.500/6.400	4.30L
Urinalysis			
UA-SPECIFIC GRAVITY	NO UNITS	1.010/1.034	1.035H

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 3
Patient Number: 353
Treatment Group: Flx

Lab Test	Units	Low/High Reference	VISIT 15
Complete Blood Count			
HEMATOCRIT	1	0.390/0.540	0.360L
HEMOGLOBIN	mml/L-Fe	7.880/11.230	7.51L
ERYTHROCYTE COUNT	TI/L	4.500/6.400	4.10L
Urinalysis			
UA-SPECIFIC GRAVITY	NO UNITS	1.010/1.034	

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 3
Patient Number: 354
Treatment Group: Flx

Lab Test	Units	Low/High Reference	VISIT 1
Blood Chemistry			
AST/SGOT	U/L	10.000/40.000	42.0H
			43.0H
ALT/SGPT	U/L	6.000/34.000	50.0H
			42.0H
			38.0H
CREATINE PHOSPHOKINASE	U/L	53.000/269.000	332H
			279H
			575H
			715H
			434H
GGT (GGPT/SGGT/YGGT)	U/L	0.000/33.000	53.0H
			55.0H
			49.0H
			43.0H
			42.0H
Urinalysis			
UA-SPECIFIC GRAVITY	NO UNITS	1.010/1.034	1.037H
UA-RBC	NO UNITS		
UA-BACTERIA	NO UNITS		1 A
UA-OCCULT BLOOD	NO UNITS		

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 3
Patient Number: 354
Treatment Group: Flx

Lab Test	Units	Low/High Reference	VISIT 15
Blood Chemistry			
AST/SGOT	U/L	10.000/40.000	
ALT/SGPT	U/L	6.000/34.000	46.0H
CREATINE PHOSPHOKINASE	U/L	53.000/269.000	388H
GGT (GGPT/SGGT/YGGT)	U/L	0.000/33.000	53.0H
Urinalysis			
UA-SPECIFIC GRAVITY	NO UNITS	1.010/1.034	1.038H
UA-RBC	NO UNITS		4 A
UA-BACTERIA	NO UNITS		
UA-OCCULT BLOOD	NO UNITS		3 A

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 3
Patient Number: 355
Treatment Group: Flx

Lab Test	Units	Low/High Reference	VISIT 1
Blood Chemistry			
ALKALINE PHOSPHATASE	U/L	51.000/300.000	331H

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 3
Patient Number: 356
Treatment Group: Placebo

Lab Test	Units	Low/High Reference	VISIT 1
Complete Blood Count			
MEAN CELL HEMOGLOBIN (MCH)	fmol(Fe)	1.600/2.100	1.49L
MEAN CELL VOLUME (MCV)	fL	79.000/96.000	75L
ANISOCYTOSIS	NO UNITS		
MICROCYTOSIS	NO UNITS		1 A
Blood Chemistry			
ALKALINE PHOSPHATASE	U/L	50.000/250.000	367H
			357H

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 3
Patient Number: 356
Treatment Group: Placebo

Lab Test	Units	Low/High Reference	VISIT 15
Complete Blood Count			
MEAN CELL HEMOGLOBIN (MCH)	fmol(Fe)	1.600/2.100	1.49L
MEAN CELL VOLUME (MCV)	fL	79.000/96.000	74L
ANISOCYTOSIS	NO UNITS		1 A
MICROCYTOSIS	NO UNITS		
Blood Chemistry			
ALKALINE PHOSPHATASE	U/L	50.000/250.000	337H

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 4
Patient Number: 401
Treatment Group: Flx

Lab Test	Units	Low/High Reference	VISIT 1
Complete Blood Count			
MEAN CELL VOLUME (MCV)	fL	79.000/96.000	75L
ANISOCYTOSIS	NO UNITS		
MICROCYTOSIS	NO UNITS		1 A

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 4
Patient Number: 401
Treatment Group: Flx

Lab Test	Units	Low/High Reference	VISIT 12
Complete Blood Count			
MEAN CELL VOLUME (MCV)	fL	79.000/96.000	73L
ANISOCYTOSIS	NO UNITS	1	A
MICROCYTOSIS	NO UNITS	1	A

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 4
Patient Number: 402
Treatment Group: NON-RAND

Lab Test	Units	Low/High Reference	VISIT 1
Complete Blood Count			
LEUKOCYTE COUNT	GI/L	6.000/11.000	4.2L
NEUTROPHILS, SEGMENTED	GI/L	4.000/13.500	2.51L
LYMPHOCYTES	GI/L	4.000/12.000	1.17L
Blood Chemistry			
TOTAL PROTEIN	g/L	55.000/71.000	77H
Urinalysis			
UA-OCCULT BLOOD	NO UNITS	1	A

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 4
Patient Number: 403
Treatment Group: Placebo

Lab Test	Units	Low/High Reference	VISIT 1
Complete Blood Count			
PLATELET COUNT	GI/L	130.000/394.000	408H
Blood Chemistry			
CREATINE PHOSPHOKINASE	U/L	91.000/391.000	87L
URIC ACID	umol/L	161.000/393.000	125L

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 4
Patient Number: 403
Treatment Group: Placebo

Lab Test	Units	Low/High Reference	VISIT 15
Complete Blood Count			
PLATELET COUNT	GI/L	130.000/394.000	414H
Blood Chemistry			
CREATINE PHOSPHOKINASE	U/L	91.000/391.000	89L
URIC ACID	umol/L	161.000/393.000	137L

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 4
Patient Number: 404
Treatment Group: Flx

Lab Test	Units	Low/High Reference	VISIT 1
Blood Chemistry			
ALKALINE PHOSPHATASE	U/L	50.000/250.000	310H

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 4
Patient Number: 405
Treatment Group: NON-RAND

Lab Test	Units	Low/High Reference	VISIT 1
Complete Blood Count			
HEMOGLOBIN	mml/L-Fe	6.520/8.380	8.75H
LEUKOCYTE COUNT	GI/L	6.000/11.000	4.7L
NEUTROPHILS, SEGMENTED	GI/L	4.000/13.500	1.19L
LYMPHOCYTES	GI/L	4.000/12.000	2.94L
MEAN CELL VOLUME (MCV)	fL	70.000/90.000	95H
PLATELET COUNT	GI/L	200.000/400.000	164L
Blood Chemistry			
GGT (GGPT/SGGT/YGGT)	U/L	0.000/24.000	
TOTAL PROTEIN	g/L	55.000/71.000	72H
Electrolytes			
BICARBONATE, HCO3	mmol/L	12.000/28.000	29.6H
Urinalysis			
UA-RBC	NO UNITS		4 A
UA-OCCULT BLOOD	NO UNITS		3 A

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 4
Patient Number: 405
Treatment Group: NON-RAND

Lab Test	Units	Low/High Reference	VISIT 2
Complete Blood Count			
HEMOGLOBIN	mml/L-Fe	6.520/8.380	
LEUKOCYTE COUNT	GI/L	6.000/11.000	
NEUTROPHILS, SEGMENTED	GI/L	4.000/13.500	
LYMPHOCYTES	GI/L	4.000/12.000	
MEAN CELL VOLUME (MCV)	fL	70.000/90.000	
PLATELET COUNT	GI/L	200.000/400.000	
Blood Chemistry			
GGT (GGPT/SGGT/YGGT)	U/L	0.000/24.000	34.0H
TOTAL PROTEIN	g/L	55.000/71.000	
Electrolytes			
BICARBONATE, HCO3	mmol/L	12.000/28.000	
Urinalysis			
UA-RBC	NO UNITS		
UA-OCCULT BLOOD	NO UNITS		

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 4
Patient Number: 407
Treatment Group: Placebo

Lab Test	Units	Low/High Reference	VISIT 1	
Blood Chemistry				
CHOLESTEROL	mmol/L	3.360/5.280	2.53L	
Urinalysis				
UA-GLUCOSE	NO UNITS			
UA-PROTEIN	NO UNITS			
UA-KETONES	NO UNITS		1	A

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 4
Patient Number: 407
Treatment Group: Placebo

Lab Test	Units	Low/High Reference	VISIT 13	
Blood Chemistry				
CHOLESTEROL	mmol/L	3.360/5.280	2.74	L
Urinalysis				
UA-GLUCOSE	NO UNITS		3	A
UA-PROTEIN	NO UNITS		1	A
UA-KETONES	NO UNITS			

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 4
Patient Number: 408
Treatment Group: Flx

Lab Test	Units	Low/High Reference	VISIT 1
Blood Chemistry			
CREATINE PHOSPHOKINASE	U/L	91.000/391.000	87L
ALKALINE PHOSPHATASE	U/L	51.000/300.000	479H

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 4
Patient Number: 409
Treatment Group: NON-RAND

Lab Test	Units	Low/High Reference	VISIT 1
Complete Blood Count			
LEUKOCYTE COUNT	GI/L	6.000/11.000	4.0L
NEUTROPHILS, SEGMENTED	GI/L	4.000/13.500	1.84L
LYMPHOCYTES	GI/L	4.000/12.000	1.84L
Electrolytes			
BICARBONATE, HCO3	mmol/L	12.000/28.000	30.9H

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 4
Patient Number: 410
Treatment Group: NON-RAND

Lab Test	Units	Low/High Reference	VISIT 1
Complete Blood Count			
LEUKOCYTE COUNT	GI/L	6.000/11.000	4.6L
NEUTROPHILS, SEGMENTED	GI/L	4.000/13.500	1.68L
LYMPHOCYTES	GI/L	4.000/12.000	2.33L
Blood Chemistry			
TOTAL PROTEIN	g/L	55.000/71.000	74H
Thyroids			
THYROXINE, TOTAL-T4	nmol/L	93.000/201.000	86L

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 4
Patient Number: 411
Treatment Group: NON-RAND

Lab Test	Units	Low/High Reference	VISIT 1
Complete Blood Count			
LEUKOCYTE COUNT	GI/L	6.000/11.000	5.8L
NEUTROPHILS, SEGMENTED	GI/L	4.000/13.500	1.90L
LYMPHOCYTES	GI/L	4.000/12.000	3.49L
MEAN CELL VOLUME (MCV)	fL	70.000/90.000	92H
Blood Chemistry			
TOTAL PROTEIN	g/L	55.000/71.000	73H
Thyroids			
THYROXINE, TOTAL-T4	nmol/L	93.000/201.000	81L

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 4
Patient Number: 412
Treatment Group: Placebo

Lab Test	Units	Low/High Reference	VISIT 1
Blood Chemistry			
CREATINE PHOSPHOKINASE	U/L	53.000/269.000	40L

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 4
Patient Number: 412
Treatment Group: Placebo

Lab Test	Units	Low/High Reference	VISIT 15
Blood Chemistry			
CREATINE PHOSPHOKINASE	U/L	53.000/269.000	43L

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 4
Patient Number: 413
Treatment Group: Flx

Lab Test	Units	Low/High Reference	VISIT 1
Blood Chemistry			
URIC ACID	umol/L	161.000/393.000	422H

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 4
Patient Number: 413
Treatment Group: Flx

Lab Test	Units	Low/High Reference	VISIT 15
Blood Chemistry			
URIC ACID	umol/L	161.000/393.000	482H

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 4
Patient Number: 414
Treatment Group: NON-RAND

Lab Test	Units	Low/High Reference	VISIT 1
Complete Blood Count			
LYMPHOCYTES	GI/L	4.000/12.000	1.47L

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 4
Patient Number: 415
Treatment Group: Flx

Lab Test	Units	Low/High Reference	VISIT 1
Blood Chemistry			
CREATINE PHOSPHOKINASE	U/L	91.000/391.000	38L
CHOLESTEROL	mmol/L	3.210/5.610	

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 4
Patient Number: 415
Treatment Group: Flx

Lab Test	Units	Low/High Reference	VISIT 15
Blood Chemistry			
CREATINE PHOSPHOKINASE	U/L	91.000/391.000	41L
CHOLESTEROL	mmol/L	3.210/5.610	3.15L

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 4
Patient Number: 416
Treatment Group: Flx

Lab Test	Units	Low/High Reference	VISIT 1
Blood Chemistry			
CREATINE PHOSPHOKINASE	U/L	53.000/269.000	49L
INORGANIC PHOSPHORUS	mmol/L	0.710/1.650	

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 4
Patient Number: 416
Treatment Group: Flx

Lab Test	Units	Low/High Reference	VISIT 15
Blood Chemistry			
CREATINE PHOSPHOKINASE	U/L	53.000/269.000	41L
INORGANIC PHOSPHORUS	mmol/L	0.710/1.650	1.71H

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 4
Patient Number: 417
Treatment Group: Placebo

Lab Test	Units	Low/High Reference	VISIT 1
Blood Chemistry			
CHOLESTEROL	mmol/L	3.360/5.280	3.34L
Thyroids			
THYROXINE, TOTAL-T4	nmol/L	72.000/151.000	

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 4
Patient Number: 417
Treatment Group: Placebo

Lab Test	Units	Low/High Reference	VISIT 9
Blood Chemistry			
CHOLESTEROL	mmol/L	3.360/5.280	
Thyroids			
THYROXINE, TOTAL-T4	nmol/L	72.000/151.000	71L

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 4
Patient Number: 419
Treatment Group: Flx

Lab Test	Units	Low/High Reference	VISIT 1
Blood Chemistry			
CREATINE PHOSPHOKINASE	U/L	91.000/391.000	60L

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 4
Patient Number: 420
Treatment Group: NON-RAND

Lab Test	Units	Low/High Reference	VISIT 1
Blood Chemistry			
TOTAL PROTEIN	g/L	55.000/71.000	72H

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 4
Patient Number: 422
Treatment Group: Flx

Lab Test	Units	Low/High Reference	VISIT 15
Blood Chemistry			
CHOLESTEROL	mmol/L	3.150/5.400	5.66H

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 4
Patient Number: 423
Treatment Group: NON-RAND

Lab Test	Units	Low/High Reference	VISIT 1
Complete Blood Count			
LEUKOCYTE COUNT	GI/L	6.000/11.000	11.6H
Blood Chemistry			
TOTAL PROTEIN	g/L	55.000/71.000	75H

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 4
Patient Number: 424
Treatment Group: Flx

Lab Test	Units	Low/High Reference	VISIT 1
Complete Blood Count			
HEMATOCRIT	1	0.340/0.440	0.320L
HEMOGLOBIN	mml/L-Fe	7.000/9.600	6.95L
PLATELET COUNT	GI/L	130.000/394.000	396H
ANISOCYTOSIS	NO UNITS		1 A
Blood Chemistry			
CHOLESTEROL	mmol/L	3.150/5.400	
Urinalysis			
UA-WBC	NO UNITS		1 A
UA-PROTEIN	NO UNITS		
UA-BACTERIA	NO UNITS		1 A
UA-OCCULT BLOOD	NO UNITS		1 A

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 4
Patient Number: 424
Treatment Group: Flx

Lab Test	Units	Low/High Reference	VISIT 15
Complete Blood Count			
HEMATOCRIT	1	0.340/0.440	
HEMOGLOBIN	mml/L-Fe	7.000/9.600	
PLATELET COUNT	GI/L	130.000/394.000	
ANISOCYTOSIS	NO UNITS		
Blood Chemistry			
CHOLESTEROL	mmol/L	3.150/5.400	5.84H
Urinalysis			
UA-WBC	NO UNITS		
UA-PROTEIN	NO UNITS		1 A
UA-BACTERIA	NO UNITS		
UA-OCCULT BLOOD	NO UNITS		

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 4
Patient Number: 425
Treatment Group: Placebo

Lab Test	Units	Low/High Reference	VISIT 1
Complete Blood Count			
HEMATOCRIT	1	0.390/0.540	0.380L
Blood Chemistry			
CHOLESTEROL	mmol/L	3.360/5.280	6.65H

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 4
Patient Number: 425
Treatment Group: Placebo

Lab Test	Units	Low/High Reference	VISIT 15
Complete Blood Count			
HEMATOCRIT	1	0.390/0.540	
Blood Chemistry			
CHOLESTEROL	mmol/L	3.360/5.280	7.16H

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 4
Patient Number: 427
Treatment Group: Placebo

Lab Test	Units	Low/High Reference	VISIT 1
Blood Chemistry			
CREATINE PHOSPHOKINASE	U/L	91.000/391.000	71L

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 4
Patient Number: 430
Treatment Group: NON-RAND

Lab Test	Units	Low/High Reference	VISIT 1
Complete Blood Count			
HEMOGLOBIN	mml/L-Fe	6.520/8.380	8.56H
LYMPHOCYTES	GI/L	4.000/12.000	1.62L

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 4
Patient Number: 431
Treatment Group: NON-RAND

Lab Test	Units	Low/High Reference	VISIT 1
Complete Blood Count			
HEMOGLOBIN	mml/L-Fe	6.520/8.380	8.69H
LEUKOCYTE COUNT	GI/L	6.000/11.000	5.0L
NEUTROPHILS, SEGMENTED	GI/L	4.000/13.500	2.72L
LYMPHOCYTES	GI/L	4.000/12.000	1.68L
Blood Chemistry			
TOTAL PROTEIN	g/L	55.000/71.000	74H
Electrolytes			
BICARBONATE, HCO3	mmol/L	12.000/28.000	29.6H

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 4
Patient Number: 432
Treatment Group: Placebo

Lab Test	Units	Low/High Reference	VISIT 1
Complete Blood Count			
MONOCYTES	GI/L	0.120/0.920	0.93H
ANISOCYTOSIS	NO UNITS	1	A
Blood Chemistry			
BILIRUBIN, TOTAL	umol/L	3.000/21.000	26H

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 4
Patient Number: 433
Treatment Group: Flx

Lab Test	Units	Low/High Reference	VISIT 13
Urinalysis			
UA-SPECIFIC GRAVITY	NO UNITS	1.010/1.034	1.036H

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 4
Patient Number: 434
Treatment Group: NON-RAND

Lab Test	Units	Low/High Reference	VISIT 1
Complete Blood Count			
HEMOGLOBIN	mml/L-Fe	6.520/8.380	8.44H
LEUKOCYTE COUNT	GI/L	6.000/11.000	4.1L
NEUTROPHILS, SEGMENTED	GI/L	4.000/13.500	1.73L
LYMPHOCYTES	GI/L	4.000/12.000	1.93L
PLATELET COUNT	GI/L	200.000/400.000	158L
ANISOCYTOSIS	NO UNITS	1	A
Blood Chemistry			
BILIRUBIN, TOTAL	umol/L	3.000/21.000	22H
Electrolytes			
BICARBONATE, HCO3	mmol/L	12.000/28.000	28.7H

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 4
Patient Number: 435
Treatment Group: NON-RAND

Lab Test	Units	Low/High Reference	VISIT 1
Complete Blood Count			
HEMOGLOBIN	mml/L-Fe	6.520/8.380	8.56H
LEUKOCYTE COUNT	GI/L	6.000/11.000	3.4L
NEUTROPHILS, SEGMENTED	GI/L	4.000/13.500	1.45L
LYMPHOCYTES	GI/L	4.000/12.000	1.59L
MEAN CELL VOLUME (MCV)	fL	70.000/90.000	91H
Blood Chemistry			
TOTAL PROTEIN	g/L	55.000/71.000	75H
Urinalysis			
UA-BACTERIA	NO UNITS		1 A

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 4
Patient Number: 437
Treatment Group: NON-RAND

Lab Test	Units	Low/High Reference	VISIT 1
Complete Blood Count			
LYMPHOCYTES	GI/L	4.000/12.000	2.45L
MICROCYTOSIS	NO UNITS	1	A

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 4
Patient Number: 438
Treatment Group: NON-RAND

Lab Test	Units	Low/High Reference	VISIT 1
Complete Blood Count			
HEMOGLOBIN	mml/L-Fe	6.520/8.380	8.94H
LEUKOCYTE COUNT	GI/L	6.000/11.000	6.0L
NEUTROPHILS, SEGMENTED	GI/L	4.000/13.500	3.16L
LYMPHOCYTES	GI/L	4.000/12.000	2.27L
Blood Chemistry			
TOTAL PROTEIN	g/L	55.000/71.000	75H
Electrolytes			
BICARBONATE, HCO3	mmol/L	12.000/28.000	28.1H
Urinalysis			
UA-SPECIFIC GRAVITY	NO UNITS	1.010/1.034	1.009L

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 4
Patient Number: 439
Treatment Group: NON-RAND

Lab Test	Units	Low/High Reference	VISIT 1
Complete Blood Count			
HEMOGLOBIN	mml/L-Fe	6.520/8.380	8.44H
NEUTROPHILS, SEGMENTED	GI/L	4.000/13.500	3.46L
LYMPHOCYTES	GI/L	4.000/12.000	2.54L
Blood Chemistry			
TOTAL PROTEIN	g/L	55.000/71.000	74H
Thyroids			
THYROXINE, TOTAL-T4	nmol/L	93.000/201.000	89L
Urinalysis			
UA-BACTERIA	NO UNITS	1	A

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 4
Patient Number: 440
Treatment Group: NON-RAND

Lab Test	Units	Low/High Reference	VISIT 1
Complete Blood Count			
HEMOGLOBIN	mml/L-Fe	6.520/8.380	8.69H
NEUTROPHILS, SEGMENTED	GI/L	4.000/13.500	3.94L
LYMPHOCYTES	GI/L	4.000/12.000	3.25L
Thyroids			
THYROXINE, TOTAL-T4	nmol/L	93.000/201.000	88L
Urinalysis			
UA-PROTEIN	NO UNITS		1 A
UA-KETONES	NO UNITS		1 A

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 4
Patient Number: 441
Treatment Group: Flx

Lab Test	Units	Low/High Reference	VISIT 8
Blood Chemistry			
URIC ACID	umol/L	202.000/535.000	190L

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 5
Patient Number: 503
Treatment Group: NON-RAND

Lab Test	Units	Low/High Reference	VISIT 1
Complete Blood Count			
NEUTROPHILS, SEGMENTED	GI/L	4.000/13.500	2.81L
LYMPHOCYTES	GI/L	4.000/12.000	2.75L
Blood Chemistry			
TOTAL PROTEIN	g/L	55.000/71.000	77H
Thyroids			
THYROXINE, TOTAL-T4	nmol/L	93.000/201.000	75L

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 5
Patient Number: 505
Treatment Group: NON-RAND

Lab Test	Units	Low/High Reference	VISIT 1
Complete Blood Count			
HEMOGLOBIN	mml/L-Fe	6.520/8.380	8.50H
NEUTROPHILS, SEGMENTED	GI/L	4.000/13.500	3.93L
LYMPHOCYTES	GI/L	4.000/12.000	1.95L
MICROCYTOSIS	NO UNITS		1 A
Blood Chemistry			
TOTAL PROTEIN	g/L	55.000/71.000	73H

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 5
Patient Number: 507
Treatment Group: NON-RAND

Lab Test	Units	Low/High Reference	VISIT 1
Complete Blood Count			
LEUKOCYTE COUNT	GI/L	6.000/11.000	4.1L
NEUTROPHILS, SEGMENTED	GI/L	4.000/13.500	2.47L
LYMPHOCYTES	GI/L	4.000/12.000	1.31L
ANISOCYTOSIS	NO UNITS	1	A
Blood Chemistry			
TOTAL PROTEIN	g/L	55.000/71.000	72H
			76H
Thyroids			
THYROXINE, TOTAL-T4	nmol/L	93.000/201.000	88L
			80L

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 6
Patient Number: 601
Treatment Group: Placebo

Lab Test	Units	Low/High Reference	VISIT 1	
Complete Blood Count				
MICROCYTOSIS	NO UNITS		1	A
Blood Chemistry				
CREATINE PHOSPHOKINASE	U/L	150.000/489.000	77	L

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 6
Patient Number: 601
Treatment Group: Placebo

Lab Test	Units	Low/High Reference	VISIT 5
Complete Blood Count			
MICROCYTOSIS	NO UNITS		
Blood Chemistry			
CREATINE PHOSPHOKINASE	U/L	150.000/489.000	124L

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 8
Patient Number: 801
Treatment Group: NON-RAND

Lab Test	Units	Low/High Reference	VISIT 1
Complete Blood Count			
HEMOGLOBIN	mml/L-Fe	6.520/8.380	8.69H
LEUKOCYTE COUNT	GI/L	6.000/11.000	5.1L
NEUTROPHILS, SEGMENTED	GI/L	4.000/13.500	2.30L
LYMPHOCYTES	GI/L	4.000/12.000	2.07L
Blood Chemistry			
TOTAL PROTEIN	g/L	55.000/71.000	72H

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 8
Patient Number: 802
Treatment Group: NON-RAND

Lab Test	Units	Low/High Reference	VISIT 1
Complete Blood Count			
NEUTROPHILS, SEGMENTED	GI/L	4.000/13.500	3.61L
LYMPHOCYTES	GI/L	4.000/12.000	2.59L
Blood Chemistry			
TOTAL PROTEIN	g/L	55.000/71.000	72H
Urinalysis			
UA-SPECIFIC GRAVITY	NO UNITS	1.010/1.034	1.037H
UA-PROTEIN	NO UNITS		1 A
UA-KETONES	NO UNITS		1 A

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 8
Patient Number: 803
Treatment Group: NON-RAND

Lab Test	Units	Low/High Reference	VISIT 1
Complete Blood Count			
HEMOGLOBIN	mml/L-Fe	6.520/8.380	8.44H
PLATELET COUNT	GI/L	200.000/400.000	428H
Blood Chemistry			
TOTAL PROTEIN	g/L	55.000/71.000	78H
Thyroids			
THYROXINE, TOTAL-T4	nmol/L	93.000/201.000	80L
FREE THYROXINE INDEX	INDEX	1.940/5.620	1.90L

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 8
Patient Number: 804
Treatment Group: Placebo

Lab Test	Units	Low/High Reference	VISIT 15	
Electrolytes				
BICARBONATE, HCO3	mmol/L	17.000/30.600	31.3	H
Urinalysis				
UA-BACTERIA	NO UNITS		1	A
UA-NITRITES	NO UNITS		POS	A

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 8
Patient Number: 805
Treatment Group: NON-RAND

Lab Test	Units	Low/High Reference	VISIT 1
Complete Blood Count			
MEAN CELL HEMOGLOBIN (MCH)	fmol(Fe)	1.430/1.920	1.99H
NEUTROPHILS, SEGMENTED	GI/L	4.000/13.500	3.56L
LYMPHOCYTES	GI/L	4.000/12.000	2.13L
MEAN CELL VOLUME (MCV)	fL	70.000/90.000	91H
Thyroids			
THYROXINE, TOTAL-T4	nmol/L	93.000/201.000	85L
UDS			
MARIJUANA (THC)	NO UNITS		POS A

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 8
Patient Number: 806
Treatment Group: Placebo

Lab Test	Units	Low/High Reference	VISIT 1
Blood Chemistry			
CREATINE PHOSPHOKINASE	U/L	94.000/499.000	89L

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 8
Patient Number: 807
Treatment Group: Placebo

Lab Test	Units	Low/High Reference	VISIT 1
Blood Chemistry			
CHOLESTEROL	mmol/L	3.210/5.610	2.69L

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 8
Patient Number: 808
Treatment Group: Placebo

Lab Test	Units	Low/High Reference	VISIT 1
Complete Blood Count			
HEMOGLOBIN	mml/L-Fe	7.880/11.230	7.82L
ERYTHROCYTE COUNT	TI/L	4.500/6.400	4.30L
Blood Chemistry			
AST/SGOT	U/L	10.000/40.000	52.0H
CREATINE PHOSPHOKINASE	U/L	94.000/499.000	925H

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 8
Patient Number: 809
Treatment Group: Placebo

Lab Test	Units	Low/High Reference	VISIT 1
Blood Chemistry			
CREATINE PHOSPHOKINASE	U/L	94.000/499.000	548H

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 8
Patient Number: 810
Treatment Group: Flx

Lab Test	Units	Low/High Reference	VISIT 15
Blood Chemistry			
CREATINE PHOSPHOKINASE	U/L	150.000/489.000	121L
CHOLESTEROL	mmol/L	3.260/4.940	5.64H

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 8
Patient Number: 811
Treatment Group: Flx

Lab Test	Units	Low/High Reference	VISIT 1
Complete Blood Count			
HEMATOCRIT	1	0.340/0.480	0.320L
HEMOGLOBIN	mml/L-Fe	7.200/10.180	6.76L
ERYTHROCYTE COUNT	TI/L	4.100/5.600	3.50L
PLATELET COUNT	GI/L	140.000/400.000	523H
Urinalysis			
UA-SPECIFIC GRAVITY	NO UNITS	1.010/1.034	1.009L

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 8
Patient Number: 811
Treatment Group: Flx

Lab Test	Units	Low/High Reference	VISIT 2
Complete Blood Count			
HEMATOCRIT	1	0.340/0.480	0.310L
HEMOGLOBIN	mml/L-Fe	7.200/10.180	6.33L
ERYTHROCYTE COUNT	TI/L	4.100/5.600	3.40L
PLATELET COUNT	GI/L	140.000/400.000	508H
Urinalysis			
UA-SPECIFIC GRAVITY	NO UNITS	1.010/1.034	

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 8
Patient Number: 811
Treatment Group: Flx

Lab Test	Units	Low/High Reference	VISIT 5
Complete Blood Count			
HEMATOCRIT	1	0.340/0.480	0.320L
HEMOGLOBIN	mml/L-Fe	7.200/10.180	6.52L
ERYTHROCYTE COUNT	TI/L	4.100/5.600	3.40L
PLATELET COUNT	GI/L	140.000/400.000	496H
Urinalysis			
UA-SPECIFIC GRAVITY	NO UNITS	1.010/1.034	

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 8
Patient Number: 813
Treatment Group: Flx

Lab Test	Units	Low/High Reference	VISIT 1
Complete Blood Count			
MEAN CELL VOLUME (MCV)	fL	79.000/96.000	78L
ANISOCYTOSIS	NO UNITS	1	A
Blood Chemistry			
CHOLESTEROL	mmol/L	3.360/5.280	

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 8
Patient Number: 813
Treatment Group: Flx

Lab Test	Units	Low/High Reference	VISIT 13
Complete Blood Count			
MEAN CELL VOLUME (MCV)	fL	79.000/96.000	
ANISOCYTOSIS	NO UNITS		
Blood Chemistry			
CHOLESTEROL	mmol/L	3.360/5.280	5.48H

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 8
Patient Number: 814
Treatment Group: Flx

Lab Test	Units	Low/High Reference	VISIT 13
Complete Blood Count			
LEUKOCYTE COUNT	GI/L	4.350/13.150	3.8L
Thyroids			
THYROID STIM. HORMONE	mU/L	0.320/5.000	0.14L
Urinalysis			
UA-PROTEIN	NO UNITS		1 A
UA-KETONES	NO UNITS		1 A

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 8
Patient Number: 815
Treatment Group: Flx

Lab Test	Units	Low/High Reference	VISIT 1
Blood Chemistry			
CREATINE PHOSPHOKINASE	U/L	150.000/489.000	81L
CHOLESTEROL	mmol/L	3.360/5.280	5.51H
Urinalysis			
UA-BACTERIA	NO UNITS		

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 8
Patient Number: 815
Treatment Group: Flx

Lab Test	Units	Low/High Reference	VISIT 15
Blood Chemistry			
CREATINE PHOSPHOKINASE	U/L	150.000/489.000	
CHOLESTEROL	mmol/L	3.360/5.280	5.43H
Urinalysis			
UA-BACTERIA	NO UNITS		1 A

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 9
Patient Number: 901
Treatment Group: Flx

Lab Test	Units	Low/High Reference	VISIT 1	
Urinalysis				
UA-OCCULT BLOOD	NO UNITS		3	A

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 9
Patient Number: 902
Treatment Group: NON-RAND

Lab Test	Units	Low/High Reference	VISIT 1
Complete Blood Count			
LEUKOCYTE COUNT	GI/L	6.000/11.000	5.4L
NEUTROPHILS, SEGMENTED	GI/L	4.000/13.500	2.13L
LYMPHOCYTES	GI/L	4.000/12.000	2.40L

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 9
Patient Number: 905
Treatment Group: Placebo

Lab Test	Units	Low/High Reference	VISIT 1
Complete Blood Count			
EOSINOPHILS	GI/L	0.000/0.570	0.86H
ANISOCYTOSIS	NO UNITS	1	A

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 9
Patient Number: 906
Treatment Group: Flx

Lab Test	Units	Low/High Reference	VISIT 1
Complete Blood Count			
EOSINOPHILS	GI/L	0.000/0.570	0.63H
Blood Chemistry			
CREATINE PHOSPHOKINASE	U/L	91.000/391.000	76L
CREATININE	umol/L	53.000/106.000	115H
URIC ACID	umol/L	161.000/393.000	410H
Urinalysis			
UA-BACTERIA	NO UNITS		1 A

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 9
Patient Number: 906
Treatment Group: Flx

Lab Test	Units	Low/High Reference	VISIT 15
Complete Blood Count			
EOSINOPHILS	GI/L	0.000/0.570	
Blood Chemistry			
CREATINE PHOSPHOKINASE	U/L	91.000/391.000	69L
CREATININE	umol/L	53.000/106.000	
URIC ACID	umol/L	161.000/393.000	470H
Urinalysis			
UA-BACTERIA	NO UNITS		

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 9
Patient Number: 907
Treatment Group: NON-RAND

Lab Test	Units	Low/High Reference	VISIT 1
Complete Blood Count			
NEUTROPHILS, SEGMENTED	GI/L	4.000/13.500	1.95L
LYMPHOCYTES	GI/L	4.000/12.000	3.67L
POLYCHROMIA	NO UNITS	1	A
Thyroids			
THYROXINE, TOTAL-T4	nmol/L	93.000/201.000	247H
THYROID STIM. HORMONE	mU/L	0.320/5.000	
T3, TOTAL (TRIIODOTHYRONINE)	nmol/L	1.200/3.100	4.4H
FREE THYROXINE INDEX	INDEX	1.940/5.620	7.00H

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 9
Patient Number: 908
Treatment Group: NON-RAND

Lab Test	Units	Low/High Reference	VISIT 1
Complete Blood Count			
HEMOGLOBIN	mml/L-Fe	6.520/8.380	8.94H
LEUKOCYTE COUNT	GI/L	6.000/11.000	4.3L
NEUTROPHILS, SEGMENTED	GI/L	4.000/13.500	3.03L
LYMPHOCYTES	GI/L	4.000/12.000	1.17L
MONOCYTES	GI/L	0.120/0.920	0.09L
Thyroids			
THYROXINE, TOTAL-T4	nmol/L	93.000/201.000	90L
Urinalysis			
UA-PROTEIN	NO UNITS		1 A

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 9
Patient Number: 909
Treatment Group: NON-RAND

Lab Test	Units	Low/High Reference	VISIT 1
Complete Blood Count			
HEMOGLOBIN	mml/L-Fe	6.520/8.380	9.68H
NEUTROPHILS, SEGMENTED	GI/L	4.000/13.500	3.69L
LYMPHOCYTES	GI/L	4.000/12.000	2.89L
PLATELET COUNT	GI/L	200.000/400.000	178L
ANISOCYTOSIS	NO UNITS		1 A
MICROCYTOSIS	NO UNITS		1 A
Blood Chemistry			
TOTAL PROTEIN	g/L	55.000/71.000	76H

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 9
Patient Number: 910
Treatment Group: NON-RAND

Lab Test	Units	Low/High Reference	VISIT 1
Complete Blood Count			
LYMPHOCYTES	GI/L	4.000/12.000	2.81L
Thyroids			
THYROXINE, TOTAL-T4	nmol/L	93.000/201.000	82L

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 9
Patient Number: 911
Treatment Group: Placebo

Lab Test	Units	Low/High Reference	VISIT 1
Complete Blood Count			
LEUKOCYTE COUNT	GI/L	4.350/13.650	3.9L
Blood Chemistry			
CREATINE PHOSPHOKINASE	U/L	150.000/489.000	120L
URIC ACID	umol/L	161.000/393.000	149L
CHOLESTEROL	mmol/L	3.260/4.940	3.03L

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 9
Patient Number: 911
Treatment Group: Placebo

Lab Test	Units	Low/High Reference	VISIT 15
Complete Blood Count			
LEUKOCYTE COUNT	GI/L	4.350/13.650	
Blood Chemistry			
CREATINE PHOSPHOKINASE	U/L	150.000/489.000	122L
URIC ACID	umol/L	161.000/393.000	
CHOLESTEROL	mmol/L	3.260/4.940	3.00L

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 9
Patient Number: 912
Treatment Group: Placebo

Lab Test	Units	Low/High Reference	VISIT 1	
Blood Chemistry				
CREATINE PHOSPHOKINASE	U/L	91.000/391.000		84L
BILIRUBIN, TOTAL	umol/L	3.000/21.000		
Urinalysis				
UA-WBC	NO UNITS		1	A
UA-BACTERIA	NO UNITS		1	A

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 9
Patient Number: 913
Treatment Group: Flx

Lab Test	Units	Low/High Reference	VISIT 1
Blood Chemistry			
ALT/SGPT	U/L	6.000/43.000	57.0H
Electrolytes			
BICARBONATE, HCO3	mmol/L	17.000/30.600	32.7H

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 9
Patient Number: 915
Treatment Group: Flx

Lab Test	Units	Low/High Reference	VISIT 1
Complete Blood Count			
HEMATOCRIT	1	0.390/0.540	
EOSINOPHILS	GI/L	0.000/0.570	0.69H
MEAN CELL VOLUME (MCV)	fL	79.000/96.000	
Blood Chemistry			
CREATINE PHOSPHOKINASE	U/L	94.000/499.000	
CHOLESTEROL	mmol/L	3.360/5.280	6.05H
Urinalysis			
UA-PROTEIN	NO UNITS		

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 9
Patient Number: 915
Treatment Group: Flx

Lab Test	Units	Low/High Reference	VISIT 15
Complete Blood Count			
HEMATOCRIT	1	0.390/0.540	0.380L
EOSINOPHILS	GI/L	0.000/0.570	
MEAN CELL VOLUME (MCV)	fL	79.000/96.000	78L
Blood Chemistry			
CREATINE PHOSPHOKINASE	U/L	94.000/499.000	84L
CHOLESTEROL	mmol/L	3.360/5.280	
Urinalysis			
UA-PROTEIN	NO UNITS	1	A

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 9
Patient Number: 916
Treatment Group: Placebo

Lab Test	Units	Low/High Reference	VISIT 1	
Complete Blood Count				
ERYTHROCYTE COUNT	TI/L	4.100/5.600		
MONOCYTES	GI/L	0.120/0.920		
Urinalysis				
UA-SPECIFIC GRAVITY	NO UNITS	1.010/1.034		
UA-WBC	NO UNITS			
UA-PROTEIN	NO UNITS		1	A
UA-BACTERIA	NO UNITS		1	A
UDS				
BUTALBITAL	NO UNITS		POS	A

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 9
Patient Number: 916
Treatment Group: Placebo

Lab Test	Units	Low/High Reference	VISIT 12
Complete Blood Count			
ERYTHROCYTE COUNT	TI/L	4.100/5.600	3.90L
MONOCYTES	GI/L	0.120/0.920	1.12H
Urinalysis			
UA-SPECIFIC GRAVITY	NO UNITS	1.010/1.034	1.037H
UA-WBC	NO UNITS		2 A
UA-PROTEIN	NO UNITS		1 A
UA-BACTERIA	NO UNITS		
UDS			
BUTALBITAL	NO UNITS		

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 9
Patient Number: 917
Treatment Group: NON-RAND

Lab Test	Units	Low/High Reference	VISIT 1
Complete Blood Count			
NEUTROPHILS, SEGMENTED	GI/L	4.000/13.500	3.77L
LYMPHOCYTES	GI/L	4.000/12.000	2.63L
Blood Chemistry			
TOTAL PROTEIN	g/L	55.000/71.000	73H
Thyroids			
THYROID STIM. HORMONE	mU/L	0.320/5.000	6.46H

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 9
Patient Number: 918
Treatment Group: NON-RAND

Lab Test	Units	Low/High Reference	VISIT 1
Complete Blood Count			
LEUKOCYTE COUNT	GI/L	6.000/11.000	4.1L
NEUTROPHILS, SEGMENTED	GI/L	4.000/13.500	1.58L
LYMPHOCYTES	GI/L	4.000/12.000	2.15L
MICROCYTOSIS	NO UNITS	1	A

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 9
Patient Number: 919
Treatment Group: Placebo

Lab Test	Units	Low/High Reference	VISIT 1	
Urinalysis				
UA-WBC	NO UNITS		1	A
UA-BACTERIA	NO UNITS		1	A
UA-NITRITES	NO UNITS		POS	A
UA-KETONES	NO UNITS		1	A

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 9
Patient Number: 920
Treatment Group: Flx

Lab Test	Units	Low/High Reference	VISIT 1
Complete Blood Count			
PLATELET COUNT	GI/L	140.000/400.000	110L
Urinalysis			
UA-WBC	NO UNITS		2 A
UA-BACTERIA	NO UNITS		1 A

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 9
Patient Number: 920
Treatment Group: Flx

Lab Test	Units	Low/High Reference	VISIT 15	
Complete Blood Count				
PLATELET COUNT	GI/L	140.000/400.000		
Urinalysis				
UA-WBC	NO UNITS			
UA-BACTERIA	NO UNITS		1	A

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 11
Patient Number: 1101
Treatment Group: Flx

Lab Test	Units	Low/High Reference	VISIT 1
Complete Blood Count			
EOSINOPHILS	GI/L	0.000/0.570	0.58H
ANISOCYTOSIS	NO UNITS		
Blood Chemistry			
CREATINE PHOSPHOKINASE	U/L	91.000/391.000	83L
Urinalysis			
UA-SPECIFIC GRAVITY	NO UNITS	1.010/1.034	

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 11
Patient Number: 1101
Treatment Group: Flx

Lab Test	Units	Low/High Reference	VISIT 15	
Complete Blood Count				
EOSINOPHILS	GI/L	0.000/0.570		
ANISOCYTOSIS	NO UNITS		1	A
Blood Chemistry				
CREATINE PHOSPHOKINASE	U/L	91.000/391.000		
Urinalysis				
UA-SPECIFIC GRAVITY	NO UNITS	1.010/1.034	1.007L	

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 11
Patient Number: 1102
Treatment Group: Placebo

Lab Test	Units	Low/High Reference	VISIT 1
Complete Blood Count			
HEMATOCRIT	1	0.390/0.540	0.370L
HEMOGLOBIN	mml/L-Fe	7.880/11.230	7.39L
			7.63L
MEAN CELL HEMOGLOBIN CONCENTRATION (MCHC	mml/L-Fe	19.000/24.000	
MEAN CELL HEMOGLOBIN (MCH)	fmol(Fe)	1.600/2.100	1.49L
			1.55L
MEAN CELL VOLUME (MCV)	fL	79.000/96.000	75L
ANISOCYTOSIS	NO UNITS		1 A
POLYCHROMIA	NO UNITS		1 A
Blood Chemistry			
CREATINE PHOSPHOKINASE	U/L	94.000/499.000	63L

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 11
Patient Number: 1102
Treatment Group: Placebo

Lab Test	Units	Low/High Reference	VISIT 9
Complete Blood Count			
HEMATOCRIT	1	0.390/0.540	
HEMOGLOBIN	mml/L-Fe	7.880/11.230	7.45L
MEAN CELL HEMOGLOBIN CONCENTRATION (MCHC	mml/L-Fe	19.000/24.000	18L
MEAN CELL HEMOGLOBIN (MCH)	fmol(Fe)	1.600/2.100	1.55L
MEAN CELL VOLUME (MCV)	fL	79.000/96.000	
ANISOCYTOSIS	NO UNITS		
POLYCHROMIA	NO UNITS		
Blood Chemistry			
CREATINE PHOSPHOKINASE	U/L	94.000/499.000	74L

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 11
Patient Number: 1104
Treatment Group: NON-RAND

Lab Test	Units	Low/High Reference	VISIT 1
Complete Blood Count			
HEMOGLOBIN	mml/L-Fe	6.520/8.380	8.69H
LEUKOCYTE COUNT	GI/L	6.000/11.000	11.5H
LYMPHOCYTES	GI/L	4.000/12.000	3.73L
MEAN CELL VOLUME (MCV)	fL	70.000/90.000	91H
Blood Chemistry			
TOTAL PROTEIN	g/L	55.000/71.000	78H
Thyroids			
THYROXINE, TOTAL-T4	nmol/L	93.000/201.000	89L
Urinalysis			
UA-WBC	NO UNITS		1 A
UA-OCCULT BLOOD	NO UNITS		1 A

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 11
Patient Number: 1105
Treatment Group: Placebo

Lab Test	Units	Low/High Reference	VISIT 1
Blood Chemistry			
CREATINE PHOSPHOKINASE	U/L	150.000/489.000	121L
CHOLESTEROL	mmol/L	3.360/5.280	3.31L

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 11
Patient Number: 1105
Treatment Group: Placebo

Lab Test	Units	Low/High Reference	VISIT 15
Blood Chemistry			
CREATINE PHOSPHOKINASE	U/L	150.000/489.000	
CHOLESTEROL	mmol/L	3.360/5.280	2.77L

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 11
Patient Number: 1106
Treatment Group: NON-RAND

Lab Test	Units	Low/High Reference	VISIT 1
Complete Blood Count			
NEUTROPHILS, SEGMENTED	GI/L	4.000/13.500	3.60L
LYMPHOCYTES	GI/L	4.000/12.000	1.91L
MEAN CELL VOLUME (MCV)	fL	70.000/90.000	96H
Thyroids			
THYROXINE, TOTAL-T4	nmol/L	93.000/201.000	90L

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 11
Patient Number: 1107
Treatment Group: Placebo

Lab Test	Units	Low/High Reference	VISIT 1
Blood Chemistry			
CHOLESTEROL	mmol/L	3.210/5.610	5.90H
			6.28H
Urinalysis			
UA-BACTERIA	NO UNITS		

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 11
Patient Number: 1107
Treatment Group: Placebo

Lab Test	Units	Low/High Reference	VISIT 14	
Blood Chemistry				
CHOLESTEROL	mmol/L	3.210/5.610		
Urinalysis				
UA-BACTERIA	NO UNITS		1	A

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 11
Patient Number: 1108
Treatment Group: NON-RAND

Lab Test	Units	Low/High Reference	VISIT 1
Complete Blood Count			
HEMOGLOBIN	mml/L-Fe	6.520/8.380	8.69H
LYMPHOCYTES	GI/L	4.000/12.000	2.12L

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 11
Patient Number: 1110
Treatment Group: NON-RAND

Lab Test	Units	Low/High Reference	VISIT 1
Complete Blood Count			
LEUKOCYTE COUNT	GI/L	6.000/11.000	4.9L
NEUTROPHILS, SEGMENTED	GI/L	4.000/13.500	1.97L
LYMPHOCYTES	GI/L	4.000/12.000	2.04L
MEAN CELL VOLUME (MCV)	fL	70.000/90.000	92H
Blood Chemistry			
GGT (GGPT/SGGT/YGGT)	U/L	0.000/24.000	40.0H
Urinalysis			
UA-PROTEIN	NO UNITS		1 A

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 11
Patient Number: 1112
Treatment Group: NON-RAND

Lab Test	Units	Low/High Reference	VISIT 1
Complete Blood Count			
HEMOGLOBIN	mml/L-Fe	6.520/8.380	8.81H
NEUTROPHILS, SEGMENTED	GI/L	4.000/13.500	3.19L
LYMPHOCYTES	GI/L	4.000/12.000	3.11L
Blood Chemistry			
GGT (GGPT/SGGT/YGGT)	U/L	0.000/24.000	27.0H
TOTAL PROTEIN	g/L	55.000/71.000	76H
Urinalysis			
UA-KETONES	NO UNITS		1 A

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 11
Patient Number: 1113
Treatment Group: NON-RAND

Lab Test	Units	Low/High Reference	VISIT 1
Complete Blood Count			
HEMOGLOBIN	mml/L-Fe	6.520/8.380	8.56H
NEUTROPHILS, SEGMENTED	GI/L	4.000/13.500	3.85L
LYMPHOCYTES	GI/L	4.000/12.000	1.99L
Thyroids			
THYROXINE, TOTAL-T4	nmol/L	93.000/201.000	76L
Urinalysis			
UA-KETONES	NO UNITS	1	A

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 11
Patient Number: 1114
Treatment Group: NON-RAND

Lab Test	Units	Low/High Reference	VISIT 1
Complete Blood Count			
HEMOGLOBIN	mml/L-Fe	6.520/8.380	9.06H
LYMPHOCYTES	GI/L	4.000/12.000	2.33L
Blood Chemistry			
TOTAL PROTEIN	g/L	55.000/71.000	75H
Electrolytes			
BICARBONATE, HCO3	mmol/L	12.000/28.000	28.4H
Thyroids			
THYROXINE, TOTAL-T4	nmol/L	93.000/201.000	85L

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 11
Patient Number: 1114
Treatment Group: NON-RAND

Lab Test	Units	Low/High Reference	VISIT 2
Complete Blood Count			
HEMOGLOBIN	mml/L-Fe	6.520/8.380	
LYMPHOCYTES	GI/L	4.000/12.000	
Blood Chemistry			
TOTAL PROTEIN	g/L	55.000/71.000	74H
Electrolytes			
BICARBONATE, HCO3	mmol/L	12.000/28.000	
Thyroids			
THYROXINE, TOTAL-T4	nmol/L	93.000/201.000	

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 11
Patient Number: 1115
Treatment Group: NON-RAND

Lab Test	Units	Low/High Reference	VISIT 1
Complete Blood Count			
LYMPHOCYTES	GI/L	4.000/12.000	2.16L
Thyroids			
THYROXINE, TOTAL-T4	nmol/L	93.000/201.000	80L
T3, TOTAL (TRIIODOTHYRONINE)	nmol/L	1.200/3.100	1.2L

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 11
Patient Number: 1116
Treatment Group: NON-RAND

Lab Test	Units	Low/High Reference	VISIT 1
Complete Blood Count			
NEUTROPHILS, SEGMENTED	GI/L	4.000/13.500	2.44L
LYMPHOCYTES	GI/L	4.000/12.000	2.75L

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 11
Patient Number: 1117
Treatment Group: NON-RAND

Lab Test	Units	Low/High Reference	VISIT 1
Complete Blood Count			
HEMOGLOBIN	mml/L-Fe	6.520/8.380	10.12H
LEUKOCYTE COUNT	GI/L	6.000/11.000	5.5L
NEUTROPHILS, SEGMENTED	GI/L	4.000/13.500	3.43L
LYMPHOCYTES	GI/L	4.000/12.000	1.53L
MEAN CELL VOLUME (MCV)	fL	70.000/90.000	93H
PLATELET COUNT	GI/L	200.000/400.000	178L
Blood Chemistry			
TOTAL PROTEIN	g/L	55.000/71.000	72H
Electrolytes			
BICARBONATE, HCO3	mmol/L	12.000/28.000	30.0H
UDS			
MARIJUANA (THC)	NO UNITS		POS A

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 11
Patient Number: 1118
Treatment Group: Flx

Lab Test	Units	Low/High Reference	VISIT 1
Blood Chemistry			
CREATINE PHOSPHOKINASE	U/L	91.000/391.000	56L
Urinalysis			
UA-OCCULT BLOOD	NO UNITS	1	A

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 11
Patient Number: 1119
Treatment Group: NON-RAND

Lab Test	Units	Low/High Reference	VISIT 1
Complete Blood Count			
LYMPHOCYTES	GI/L	4.000/12.000	2.41L
Blood Chemistry			
TOTAL PROTEIN	g/L	55.000/71.000	79H

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 11
Patient Number: 1120
Treatment Group: Placebo

Lab Test	Units	Low/High Reference	VISIT 1
Blood Chemistry			
CREATINE PHOSPHOKINASE	U/L	91.000/391.000	44L
ALKALINE PHOSPHATASE	U/L	51.000/300.000	307H
Urinalysis			
UA-PROTEIN	NO UNITS		

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 11
Patient Number: 1120
Treatment Group: Placebo

Lab Test	Units	Low/High Reference	VISIT 15
Blood Chemistry			
CREATINE PHOSPHOKINASE	U/L	91.000/391.000	47L
ALKALINE PHOSPHATASE	U/L	51.000/300.000	
Urinalysis			
UA-PROTEIN	NO UNITS		1 A

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 11
Patient Number: 1121
Treatment Group: Placebo

Lab Test	Units	Low/High Reference	VISIT 1
Blood Chemistry			
CHOLESTEROL	mmol/L	3.230/5.480	2.92L
Urinalysis			
UA-BACTERIA	NO UNITS		

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 11
Patient Number: 1121
Treatment Group: Placebo

Lab Test	Units	Low/High Reference	VISIT 15
Blood Chemistry			
CHOLESTEROL	mmol/L	3.230/5.480	3.18L
Urinalysis			
UA-BACTERIA	NO UNITS		1 A

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 11
Patient Number: 1122
Treatment Group: Placebo

Lab Test	Units	Low/High Reference	VISIT 1
Thyroids			
THYROXINE, TOTAL-T4	nmol/L	82.000/171.000	77L
Urinalysis			
UA-SPECIFIC GRAVITY	NO UNITS	1.010/1.034	

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 11
Patient Number: 1122
Treatment Group: Placebo

Lab Test	Units	Low/High Reference	VISIT 15
Thyroids			
THYROXINE, TOTAL-T4	nmol/L	82.000/171.000	
Urinalysis			
UA-SPECIFIC GRAVITY	NO UNITS	1.010/1.034	1.008L

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 11
Patient Number: 1123
Treatment Group: NON-RAND

Lab Test	Units	Low/High Reference	VISIT 1
Complete Blood Count			
NEUTROPHILS, SEGMENTED	GI/L	4.000/13.500	2.92L
LYMPHOCYTES	GI/L	4.000/12.000	2.80L

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 11
Patient Number: 1124
Treatment Group: NON-RAND

Lab Test	Units	Low/High Reference	VISIT 1
Complete Blood Count			
LEUKOCYTE COUNT	GI/L	6.000/11.000	3.8L
NEUTROPHILS, SEGMENTED	GI/L	4.000/13.500	1.63L
LYMPHOCYTES	GI/L	4.000/12.000	1.75L
PLATELET COUNT	GI/L	200.000/400.000	184L
Thyroids			
THYROXINE, TOTAL-T4	nmol/L	93.000/201.000	85L

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 11
Patient Number: 1125
Treatment Group: NON-RAND

Lab Test	Units	Low/High Reference	VISIT 1
Complete Blood Count			
LYMPHOCYTES	GI/L	4.000/12.000	2.36L
Blood Chemistry			
TOTAL PROTEIN	g/L	55.000/71.000	72H

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 11
Patient Number: 1126
Treatment Group: Placebo

Lab Test	Units	Low/High Reference	VISIT 1
Blood Chemistry			
BILIRUBIN, TOTAL	umol/L	3.000/21.000	26H
Electrolytes			
BICARBONATE, HCO3	mmol/L	17.000/30.600	
Urinalysis			
UA-KETONES	NO UNITS		

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 11
Patient Number: 1126
Treatment Group: Placebo

Lab Test	Units	Low/High Reference	VISIT 15
Blood Chemistry			
BILIRUBIN, TOTAL	umol/L	3.000/21.000	
Electrolytes			
BICARBONATE, HCO3	mmol/L	17.000/30.600	32.3H
Urinalysis			
UA-KETONES	NO UNITS		1 A

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 11
Patient Number: 1127
Treatment Group: NON-RAND

Lab Test	Units	Low/High Reference	VISIT 1
Complete Blood Count			
HEMOGLOBIN	mml/L-Fe	6.520/8.380	9.68H
NEUTROPHILS, SEGMENTED	GI/L	4.000/13.500	3.83L
LYMPHOCYTES	GI/L	4.000/12.000	1.97L
Blood Chemistry			
GGT (GGPT/SGGT/YGGT)	U/L	0.000/24.000	25.0H
Thyroids			
THYROXINE, TOTAL-T4	nmol/L	93.000/201.000	86L
UDS			
MARIJUANA (THC)	NO UNITS		POS A

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 11
Patient Number: 1128
Treatment Group: NON-RAND

Lab Test	Units	Low/High Reference	VISIT 1
Complete Blood Count			
HEMOGLOBIN	mml/L-Fe	6.520/8.380	9.43H
NEUTROPHILS, SEGMENTED	GI/L	4.000/13.500	3.32L
LYMPHOCYTES	GI/L	4.000/12.000	2.49L
Electrolytes			
BICARBONATE, HCO3	mmol/L	12.000/28.000	28.8H
Thyroids			
THYROXINE, TOTAL-T4	nmol/L	93.000/201.000	67L

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 11
Patient Number: 1129
Treatment Group: Flx

Lab Test	Units	Low/High Reference	VISIT 1
Complete Blood Count			
EOSINOPHILS	GI/L	0.000/0.570	0.77H
			0.81H
Blood Chemistry			
CREATINE PHOSPHOKINASE	U/L	150.000/489.000	93L
Thyroids			
THYROXINE, TOTAL-T4	nmol/L	82.000/171.000	72L
			75L

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 11
Patient Number: 1129
Treatment Group: Flx

Lab Test	Units	Low/High Reference	VISIT 15
Complete Blood Count			
EOSINOPHILS	GI/L	0.000/0.570	0.88H
Blood Chemistry			
CREATINE PHOSPHOKINASE	U/L	150.000/489.000	147L
Thyroids			
THYROXINE, TOTAL-T4	nmol/L	82.000/171.000	

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 11
Patient Number: 1130
Treatment Group: NON-RAND

Lab Test	Units	Low/High Reference	VISIT 1
Complete Blood Count			
LYMPHOCYTES	GI/L	4.000/12.000	1.58L
Electrolytes			
BICARBONATE, HCO3	mmol/L	12.000/28.000	28.1H

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 11
Patient Number: 1131
Treatment Group: Flx

Lab Test	Units	Low/High Reference	VISIT 1
Complete Blood Count			
LEUKOCYTE COUNT	GI/L	4.350/13.150	4.0L
Blood Chemistry			
CREATINE PHOSPHOKINASE	U/L	94.000/499.000	
Urinalysis			
UA-SPECIFIC GRAVITY	NO UNITS	1.010/1.034	1.009L

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 11
Patient Number: 1131
Treatment Group: Flx

Lab Test	Units	Low/High Reference	VISIT 12
Complete Blood Count			
LEUKOCYTE COUNT	GI/L	4.350/13.150	3.8L
Blood Chemistry			
CREATINE PHOSPHOKINASE	U/L	94.000/499.000	82L
Urinalysis			
UA-SPECIFIC GRAVITY	NO UNITS	1.010/1.034	

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 11
Patient Number: 1132
Treatment Group: NON-RAND

Lab Test	Units	Low/High Reference	VISIT 1
Complete Blood Count			
HEMOGLOBIN	mml/L-Fe	6.520/8.380	10.18H
LEUKOCYTE COUNT	GI/L	6.000/11.000	4.7L
NEUTROPHILS, SEGMENTED	GI/L	4.000/13.500	2.07L
LYMPHOCYTES	GI/L	4.000/12.000	2.37L
Blood Chemistry			
TOTAL PROTEIN	g/L	55.000/71.000	77H
Thyroids			
THYROXINE, TOTAL-T4	nmol/L	93.000/201.000	81L

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 11
Patient Number: 1133
Treatment Group: NON-RAND

Lab Test	Units	Low/High Reference	VISIT 1
Complete Blood Count			
LYMPHOCYTES	GI/L	4.000/12.000	3.12L
PLATELET COUNT	GI/L	200.000/400.000	426H
Blood Chemistry			
GGT (GGPT/SGGT/YGGT)	U/L	0.000/24.000	27.0H
TOTAL PROTEIN	g/L	55.000/71.000	75H

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 11
Patient Number: 1135
Treatment Group: Placebo

Lab Test	Units	Low/High Reference	VISIT 1	
Complete Blood Count				
ANISOCYTOSIS	NO UNITS		1	A
Blood Chemistry				
AST/SGOT	U/L	10.000/40.000		
ALT/SGPT	U/L	6.000/43.000		
CREATINE PHOSPHOKINASE	U/L	150.000/489.000	72L	
CHOLESTEROL	mmol/L	3.260/4.940	5.22H	
Urinalysis				
UA-RBC	NO UNITS		1	A
UA-NITRITES	NO UNITS			
UA-OCCULT BLOOD	NO UNITS			

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 11
Patient Number: 1135
Treatment Group: Placebo

Lab Test	Units	Low/High Reference	VISIT 15
Complete Blood Count			
ANISOCYTOSIS	NO UNITS		
Blood Chemistry			
AST/SGOT	U/L	10.000/40.000	44.0H
ALT/SGPT	U/L	6.000/43.000	44.0H
CREATINE PHOSPHOKINASE	U/L	150.000/489.000	98L
CHOLESTEROL	mmol/L	3.260/4.940	4.97H
Urinalysis			
UA-RBC	NO UNITS		1 A
UA-NITRITES	NO UNITS		POS A
UA-OCCULT BLOOD	NO UNITS		1 A

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 11
Patient Number: 1136
Treatment Group: NON-RAND

Lab Test	Units	Low/High Reference	VISIT 1
Complete Blood Count			
NEUTROPHILS, SEGMENTED	GI/L	4.000/13.500	2.30L
LYMPHOCYTES	GI/L	4.000/12.000	3.60L

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 11
Patient Number: 1137
Treatment Group: Flx

Lab Test	Units	Low/High Reference	VISIT 1
Urinalysis			
UA-SPECIFIC GRAVITY	NO UNITS	1.010/1.034	1.005L

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 11
Patient Number: 1138
Treatment Group: Placebo

Lab Test	Units	Low/High Reference	VISIT 1
Blood Chemistry			
CREATINE PHOSPHOKINASE	U/L	94.000/499.000	82L
CREATININE	umol/L	53.000/106.000	
CHOLESTEROL	mmol/L	2.950/5.120	
Urinalysis			
UA-PROTEIN	NO UNITS		

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 11
Patient Number: 1138
Treatment Group: Placebo

Lab Test	Units	Low/High Reference	VISIT 15
Blood Chemistry			
CREATINE PHOSPHOKINASE	U/L	94.000/499.000	
CREATININE	umol/L	53.000/106.000	133H
CHOLESTEROL	mmol/L	2.950/5.120	5.40H
Urinalysis			
UA-PROTEIN	NO UNITS		1 A

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 11
Patient Number: 1139
Treatment Group: Placebo

Lab Test	Units	Low/High Reference	VISIT 1	
Blood Chemistry				
CREATINE PHOSPHOKINASE	U/L	91.000/391.000	72L	
Urinalysis				
UA-WBC	NO UNITS		1	A
UA-BACTERIA	NO UNITS		1	A

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 11
Patient Number: 1139
Treatment Group: Placebo

Lab Test	Units	Low/High Reference	VISIT 4
Blood Chemistry			
CREATINE PHOSPHOKINASE	U/L	91.000/391.000	57L
Urinalysis			
UA-WBC	NO UNITS		1 A
UA-BACTERIA	NO UNITS		1 A

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 11
Patient Number: 1140
Treatment Group: NON-RAND

Lab Test	Units	Low/High Reference	VISIT 1
Complete Blood Count			
HEMOGLOBIN	mml/L-Fe	6.520/8.380	9.43H
LYMPHOCYTES	GI/L	4.000/12.000	1.91L
UDS			
MARIJUANA (THC)	NO UNITS		POS A

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 11
Patient Number: 1141
Treatment Group: Flx

Lab Test	Units	Low/High Reference	VISIT 1	
Urinalysis				
UA-YEAST	NO UNITS		1	A
UA-BACTERIA	NO UNITS		1	A

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 11
Patient Number: 1142
Treatment Group: NON-RAND

Lab Test	Units	Low/High Reference	VISIT 1
Complete Blood Count			
MONOCYTES	GI/L	0.120/0.920	0.00L
ANISOCYTOSIS	NO UNITS	1	A
Blood Chemistry			
GGT (GGPT/SGGT/YGGT)	U/L	0.000/24.000	38.0H
TOTAL PROTEIN	g/L	55.000/71.000	73H

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 11
Patient Number: 1143
Treatment Group: Placebo

Lab Test	Units	Low/High Reference	VISIT 1
Blood Chemistry			
CREATINE PHOSPHOKINASE	U/L	150.000/489.000	112L
ALKALINE PHOSPHATASE	U/L	95.000/385.000	409H

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 11
Patient Number: 1143
Treatment Group: Placebo

Lab Test	Units	Low/High Reference	VISIT 15
Blood Chemistry			
CREATINE PHOSPHOKINASE	U/L	150.000/489.000	99L
ALKALINE PHOSPHATASE	U/L	95.000/385.000	

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 11
Patient Number: 1144
Treatment Group: Placebo

Lab Test	Units	Low/High Reference	VISIT 1	
Blood Chemistry				
BILIRUBIN, TOTAL	umol/L	3.000/21.000		
Urinalysis				
UA-BACTERIA	NO UNITS		1	A
UDS				
BUTALBITAL	NO UNITS		POS	A

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 11
Patient Number: 1144
Treatment Group: Placebo

Lab Test	Units	Low/High Reference	VISIT 15	
Blood Chemistry				
BILIRUBIN, TOTAL	umol/L	3.000/21.000		
Urinalysis				
UA-BACTERIA	NO UNITS		1	A
UDS				
BUTALBITAL	NO UNITS			

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 11
Patient Number: 1146
Treatment Group: NON-RAND

Lab Test	Units	Low/High Reference	VISIT 1
Complete Blood Count			
LEUKOCYTE COUNT	GI/L	6.000/11.000	5.5L
NEUTROPHILS, SEGMENTED	GI/L	4.000/13.500	2.75L
LYMPHOCYTES	GI/L	4.000/12.000	2.28L
Urinalysis			
UA-SPECIFIC GRAVITY	NO UNITS	1.010/1.034	1.007L

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 11
Patient Number: 1147
Treatment Group: NON-RAND

Lab Test	Units	Low/High Reference	VISIT 1
Complete Blood Count			
HEMOGLOBIN	mml/L-Fe	6.520/8.380	9.99H
LYMPHOCYTES	GI/L	4.000/12.000	1.28L
MEAN CELL VOLUME (MCV)	fL	70.000/90.000	91H
Blood Chemistry			
TOTAL PROTEIN	g/L	55.000/71.000	72H
Electrolytes			
BICARBONATE, HCO3	mmol/L	12.000/28.000	31.6H
Thyroids			
THYROXINE, TOTAL-T4	nmol/L	93.000/201.000	76L
Urinalysis			
UA-GLUCOSE	NO UNITS		1 A
UA-PROTEIN	NO UNITS		1 A
UA-KETONES	NO UNITS		1 A

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 11
Patient Number: 1149
Treatment Group: NON-RAND

Lab Test	Units	Low/High Reference	VISIT 1
Complete Blood Count			
HEMOGLOBIN	mml/L-Fe	6.520/8.380	8.81H
LEUKOCYTE COUNT	GI/L	6.000/11.000	5.1L
NEUTROPHILS, SEGMENTED	GI/L	4.000/13.500	2.69L
LYMPHOCYTES	GI/L	4.000/12.000	1.86L
Blood Chemistry			
CALCIUM	mmol/L	2.250/2.740	2.22L
Thyroids			
THYROXINE, TOTAL-T4	nmol/L	93.000/201.000	85L

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 11
Patient Number: 1151
Treatment Group: NON-RAND

Lab Test	Units	Low/High Reference	VISIT 1	
Complete Blood Count				
MEAN CELL HEMOGLOBIN (MCH)	fmol(Fe)	1.430/1.920	1.30L	
LEUKOCYTE COUNT	GI/L	6.000/11.000	5.4L	
NEUTROPHILS, SEGMENTED	GI/L	4.000/13.500	2.88L	
LYMPHOCYTES	GI/L	4.000/12.000	1.81L	
ANISOCYTOSIS	NO UNITS		1	A
HYPOCHROMIA	NO UNITS		1	A
Blood Chemistry				
TOTAL PROTEIN	g/L	55.000/71.000	73H	
Electrolytes				
BICARBONATE, HCO3	mmol/L	12.000/28.000	32.1H	
Thyroids				
THYROXINE, TOTAL-T4	nmol/L	93.000/201.000	86L	
UDS				
MARIJUANA (THC)	NO UNITS		POS	A

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 11
Patient Number: 1152
Treatment Group: Flx

Lab Test	Units	Low/High Reference	VISIT 1
Complete Blood Count			
HEMATOCRIT	1	0.390/0.540	0.360L
HEMOGLOBIN	mml/L-Fe	7.880/11.230	7.51L
ANISOCYTOSIS	NO UNITS	1	A
Blood Chemistry			
CREATINE PHOSPHOKINASE	U/L	94.000/499.000	66L
ALKALINE PHOSPHATASE	U/L	95.000/385.000	396H

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 11
Patient Number: 1153
Treatment Group: Flx

Lab Test	Units	Low/High Reference	VISIT 1
Blood Chemistry			
CREATINE PHOSPHOKINASE	U/L	91.000/391.000	62L
Urinalysis			
UA-SPECIFIC GRAVITY	NO UNITS	1.010/1.034	1.006L

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 11
Patient Number: 1153
Treatment Group: Flx

Lab Test	Units	Low/High Reference	VISIT 15
Blood Chemistry			
CREATINE PHOSPHOKINASE	U/L	91.000/391.000	82L
Urinalysis			
UA-SPECIFIC GRAVITY	NO UNITS	1.010/1.034	

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 11
Patient Number: 1155
Treatment Group: NON-RAND

Lab Test	Units	Low/High Reference	VISIT 1
Complete Blood Count			
LYMPHOCYTES	GI/L	4.000/12.000	2.21L
MEAN CELL VOLUME (MCV)	fL	70.000/90.000	93H
Electrolytes			
BICARBONATE, HCO3	mmol/L	12.000/28.000	29.3H

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 11
Patient Number: 1156
Treatment Group: Flx

Lab Test	Units	Low/High Reference	VISIT 1
Complete Blood Count			
LEUKOCYTE COUNT	GI/L	4.350/13.650	3.2L
EOSINOPHILS	GI/L	0.000/0.570	
Blood Chemistry			
CREATINE PHOSPHOKINASE	U/L	91.000/391.000	
CHOLESTEROL	mmol/L	3.150/5.400	
Urinalysis			
UA-SPECIFIC GRAVITY	NO UNITS	1.010/1.034	1.005L

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 11
Patient Number: 1156
Treatment Group: Flx

Lab Test	Units	Low/High Reference	VISIT 15
Complete Blood Count			
LEUKOCYTE COUNT	GI/L	4.350/13.650	
EOSINOPHILS	GI/L	0.000/0.570	0.70H
Blood Chemistry			
CREATINE PHOSPHOKINASE	U/L	91.000/391.000	88L
CHOLESTEROL	mmol/L	3.150/5.400	6.13H
Urinalysis			
UA-SPECIFIC GRAVITY	NO UNITS	1.010/1.034	

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 12
Patient Number: 1201
Treatment Group: Placebo

Lab Test	Units	Low/High Reference	VISIT 13	
Urinalysis				
UA-BACTERIA	NO UNITS		1	A

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 12
Patient Number: 1202
Treatment Group: Flx

Lab Test	Units	Low/High Reference	VISIT 1
Blood Chemistry			
ALKALINE PHOSPHATASE	U/L	51.000/300.000	314H
ALBUMIN	g/L	29.000/47.000	48H
CHOLESTEROL	mmol/L	3.210/5.610	5.84H

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 12
Patient Number: 1203
Treatment Group: Flx

Lab Test	Units	Low/High Reference	VISIT 1
Complete Blood Count			
LEUKOCYTE COUNT	GI/L	4.350/13.150	3.9L
Urinalysis			
UA-RBC	NO UNITS		
UA-PROTEIN	NO UNITS		
UA-OCCULT BLOOD	NO UNITS		

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 12
Patient Number: 1203
Treatment Group: Flx

Lab Test	Units	Low/High Reference	VISIT 2	
Complete Blood Count				
LEUKOCYTE COUNT	GI/L	4.350/13.150		
Urinalysis				
UA-RBC	NO UNITS		2	A
UA-PROTEIN	NO UNITS		1	A
UA-OCCULT BLOOD	NO UNITS		3	A

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 12
Patient Number: 1204
Treatment Group: Flx

Lab Test	Units	Low/High Reference	VISIT 1
Blood Chemistry			
CREATINE PHOSPHOKINASE	U/L	94.000/499.000	69L
Thyroids			
THYROID STIM. HORMONE	mU/L	0.320/5.000	6.58H

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 12
Patient Number: 1205
Treatment Group: Flx

Lab Test	Units	Low/High Reference	VISIT 1
Blood Chemistry			
BILIRUBIN, TOTAL	umol/L	3.000/21.000	34H
Thyroids			
T3, TOTAL (TRIIODOTHYRONINE)	nmol/L	1.200/3.100	1.2L

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 12
Patient Number: 1205
Treatment Group: Flx

Lab Test	Units	Low/High Reference	VISIT 2
Blood Chemistry			
BILIRUBIN, TOTAL	umol/L	3.000/21.000	22H
Thyroids			
T3, TOTAL (TRIIODOTHYRONINE)	nmol/L	1.200/3.100	

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 12
Patient Number: 1205
Treatment Group: Flx

Lab Test	Units	Low/High Reference	VISIT 15
Blood Chemistry			
BILIRUBIN, TOTAL	umol/L	3.000/21.000	24H
Thyroids			
T3, TOTAL (TRIIODOTHYRONINE)	nmol/L	1.200/3.100	

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 12
Patient Number: 1206
Treatment Group: Placebo

Lab Test	Units	Low/High Reference	VISIT 1	
Blood Chemistry				
CREATINE PHOSPHOKINASE	U/L	91.000/391.000	66L	
Urinalysis				
UA-WBC	NO UNITS		1	A
UA-BACTERIA	NO UNITS		1	A
UA-NITRITES	NO UNITS		POS	A
UA-KETONES	NO UNITS		1	A

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 12
Patient Number: 1207
Treatment Group: Placebo

Lab Test	Units	Low/High Reference	VISIT 1
Blood Chemistry			
CHOLESTEROL	mmol/L	2.950/5.120	5.28H

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 12
Patient Number: 1208
Treatment Group: Flx

Lab Test	Units	Low/High Reference	VISIT 1
Blood Chemistry			
INORGANIC PHOSPHORUS	mmol/L	0.710/1.650	2.00H
ALBUMIN	g/L	29.000/47.000	48H

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 12
Patient Number: 1209
Treatment Group: Flx

Lab Test	Units	Low/High Reference	VISIT 1
Blood Chemistry			
CREATINE PHOSPHOKINASE	U/L	91.000/391.000	86L
Urinalysis			
UA-WBC	NO UNITS		2 A
UA-BACTERIA	NO UNITS		1 A

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 12
Patient Number: 1209
Treatment Group: Flx

Lab Test	Units	Low/High Reference	VISIT 11	
Blood Chemistry				
CREATINE PHOSPHOKINASE	U/L	91.000/391.000		
Urinalysis				
UA-WBC	NO UNITS			
UA-BACTERIA	NO UNITS		1	A

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 12
Patient Number: 1210
Treatment Group: NON-RAND

Lab Test	Units	Low/High Reference	VISIT 1
Complete Blood Count			
LYMPHOCYTES	GI/L	4.000/12.000	2.51L
MEAN CELL VOLUME (MCV)	fL	70.000/90.000	91H
Blood Chemistry			
TOTAL PROTEIN	g/L	55.000/71.000	72H
Urinalysis			
UA-BACTERIA	NO UNITS		1 A

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 12
Patient Number: 1211
Treatment Group: Flx

Lab Test	Units	Low/High Reference	VISIT 1	
Urinalysis				
UA-OCCULT BLOOD	NO UNITS		1	A

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 12
Patient Number: 1212
Treatment Group: Placebo

Lab Test	Units	Low/High Reference	VISIT 1
Urinalysis			
UA-SPECIFIC GRAVITY	NO UNITS	1.010/1.034	1.008L

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 12
Patient Number: 1213
Treatment Group: Flx

Lab Test	Units	Low/High Reference	VISIT 1
Blood Chemistry			
CREATINE PHOSPHOKINASE	U/L	150.000/489.000	149L
ALBUMIN	g/L	29.000/47.000	
Urinalysis			
UA-SPECIFIC GRAVITY	NO UNITS	1.010/1.034	1.007L

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 12
Patient Number: 1213
Treatment Group: Flx

Lab Test	Units	Low/High Reference	VISIT 15
Blood Chemistry			
CREATINE PHOSPHOKINASE	U/L	150.000/489.000	128L
ALBUMIN	g/L	29.000/47.000	48H
Urinalysis			
UA-SPECIFIC GRAVITY	NO UNITS	1.010/1.034	1.009L

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 12
Patient Number: 1214
Treatment Group: NON-RAND

Lab Test	Units	Low/High Reference	VISIT 1
Complete Blood Count			
LYMPHOCYTES	GI/L	4.000/12.000	2.81L

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 12
Patient Number: 1215
Treatment Group: Flx

Lab Test	Units	Low/High Reference	VISIT 1
Complete Blood Count			
HEMATOCRIT	1	0.390/0.540	0.370L
MEAN CELL VOLUME (MCV)	fL	79.000/96.000	73L
ANISOCYTOSIS	NO UNITS		1 A
Urinalysis			
UA-RBC	NO UNITS		1 A
UA-OCCULT BLOOD	NO UNITS		1 A

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 12
Patient Number: 1215
Treatment Group: Flx

Lab Test	Units	Low/High Reference	VISIT 7
Complete Blood Count			
HEMATOCRIT	1	0.390/0.540	0.380L
MEAN CELL VOLUME (MCV)	fL	79.000/96.000	
ANISOCYTOSIS	NO UNITS		
Urinalysis			
UA-RBC	NO UNITS		
UA-OCCULT BLOOD	NO UNITS		

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 12
Patient Number: 1216
Treatment Group: Placebo

Lab Test	Units	Low/High Reference	VISIT 1
Complete Blood Count			
HEMATOCRIT	1	0.340/0.440	0.450H
PLATELET COUNT	GI/L	130.000/394.000	401H
Blood Chemistry			
AST/SGOT	U/L	10.000/40.000	45.0H
ALT/SGPT	U/L	6.000/43.000	56.0H
CREATINE PHOSPHOKINASE	U/L	150.000/489.000	97L
			130L
URIC ACID	umol/L	161.000/393.000	399H
Urinalysis			
UA-RBC	NO UNITS		1 A
UA-PROTEIN	NO UNITS		

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 12
Patient Number: 1216
Treatment Group: Placebo

Lab Test	Units	Low/High Reference	VISIT 15
Complete Blood Count			
HEMATOCRIT	1	0.340/0.440	
PLATELET COUNT	GI/L	130.000/394.000	399H
Blood Chemistry			
AST/SGOT	U/L	10.000/40.000	
ALT/SGPT	U/L	6.000/43.000	
CREATINE PHOSPHOKINASE	U/L	150.000/489.000	126L
URIC ACID	umol/L	161.000/393.000	
Urinalysis			
UA-RBC	NO UNITS		
UA-PROTEIN	NO UNITS		1 A

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 12
Patient Number: 1218
Treatment Group: NON-RAND

Lab Test	Units	Low/High Reference	VISIT 1
Complete Blood Count			
LYMPHOCYTES	GI/L	4.000/12.000	2.62L
Blood Chemistry			
TOTAL PROTEIN	g/L	55.000/71.000	72H
Thyroids			
THYROXINE, TOTAL-T4	nmol/L	93.000/201.000	86L

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 12
Patient Number: 1219
Treatment Group: NON-RAND

Lab Test	Units	Low/High Reference	VISIT 1
Complete Blood Count			
LYMPHOCYTES	GI/L	4.000/12.000	2.90L
Blood Chemistry			
TOTAL PROTEIN	g/L	55.000/71.000	73H
Thyroids			
THYROXINE, TOTAL-T4	nmol/L	93.000/201.000	80L
Urinalysis			
UA-SPECIFIC GRAVITY	NO UNITS	1.010/1.034	1.008L

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 12
Patient Number: 1220
Treatment Group: Flx

Lab Test	Units	Low/High Reference	VISIT 1
Blood Chemistry			
GGT (GGPT/SGGT/YGGT)	U/L	0.000/33.000	39.0H
Thyroids			
T3 % UPTAKE	1	0.270/0.490	0.26L

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 12
Patient Number: 1221
Treatment Group: Placebo

Lab Test	Units	Low/High Reference	VISIT 1
Complete Blood Count			
HEMATOCRIT	1	0.340/0.440	0.450H
Blood Chemistry			
CREATINE PHOSPHOKINASE	U/L	91.000/391.000	
ALBUMIN	g/L	29.000/47.000	49H
CHOLESTEROL	mmol/L	3.210/5.610	

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 12
Patient Number: 1221
Treatment Group: Placebo

Lab Test	Units	Low/High Reference	VISIT 15
Complete Blood Count			
HEMATOCRIT	1	0.340/0.440	
Blood Chemistry			
CREATINE PHOSPHOKINASE	U/L	91.000/391.000	53L
ALBUMIN	g/L	29.000/47.000	
CHOLESTEROL	mmol/L	3.210/5.610	2.61L

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 12
Patient Number: 1222
Treatment Group: Placebo

Lab Test	Units	Low/High Reference	VISIT 1	
Blood Chemistry				
CREATINE PHOSPHOKINASE	U/L	150.000/489.000	119	L
Urinalysis				
UA-BACTERIA	NO UNITS		1	A

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 12
Patient Number: 1223
Treatment Group: Placebo

Lab Test	Units	Low/High Reference	VISIT 1
Blood Chemistry			
ALBUMIN	g/L	29.000/47.000	50H

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 12
Patient Number: 1224
Treatment Group: NON-RAND

Lab Test	Units	Low/High Reference	VISIT 1
Complete Blood Count			
HEMOGLOBIN	mml/L-Fe	6.520/8.380	8.44H
NEUTROPHILS, SEGMENTED	GI/L	4.000/13.500	3.70L
LYMPHOCYTES	GI/L	4.000/12.000	2.34L
Blood Chemistry			
GGT (GGPT/SGGT/YGGT)	U/L	0.000/24.000	36.0H
TOTAL PROTEIN	g/L	55.000/71.000	80H
ALBUMIN	g/L	28.000/48.000	50H

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 12
Patient Number: 1225
Treatment Group: Flx

Lab Test	Units	Low/High Reference	VISIT 1
Urinalysis			
UA-SPECIFIC GRAVITY	NO UNITS	1.010/1.034	1.007L

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 12
Patient Number: 1227
Treatment Group: NON-RAND

Lab Test	Units	Low/High Reference	VISIT 1
Complete Blood Count			
HEMOGLOBIN	mml/L-Fe	6.520/8.380	9.50H
LEUKOCYTE COUNT	GI/L	6.000/11.000	5.8L
NEUTROPHILS, SEGMENTED	GI/L	4.000/13.500	2.53L
LYMPHOCYTES	GI/L	4.000/12.000	2.64L
Blood Chemistry			
TOTAL PROTEIN	g/L	55.000/71.000	76H
Electrolytes			
BICARBONATE, HCO3	mmol/L	12.000/28.000	28.6H
Thyroids			
THYROXINE, TOTAL-T4	nmol/L	93.000/201.000	91L

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 13
Patient Number: 1301
Treatment Group: Placebo

Lab Test	Units	Low/High Reference	VISIT 1
Blood Chemistry			
ALT/SGPT	U/L	6.000/34.000	4.0L
CREATINE PHOSPHOKINASE	U/L	53.000/269.000	

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 13
Patient Number: 1302
Treatment Group: NON-RAND

Lab Test	Units	Low/High Reference	VISIT 1
Blood Chemistry			
TOTAL PROTEIN	g/L	55.000/71.000	73H
Electrolytes			
BICARBONATE, HCO3	mmol/L	12.000/28.000	31.1H

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 13
Patient Number: 1303
Treatment Group: Placebo

Lab Test	Units	Low/High Reference	VISIT 1
Blood Chemistry			
CREATINE PHOSPHOKINASE	U/L	91.000/391.000	57L
ALBUMIN	g/L	29.000/47.000	50H
CHOLESTEROL	mmol/L	3.210/5.610	6.10H
Urinalysis			
UA-PROTEIN	NO UNITS		
UA-KETONES	NO UNITS		

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 13
Patient Number: 1303
Treatment Group: Placebo

Lab Test	Units	Low/High Reference	VISIT 15
Blood Chemistry			
CREATINE PHOSPHOKINASE	U/L	91.000/391.000	85L
ALBUMIN	g/L	29.000/47.000	50H
CHOLESTEROL	mmol/L	3.210/5.610	
Urinalysis			
UA-PROTEIN	NO UNITS		1 A
UA-KETONES	NO UNITS		1 A

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 13
Patient Number: 1305
Treatment Group: Flx

Lab Test	Units	Low/High Reference	VISIT 1
Complete Blood Count			
EOSINOPHILS	GI/L	0.000/0.570	0.62H
Blood Chemistry			
CREATINE PHOSPHOKINASE	U/L	94.000/499.000	76L
Electrolytes			
BICARBONATE, HCO3	mmol/L	17.000/30.600	
Urinalysis			
UA-SPECIFIC GRAVITY	NO UNITS	1.010/1.034	
UA-KETONES	NO UNITS		

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 13
Patient Number: 1305
Treatment Group: Flx

Lab Test	Units	Low/High Reference	VISIT 15
Complete Blood Count			
EOSINOPHILS	GI/L	0.000/0.570	
Blood Chemistry			
CREATINE PHOSPHOKINASE	U/L	94.000/499.000	
Electrolytes			
BICARBONATE, HCO3	mmol/L	17.000/30.600	32.4H
Urinalysis			
UA-SPECIFIC GRAVITY	NO UNITS	1.010/1.034	1.035H
UA-KETONES	NO UNITS		1 A

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 13
Patient Number: 1306
Treatment Group: NON-RAND

Lab Test	Units	Low/High Reference	VISIT 1
Complete Blood Count			
HEMOGLOBIN	mml/L-Fe	6.520/8.380	9.56H
LEUKOCYTE COUNT	GI/L	6.000/11.000	4.1L
NEUTROPHILS, SEGMENTED	GI/L	4.000/13.500	2.17L
LYMPHOCYTES	GI/L	4.000/12.000	1.64L
PLATELET COUNT	GI/L	200.000/400.000	197L
Blood Chemistry			
TOTAL PROTEIN	g/L	55.000/71.000	76H
Electrolytes			
BICARBONATE, HCO3	mmol/L	12.000/28.000	29.9H

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 13
Patient Number: 1307
Treatment Group: Placebo

Lab Test	Units	Low/High Reference	VISIT 15
Blood Chemistry			
ALKALINE PHOSPHATASE	U/L	95.000/385.000	87L

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 13
Patient Number: 1308
Treatment Group: Placebo

Lab Test	Units	Low/High Reference	VISIT 1	
Urinalysis				
UA-WBC	NO UNITS		1	A
UA-BACTERIA	NO UNITS		1	A

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 13
Patient Number: 1309
Treatment Group: Placebo

Lab Test	Units	Low/High Reference	VISIT 1
Blood Chemistry			
ALKALINE PHOSPHATASE	U/L	95.000/385.000	388H
CHOLESTEROL	mmol/L	3.360/5.280	3.15L

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 13
Patient Number: 1310
Treatment Group: Placebo

Lab Test	Units	Low/High Reference	VISIT 1	
Complete Blood Count				
LEUKOCYTE COUNT	GI/L	4.350/13.150	4.3L	
Blood Chemistry				
TOTAL PROTEIN	g/L	61.000/84.000	86H	
URIC ACID	umol/L	202.000/535.000	161L	
Urinalysis				
UA-WBC	NO UNITS		2	A
UA-BACTERIA	NO UNITS		1	A
UDS				
DESIPRAMINE	NO UNITS		POS	A
			POS	A
			POS	A
IMIPRAMINE	NO UNITS		POS	A

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 13
Patient Number: 1311
Treatment Group: Placebo

Lab Test	Units	Low/High Reference	VISIT 1	
Urinalysis				
UA-WBC	NO UNITS		2	A
UA-PROTEIN	NO UNITS		1	A
UA-KETONES	NO UNITS		1	A
UA-OCCULT BLOOD	NO UNITS		1	A

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 15
Patient Number: 1501
Treatment Group: Placebo

Lab Test	Units	Low/High Reference	VISIT 1
Blood Chemistry			
CREATINE PHOSPHOKINASE	U/L	53.000/269.000	45L

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 15
Patient Number: 1503
Treatment Group: Flx

Lab Test	Units	Low/High Reference	VISIT 1
Blood Chemistry			
CREATINE PHOSPHOKINASE	U/L	94.000/499.000	31L
Urinalysis			
UA-PROTEIN	NO UNITS		

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 15
Patient Number: 1503
Treatment Group: Flx

Lab Test	Units	Low/High Reference	VISIT 11
Blood Chemistry			
CREATINE PHOSPHOKINASE	U/L	94.000/499.000	31L
Urinalysis			
UA-PROTEIN	NO UNITS	1	A

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 15
Patient Number: 1504
Treatment Group: Placebo

Lab Test	Units	Low/High Reference	VISIT 1
Complete Blood Count			
HEMOGLOBIN	mml/L-Fe	7.200/10.180	
Blood Chemistry			
CREATINE PHOSPHOKINASE	U/L	91.000/391.000	55L
Urinalysis			
UA-BACTERIA	NO UNITS		1 A

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 15
Patient Number: 1504
Treatment Group: Placebo

Lab Test	Units	Low/High Reference	VISIT 9
Complete Blood Count			
HEMOGLOBIN	mml/L-Fe	7.200/10.180	7.01L
Blood Chemistry			
CREATINE PHOSPHOKINASE	U/L	91.000/391.000	87L
Urinalysis			
UA-BACTERIA	NO UNITS		

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 15
Patient Number: 1506
Treatment Group: Placebo

Lab Test	Units	Low/High Reference	VISIT 1
Complete Blood Count			
MONOCYTES	GI/L	0.120/0.920	1.00H
Blood Chemistry			
CREATINE PHOSPHOKINASE	U/L	91.000/391.000	83L
Urinalysis			
UA-PROTEIN	NO UNITS		

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 15
Patient Number: 1506
Treatment Group: Placebo

Lab Test	Units	Low/High Reference	VISIT 15
Complete Blood Count			
MONOCYTES	GI/L	0.120/0.920	
Blood Chemistry			
CREATINE PHOSPHOKINASE	U/L	91.000/391.000	66L
Urinalysis			
UA-PROTEIN	NO UNITS	1	A

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 15
Patient Number: 1508
Treatment Group: NON-RAND

Lab Test	Units	Low/High Reference	VISIT 1
Complete Blood Count			
HEMOGLOBIN	mml/L-Fe	6.520/8.380	8.56H
LEUKOCYTE COUNT	GI/L	6.000/11.000	4.8L
NEUTROPHILS, SEGMENTED	GI/L	4.000/13.500	2.39L
LYMPHOCYTES	GI/L	4.000/12.000	1.93L
Electrolytes			
BICARBONATE, HCO3	mmol/L	12.000/28.000	31.5H
Thyroids			
THYROXINE, TOTAL-T4	nmol/L	93.000/201.000	81L

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 15
Patient Number: 1510
Treatment Group: Flx

Lab Test	Units	Low/High Reference	VISIT 1	
Blood Chemistry				
ALT/SGPT	U/L	6.000/34.000		
Urinalysis				
UA-RBC	NO UNITS		4	A
UA-BACTERIA	NO UNITS			
UA-OCCULT BLOOD	NO UNITS		3	A

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 15
Patient Number: 1510
Treatment Group: Flx

Lab Test	Units	Low/High Reference	VISIT 15
Blood Chemistry			
ALT/SGPT	U/L	6.000/34.000	38.0H
Urinalysis			
UA-RBC	NO UNITS		
UA-BACTERIA	NO UNITS		1 A
UA-OCCULT BLOOD	NO UNITS		

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 15
Patient Number: 1512
Treatment Group: NON-RAND

Lab Test	Units	Low/High Reference	VISIT 1
Complete Blood Count			
HEMOGLOBIN	mml/L-Fe	6.520/8.380	8.87H
LEUKOCYTE COUNT	GI/L	6.000/11.000	4.7L
NEUTROPHILS, SEGMENTED	GI/L	4.000/13.500	2.47L
LYMPHOCYTES	GI/L	4.000/12.000	1.72L
Blood Chemistry			
TOTAL PROTEIN	g/L	55.000/71.000	81H
Urinalysis			
UA-RBC	NO UNITS		1 A
UA-PROTEIN	NO UNITS		1 A
UA-KETONES	NO UNITS		1 A
UA-OCCULT BLOOD	NO UNITS		1 A

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 15
Patient Number: 1513
Treatment Group: Placebo

Lab Test	Units	Low/High Reference	VISIT 1
Complete Blood Count			
HEMATOCRIT	1	0.340/0.440	0.460H
Electrolytes			
POTASSIUM	mmol/L	3.400/5.400	5.5H
Urinalysis			
UA-SPECIFIC GRAVITY	NO UNITS	1.010/1.034	1.004L

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 15
Patient Number: 1515
Treatment Group: Flx

Lab Test	Units	Low/High Reference	VISIT 1	
Urinalysis				
UA-PROTEIN	NO UNITS		1	A

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 15
Patient Number: 1516
Treatment Group: Flx

Lab Test	Units	Low/High Reference	VISIT 1
Blood Chemistry			
URIC ACID	umol/L	161.000/393.000	149L
BILIRUBIN, TOTAL	umol/L	3.000/21.000	

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 15
Patient Number: 1516
Treatment Group: Flx

Lab Test	Units	Low/High Reference	VISIT 15
Blood Chemistry			
URIC ACID	umol/L	161.000/393.000	137L
BILIRUBIN, TOTAL	umol/L	3.000/21.000	

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 15
Patient Number: 1517
Treatment Group: NON-RAND

Lab Test	Units	Low/High Reference	VISIT 1
Complete Blood Count			
LEUKOCYTE COUNT	GI/L	6.000/11.000	4.4L
NEUTROPHILS, SEGMENTED	GI/L	4.000/13.500	1.83L
LYMPHOCYTES	GI/L	4.000/12.000	1.72L
Thyroids			
THYROXINE, TOTAL-T4	nmol/L	93.000/201.000	91L

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 16
Patient Number: 1601
Treatment Group: Flx

Lab Test	Units	Low/High Reference	VISIT 1
Complete Blood Count			
HEMATOCRIT	1	0.390/0.540	0.380L
Urinalysis			
UA-SPECIFIC GRAVITY	NO UNITS	1.010/1.034	1.008L

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 16
Patient Number: 1601
Treatment Group: Flx

Lab Test	Units	Low/High Reference	VISIT 15
Complete Blood Count			
HEMATOCRIT	1	0.390/0.540	0.370L
Urinalysis			
UA-SPECIFIC GRAVITY	NO UNITS	1.010/1.034	

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 16
Patient Number: 1602
Treatment Group: Flx

Lab Test	Units	Low/High Reference	VISIT 1
Complete Blood Count			
PLATELET COUNT	GI/L	130.000/394.000	
Blood Chemistry			
URIC ACID	umol/L	161.000/393.000	131L
Urinalysis			
UA-SPECIFIC GRAVITY	NO UNITS	1.010/1.034	1.009L

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 16
Patient Number: 1602
Treatment Group: Flx

Lab Test	Units	Low/High Reference	VISIT 13
Complete Blood Count			
PLATELET COUNT	GI/L	130.000/394.000	414H
Blood Chemistry			
URIC ACID	umol/L	161.000/393.000	119L
Urinalysis			
UA-SPECIFIC GRAVITY	NO UNITS	1.010/1.034	

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 16
Patient Number: 1603
Treatment Group: Flx

Lab Test	Units	Low/High Reference	VISIT 1
Complete Blood Count			
MONOCYTES	GI/L	0.120/0.920	1.24H
EOSINOPHILS	GI/L	0.000/0.570	0.71H
Blood Chemistry			
CREATINE PHOSPHOKINASE	U/L	150.000/489.000	46L
CHOLESTEROL	mmol/L	3.360/5.280	2.95L

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 16
Patient Number: 1603
Treatment Group: Flx

Lab Test	Units	Low/High Reference	VISIT 8
Complete Blood Count			
MONOCYTES	GI/L	0.120/0.920	
EOSINOPHILS	GI/L	0.000/0.570	
Blood Chemistry			
CREATINE PHOSPHOKINASE	U/L	150.000/489.000	80L
CHOLESTEROL	mmol/L	3.360/5.280	

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 16
Patient Number: 1604
Treatment Group: Flx

Lab Test	Units	Low/High Reference	VISIT 1
Complete Blood Count			
PLATELET COUNT	GI/L	130.000/394.000	415H
Blood Chemistry			
CREATINE PHOSPHOKINASE	U/L	150.000/489.000	68L
GGT (GGPT/SGGT/YGGT)	U/L	0.000/24.000	

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 16
Patient Number: 1604
Treatment Group: Flx

Lab Test	Units	Low/High Reference	VISIT 15
Complete Blood Count			
PLATELET COUNT	GI/L	130.000/394.000	
Blood Chemistry			
CREATINE PHOSPHOKINASE	U/L	150.000/489.000	69L
GGT (GGPT/SGGT/YGGT)	U/L	0.000/24.000	32.0H

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 16
Patient Number: 1605
Treatment Group: Flx

Lab Test	Units	Low/High Reference	VISIT 1
Blood Chemistry			
CREATINE PHOSPHOKINASE	U/L	150.000/489.000	91L

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 16
Patient Number: 1605
Treatment Group: Flx

Lab Test	Units	Low/High Reference	VISIT 15
Blood Chemistry			
CREATINE PHOSPHOKINASE	U/L	150.000/489.000	84L

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 16
Patient Number: 1607
Treatment Group: NON-RAND

Lab Test	Units	Low/High Reference	VISIT 1
Complete Blood Count			
HEMOGLOBIN	mml/L-Fe	6.520/8.380	9.12H
NEUTROPHILS, SEGMENTED	GI/L	4.000/13.500	2.79L
LYMPHOCYTES	GI/L	4.000/12.000	2.85L
Thyroids			
THYROXINE, TOTAL-T4	nmol/L	93.000/201.000	59L

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 16
Patient Number: 1608
Treatment Group: Placebo

Lab Test	Units	Low/High Reference	VISIT 1
Complete Blood Count			
MEAN CELL HEMOGLOBIN (MCH)	fmol(Fe)	1.500/2.100	1.49L
MEAN CELL VOLUME (MCV)	fL	76.000/93.000	74L
ANISOCYTOSIS	NO UNITS		1 A
MICROCYTOSIS	NO UNITS		1 A
Blood Chemistry			
AST/SGOT	U/L	10.000/40.000	
CREATINE PHOSPHOKINASE	U/L	150.000/489.000	133L
CHOLESTEROL	mmol/L	3.360/5.280	3.05L

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 16
Patient Number: 1608
Treatment Group: Placebo

Lab Test	Units	Low/High Reference	VISIT 6
Complete Blood Count			
MEAN CELL HEMOGLOBIN (MCH)	fmol(Fe)	1.500/2.100	1.49L
MEAN CELL VOLUME (MCV)	fL	76.000/93.000	74L
ANISOCYTOSIS	NO UNITS		1 A
MICROCYTOSIS	NO UNITS		1 A
Blood Chemistry			
AST/SGOT	U/L	10.000/40.000	41.0H
CREATINE PHOSPHOKINASE	U/L	150.000/489.000	
CHOLESTEROL	mmol/L	3.360/5.280	

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 16
Patient Number: 1609
Treatment Group: Flx

Lab Test	Units	Low/High Reference	VISIT 1
Blood Chemistry			
ALKALINE PHOSPHATASE	U/L	69.000/325.000	341H
Urinalysis			
UA-SPECIFIC GRAVITY	NO UNITS	1.010/1.034	

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 16
Patient Number: 1609
Treatment Group: Flx

Lab Test	Units	Low/High Reference	VISIT 15
Blood Chemistry			
ALKALINE PHOSPHATASE	U/L	69.000/325.000	
Urinalysis			
UA-SPECIFIC GRAVITY	NO UNITS	1.010/1.034	1.035H

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 16
Patient Number: 1610
Treatment Group: NON-RAND

Lab Test	Units	Low/High Reference	VISIT 1
Complete Blood Count			
LEUKOCYTE COUNT	GI/L	6.000/11.000	5.4L
NEUTROPHILS, SEGMENTED	GI/L	4.000/13.500	3.08L
LYMPHOCYTES	GI/L	4.000/12.000	1.64L
Blood Chemistry			
TOTAL PROTEIN	g/L	55.000/71.000	72H

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 16
Patient Number: 1612
Treatment Group: Flx

Lab Test	Units	Low/High Reference	VISIT 1
Blood Chemistry			
CREATINE PHOSPHOKINASE	U/L	150.000/489.000	105L

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 16
Patient Number: 1651
Treatment Group: Placebo

Lab Test	Units	Low/High Reference	VISIT 1	
Blood Chemistry				
URIC ACID	umol/L	202.000/535.000	190L	
Urinalysis				
UA-KETONES	NO UNITS		1	A

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 16
Patient Number: 1652
Treatment Group: Flx

Lab Test	Units	Low/High Reference	VISIT 1
Blood Chemistry			
AST/SGOT	U/L	10.000/40.000	
CHOLESTEROL	mmol/L	3.260/4.940	5.09H
Urinalysis			
UA-SPECIFIC GRAVITY	NO UNITS	1.010/1.034	1.038H

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 16
Patient Number: 1652
Treatment Group: Flx

Lab Test	Units	Low/High Reference	VISIT 11
Blood Chemistry			
AST/SGOT	U/L	10.000/40.000	46.0H
CHOLESTEROL	mmol/L	3.260/4.940	5.35H
Urinalysis			
UA-SPECIFIC GRAVITY	NO UNITS	1.010/1.034	1.036H

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 16
Patient Number: 1653
Treatment Group: Placebo

Lab Test	Units	Low/High Reference	VISIT 1
Blood Chemistry			
CREATINE PHOSPHOKINASE	U/L	94.000/499.000	80L
CHOLESTEROL	mmol/L	3.360/5.280	6.00H

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 16
Patient Number: 1654
Treatment Group: Flx

Lab Test	Units	Low/High Reference	VISIT 1	
UDS				
HYDROCODONE	NO UNITS		POS	A
DIHYDROCODEINE	NO UNITS		POS	A

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 16
Patient Number: 1655
Treatment Group: Placebo

Lab Test	Units	Low/High Reference	VISIT 1
Complete Blood Count			
HEMATOCRIT	1	0.390/0.540	0.380L
LYMPHOCYTES, ATYPICAL	GI/L	0.000/0.100	

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 16
Patient Number: 1655
Treatment Group: Placebo

Lab Test	Units	Low/High Reference	VISIT 15
Complete Blood Count			
HEMATOCRIT	1	0.390/0.540	
LYMPHOCYTES, ATYPICAL	GI/L	0.000/0.100	0.12H

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 16
Patient Number: 1656
Treatment Group: Placebo

Lab Test	Units	Low/High Reference	VISIT 1
Blood Chemistry			
ALKALINE PHOSPHATASE	U/L	86.000/315.000	349H
URIC ACID	umol/L	161.000/393.000	155L
CHOLESTEROL	mmol/L	3.260/4.940	5.33H
BILIRUBIN, TOTAL	umol/L	3.000/21.000	

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 16
Patient Number: 1656
Treatment Group: Placebo

Lab Test	Units	Low/High Reference	VISIT 15
Blood Chemistry			
ALKALINE PHOSPHATASE	U/L	86.000/315.000	370H
URIC ACID	umol/L	161.000/393.000	
CHOLESTEROL	mmol/L	3.260/4.940	5.79H
BILIRUBIN, TOTAL	umol/L	3.000/21.000	

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 16
Patient Number: 1657
Treatment Group: Placebo

Lab Test	Units	Low/High Reference	VISIT 1
Blood Chemistry			
ALKALINE PHOSPHATASE	U/L	69.000/325.000	353H

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 16
Patient Number: 1658
Treatment Group: Flx

Lab Test	Units	Low/High Reference	VISIT 1
Blood Chemistry			
ALT/SGPT	U/L	6.000/34.000	41.0H
CREATINE PHOSPHOKINASE	U/L	91.000/391.000	85L
Urinalysis			
UA-WBC	NO UNITS		
UA-BACTERIA	NO UNITS		1 A

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 16
Patient Number: 1658
Treatment Group: Flx

Lab Test	Units	Low/High Reference	VISIT 13	
Blood Chemistry				
ALT/SGPT	U/L	6.000/34.000		
CREATINE PHOSPHOKINASE	U/L	91.000/391.000		
Urinalysis				
UA-WBC	NO UNITS		1	A
UA-BACTERIA	NO UNITS		1	A

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 16
Patient Number: 1659
Treatment Group: Flx

Lab Test	Units	Low/High Reference	VISIT 15
Complete Blood Count			
HEMATOCRIT	1	0.390/0.540	0.370L
MEAN CELL VOLUME (MCV)	fL	79.000/96.000	78L

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 16
Patient Number: 1661
Treatment Group: NON-RAND

Lab Test	Units	Low/High Reference	VISIT 1
Complete Blood Count			
LYMPHOCYTES	GI/L	4.000/12.000	2.46L
Blood Chemistry			
TOTAL PROTEIN	g/L	55.000/71.000	76H
Urinalysis			
UA-WBC	NO UNITS	1	A

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 16
Patient Number: 1664
Treatment Group: NON-RAND

Lab Test	Units	Low/High Reference	VISIT 1
Complete Blood Count			
HEMOGLOBIN	mml/L-Fe	6.520/8.380	8.63H
MEAN CELL HEMOGLOBIN (MCH)	fmol(Fe)	1.430/1.920	1.99H
LYMPHOCYTES	GI/L	4.000/12.000	1.93L
MEAN CELL VOLUME (MCV)	fL	70.000/90.000	96H
UDS			
MARIJUANA (THC)	NO UNITS		POS A

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 16
Patient Number: 1667
Treatment Group: Flx

Lab Test	Units	Low/High Reference	VISIT 1
Blood Chemistry			
CREATINE PHOSPHOKINASE	U/L	150.000/489.000	105L
CHOLESTEROL	mmol/L	3.260/4.940	3.18L
Urinalysis			
UA-OCCULT BLOOD	NO UNITS		1 A

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 16
Patient Number: 1668
Treatment Group: NON-RAND

Lab Test	Units	Low/High Reference	VISIT 1
Complete Blood Count			
HEMOGLOBIN	mml/L-Fe	6.520/8.380	9.00H
LYMPHOCYTES	GI/L	4.000/12.000	2.97L
Blood Chemistry			
GGT (GGPT/SGGT/YGGT)	U/L	0.000/24.000	25.0H
TOTAL PROTEIN	g/L	55.000/71.000	79H
Electrolytes			
BICARBONATE, HCO3	mmol/L	12.000/28.000	28.2H
Urinalysis			
UA-KETONES	NO UNITS	1	A

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 16
Patient Number: 1669
Treatment Group: Placebo

Lab Test	Units	Low/High Reference	VISIT 1
Blood Chemistry			
CHOLESTEROL	mmol/L	3.360/5.280	5.59H

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 16
Patient Number: 1669
Treatment Group: Placebo

Lab Test	Units	Low/High Reference	VISIT 12
Blood Chemistry			
CHOLESTEROL	mmol/L	3.360/5.280	5.33H

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 17
Patient Number: 1701
Treatment Group: Flx

Lab Test	Units	Low/High Reference	VISIT 1
Blood Chemistry			
ALKALINE PHOSPHATASE	U/L	95.000/385.000	409H
Urinalysis			
UA-SPECIFIC GRAVITY	NO UNITS	1.010/1.034	

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 17
Patient Number: 1701
Treatment Group: Flx

Lab Test	Units	Low/High Reference	VISIT 15
Blood Chemistry			
ALKALINE PHOSPHATASE	U/L	95.000/385.000	
Urinalysis			
UA-SPECIFIC GRAVITY	NO UNITS	1.010/1.034	1.035H

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 17
Patient Number: 1702
Treatment Group: Flx

Lab Test	Units	Low/High Reference	VISIT 1
Complete Blood Count			
PLATELET COUNT	GI/L	130.000/394.000	
Blood Chemistry			
CREATINE PHOSPHOKINASE	U/L	150.000/489.000	105L
BILIRUBIN, TOTAL	umol/L	3.000/21.000	

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 17
Patient Number: 1702
Treatment Group: Flx

Lab Test	Units	Low/High Reference	VISIT 15
Complete Blood Count			
PLATELET COUNT	GI/L	130.000/394.000	415H
Blood Chemistry			
CREATINE PHOSPHOKINASE	U/L	150.000/489.000	107L
BILIRUBIN, TOTAL	umol/L	3.000/21.000	

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 17
Patient Number: 1703
Treatment Group: NON-RAND

Lab Test	Units	Low/High Reference	VISIT 1
Complete Blood Count			
LEUKOCYTE COUNT	GI/L	6.000/11.000	5.4L
NEUTROPHILS, SEGMENTED	GI/L	4.000/13.500	1.81L
LYMPHOCYTES	GI/L	4.000/12.000	2.49L
EOSINOPHILS	GI/L	0.000/0.570	0.68H
ANISOCYTOSIS	NO UNITS		1 A
Blood Chemistry			
TOTAL PROTEIN	g/L	55.000/71.000	75H

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 17
Patient Number: 1704
Treatment Group: NON-RAND

Lab Test	Units	Low/High Reference	VISIT 1
Complete Blood Count			
LYMPHOCYTES	GI/L	4.000/12.000	2.13L

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 17
Patient Number: 1705
Treatment Group: Placebo

Lab Test	Units	Low/High Reference	VISIT 1	
Complete Blood Count				
EOSINOPHILS	GI/L	0.000/0.570		
ANISOCYTOSIS	NO UNITS		1	A
MICROCYTOSIS	NO UNITS		1	A
HYPOCHROMIA	NO UNITS			
Blood Chemistry				
ALKALINE PHOSPHATASE	U/L	69.000/325.000	344H	
CHOLESTEROL	mmol/L	3.150/5.400	5.84H	

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 17
Patient Number: 1705
Treatment Group: Placebo

Lab Test	Units	Low/High Reference	VISIT 15
Complete Blood Count			
EOSINOPHILS	GI/L	0.000/0.570	0.60H
ANISOCYTOSIS	NO UNITS		
MICROCYTOSIS	NO UNITS		
HYPOCHROMIA	NO UNITS		1 A
Blood Chemistry			
ALKALINE PHOSPHATASE	U/L	69.000/325.000	394H
CHOLESTEROL	mmol/L	3.150/5.400	

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 17
Patient Number: 1707
Treatment Group: Placebo

Lab Test	Units	Low/High Reference	VISIT 1
Complete Blood Count			
NEUTROPHILS, SEGMENTED	GI/L	1.650/8.150	
Blood Chemistry			
ALT/SGPT	U/L	6.000/34.000	45.0H
GGT (GGPT/SGGT/YGGT)	U/L	0.000/33.000	34.0H
CHOLESTEROL	mmol/L	3.210/5.610	
Urinalysis			
UA-SPECIFIC GRAVITY	NO UNITS	1.010/1.034	1.008L
UA-BACTERIA	NO UNITS		

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 17
Patient Number: 1707
Treatment Group: Placebo

Lab Test	Units	Low/High Reference	VISIT 15
Complete Blood Count			
NEUTROPHILS, SEGMENTED	GI/L	1.650/8.150	9.21H
Blood Chemistry			
ALT/SGPT	U/L	6.000/34.000	
GGT (GGPT/SGGT/YGGT)	U/L	0.000/33.000	
CHOLESTEROL	mmol/L	3.210/5.610	6.13H
Urinalysis			
UA-SPECIFIC GRAVITY	NO UNITS	1.010/1.034	
UA-BACTERIA	NO UNITS		1 A

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 18
Patient Number: 1801
Treatment Group: NON-RAND

Lab Test	Units	Low/High Reference	VISIT 1
Complete Blood Count			
MEAN CELL HEMOGLOBIN (MCH)	fmol(Fe)	1.430/1.920	1.99H
LEUKOCYTE COUNT	GI/L	6.000/11.000	3.6L
NEUTROPHILS, SEGMENTED	GI/L	4.000/13.500	2.30L
LYMPHOCYTES	GI/L	4.000/12.000	0.94L
MEAN CELL VOLUME (MCV)	fL	70.000/90.000	93H
Electrolytes			
BICARBONATE, HCO3	mmol/L	12.000/28.000	28.1H
Thyroids			
THYROXINE, TOTAL-T4	nmol/L	93.000/201.000	88L
T3, TOTAL (TRIIODOTHYRONINE)	nmol/L	1.200/3.100	1.1L

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 19
Patient Number: 1901
Treatment Group: Placebo

Lab Test	Units	Low/High Reference	VISIT 1
Blood Chemistry			
CREATINE PHOSPHOKINASE	U/L	91.000/391.000	89L
ALKALINE PHOSPHATASE	U/L	51.000/300.000	

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 19
Patient Number: 1901
Treatment Group: Placebo

Lab Test	Units	Low/High Reference	VISIT 15
Blood Chemistry			
CREATINE PHOSPHOKINASE	U/L	91.000/391.000	
ALKALINE PHOSPHATASE	U/L	51.000/300.000	325H

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 19
Patient Number: 1902
Treatment Group: NON-RAND

Lab Test	Units	Low/High Reference	VISIT 1
Complete Blood Count			
LEUKOCYTE COUNT	GI/L	6.000/11.000	5.8L
NEUTROPHILS, SEGMENTED	GI/L	4.000/13.500	2.54L
LYMPHOCYTES	GI/L	4.000/12.000	2.35L
Blood Chemistry			
TOTAL PROTEIN	g/L	55.000/71.000	74H
Thyroids			
THYROXINE, TOTAL-T4	nmol/L	93.000/201.000	84L

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 19
Patient Number: 1903
Treatment Group: Placebo

Lab Test	Units	Low/High Reference	VISIT 1	
Urinalysis				
UA-KETONES	NO UNITS		1	A

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 19
Patient Number: 1904
Treatment Group: Flx

Lab Test	Units	Low/High Reference	VISIT 1
Blood Chemistry			
CREATINE PHOSPHOKINASE	U/L	150.000/489.000	97L

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 19
Patient Number: 1904
Treatment Group: Flx

Lab Test	Units	Low/High Reference	VISIT 11
Blood Chemistry			
CREATINE PHOSPHOKINASE	U/L	150.000/489.000	122L

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 19
Patient Number: 1905
Treatment Group: Flx

Lab Test	Units	Low/High Reference	VISIT 1
Blood Chemistry			
CREATINE PHOSPHOKINASE	U/L	91.000/391.000	33L
Urinalysis			
UA-RBC	NO UNITS		1 A
UA-OCCULT BLOOD	NO UNITS		2 A

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 19
Patient Number: 1905
Treatment Group: Flx

Lab Test	Units	Low/High Reference	VISIT 15
Blood Chemistry			
CREATINE PHOSPHOKINASE	U/L	91.000/391.000	46L
Urinalysis			
UA-RBC	NO UNITS		
UA-OCCULT BLOOD	NO UNITS		

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 19
Patient Number: 1906
Treatment Group: Flx

Lab Test	Units	Low/High Reference	VISIT 1
Blood Chemistry			
CREATINE PHOSPHOKINASE	U/L	150.000/489.000	103L

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 19
Patient Number: 1906
Treatment Group: Flx

Lab Test	Units	Low/High Reference	VISIT 15
Blood Chemistry			
CREATINE PHOSPHOKINASE	U/L	150.000/489.000	81L

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 19
Patient Number: 1907
Treatment Group: Placebo

Lab Test	Units	Low/High Reference	VISIT 1
Blood Chemistry			
ALT/SGPT	U/L	6.000/34.000	
CREATINE PHOSPHOKINASE	U/L	91.000/391.000	72L
CHOLESTEROL	mmol/L	3.210/5.610	5.77H
Urinalysis			
UA-SPECIFIC GRAVITY	NO UNITS	1.010/1.034	

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 19
Patient Number: 1907
Treatment Group: Placebo

Lab Test	Units	Low/High Reference	VISIT 13
Blood Chemistry			
ALT/SGPT	U/L	6.000/34.000	5.0L
CREATINE PHOSPHOKINASE	U/L	91.000/391.000	
CHOLESTEROL	mmol/L	3.210/5.610	
Urinalysis			
UA-SPECIFIC GRAVITY	NO UNITS	1.010/1.034	1.008L

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 19
Patient Number: 1908
Treatment Group: NON-RAND

Lab Test	Units	Low/High Reference	VISIT 1
Complete Blood Count			
NEUTROPHILS, SEGMENTED	GI/L	4.000/13.500	3.81L
LYMPHOCYTES	GI/L	4.000/12.000	2.63L

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 19
Patient Number: 1910
Treatment Group: NON-RAND

Lab Test	Units	Low/High Reference	VISIT 1
Complete Blood Count			
HEMOGLOBIN	mml/L-Fe	6.520/8.380	8.63H
LEUKOCYTE COUNT	GI/L	6.000/11.000	4.8L
NEUTROPHILS, SEGMENTED	GI/L	4.000/13.500	2.27L
LYMPHOCYTES	GI/L	4.000/12.000	1.73L

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 19
Patient Number: 1911
Treatment Group: NON-RAND

Lab Test	Units	Low/High Reference	VISIT 1
Complete Blood Count			
HEMOGLOBIN	mml/L-Fe	6.520/8.380	9.00H
LYMPHOCYTES	GI/L	4.000/12.000	2.59L
EOSINOPHILS	GI/L	0.000/0.570	0.70H
Blood Chemistry			
TOTAL PROTEIN	g/L	55.000/71.000	78H

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 19
Patient Number: 1912
Treatment Group: NON-RAND

Lab Test	Units	Low/High Reference	VISIT 1
Complete Blood Count			
LYMPHOCYTES	GI/L	4.000/12.000	2.12L
Thyroids			
THYROXINE, TOTAL-T4	nmol/L	93.000/201.000	80L

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 19
Patient Number: 1913
Treatment Group: Placebo

Lab Test	Units	Low/High Reference	VISIT 1
Complete Blood Count			
HEMATOCRIT	1	0.340/0.480	
HEMOGLOBIN	mml/L-Fe	7.200/10.180	
ERYTHROCYTE COUNT	TI/L	4.100/5.600	4.00L
Blood Chemistry			
CREATINE PHOSPHOKINASE	U/L	53.000/269.000	49L
URIC ACID	umol/L	202.000/535.000	
Urinalysis			
UA-YEAST	NO UNITS		1 A
UA-BACTERIA	NO UNITS		1 A

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 19
Patient Number: 1913
Treatment Group: Placebo

Lab Test	Units	Low/High Reference	VISIT 15
Complete Blood Count			
HEMATOCRIT	1	0.340/0.480	0.330L
HEMOGLOBIN	mml/L-Fe	7.200/10.180	7.07L
ERYTHROCYTE COUNT	TI/L	4.100/5.600	3.80L
Blood Chemistry			
CREATINE PHOSPHOKINASE	U/L	53.000/269.000	46L
URIC ACID	umol/L	202.000/535.000	190L
Urinalysis			
UA-YEAST	NO UNITS		
UA-BACTERIA	NO UNITS		1 A

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 19
Patient Number: 1914
Treatment Group: Placebo

Lab Test	Units	Low/High Reference	VISIT 1
Complete Blood Count			
PLATELET COUNT	GI/L	140.000/400.000	427H
Blood Chemistry			
AST/SGOT	U/L	10.000/40.000	51.0H
ALT/SGPT	U/L	6.000/34.000	50.0H
ALKALINE PHOSPHATASE	U/L	51.000/300.000	342H
Urinalysis			
UA-RBC	NO UNITS		
UA-OCCULT BLOOD	NO UNITS		

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 19
Patient Number: 1914
Treatment Group: Placebo

Lab Test	Units	Low/High Reference	VISIT 15	
Complete Blood Count				
PLATELET COUNT	GI/L	140.000/400.000	415H	
Blood Chemistry				
AST/SGOT	U/L	10.000/40.000		
ALT/SGPT	U/L	6.000/34.000		
ALKALINE PHOSPHATASE	U/L	51.000/300.000		
Urinalysis				
UA-RBC	NO UNITS		4	A
UA-OCCULT BLOOD	NO UNITS		3	A

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 19
Patient Number: 1915
Treatment Group: Flx

Lab Test	Units	Low/High Reference	VISIT 1
Blood Chemistry			
CREATINE PHOSPHOKINASE	U/L	53.000/269.000	324H

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 19
Patient Number: 1918
Treatment Group: Placebo

Lab Test	Units	Low/High Reference	VISIT 1	
Blood Chemistry				
ALKALINE PHOSPHATASE	U/L	50.000/250.000	369H	
CHOLESTEROL	mmol/L	2.950/5.120		
Electrolytes				
BICARBONATE, HCO3	mmol/L	17.000/30.600		
Urinalysis				
UA-KETONES	NO UNITS		1	A

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 19
Patient Number: 1918
Treatment Group: Placebo

Lab Test	Units	Low/High Reference	VISIT 15
Blood Chemistry			
ALKALINE PHOSPHATASE	U/L	50.000/250.000	313H
CHOLESTEROL	mmol/L	2.950/5.120	5.22H
Electrolytes			
BICARBONATE, HCO3	mmol/L	17.000/30.600	31.1H
Urinalysis			
UA-KETONES	NO UNITS		

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 19
Patient Number: 1919
Treatment Group: Flx

Lab Test	Units	Low/High Reference	VISIT 1
Blood Chemistry			
CHOLESTEROL	mmol/L	3.230/5.480	3.08L

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 19
Patient Number: 1919
Treatment Group: Flx

Lab Test	Units	Low/High Reference	VISIT 15
Blood Chemistry			
CHOLESTEROL	mmol/L	3.230/5.480	2.87L

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 19
Patient Number: 1920
Treatment Group: NON-RAND

Lab Test	Units	Low/High Reference	VISIT 1
Complete Blood Count			
HEMOGLOBIN	mml/L-Fe	6.520/8.380	8.87H
LEUKOCYTE COUNT	GI/L	6.000/11.000	5.4L
NEUTROPHILS, SEGMENTED	GI/L	4.000/13.500	3.24L
LYMPHOCYTES	GI/L	4.000/12.000	1.61L
Urinalysis			
UA-SPECIFIC GRAVITY	NO UNITS	1.010/1.034	1.007L

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 19
Patient Number: 1921
Treatment Group: Flx

Lab Test	Units	Low/High Reference	VISIT 1
Blood Chemistry			
URIC ACID	umol/L	202.000/535.000	190L
Urinalysis			
UA-BACTERIA	NO UNITS	1	A

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 19
Patient Number: 1922
Treatment Group: NON-RAND

Lab Test	Units	Low/High Reference	VISIT 1
Complete Blood Count			
LEUKOCYTE COUNT	GI/L	6.000/11.000	5.3L
NEUTROPHILS, SEGMENTED	GI/L	4.000/13.500	2.58L
LYMPHOCYTES	GI/L	4.000/12.000	2.08L
Blood Chemistry			
TOTAL PROTEIN	g/L	55.000/71.000	75H
Thyroids			
THYROXINE, TOTAL-T4	nmol/L	93.000/201.000	82L

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 19
Patient Number: 1923
Treatment Group: NON-RAND

Lab Test	Units	Low/High Reference	VISIT 1
Complete Blood Count			
HEMOGLOBIN	mml/L-Fe	6.520/8.380	8.63H
LYMPHOCYTES	GI/L	4.000/12.000	1.38L
Blood Chemistry			
TOTAL PROTEIN	g/L	55.000/71.000	73H
Electrolytes			
BICARBONATE, HCO3	mmol/L	12.000/28.000	29.8H

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 19
Patient Number: 1924
Treatment Group: Flx

Lab Test	Units	Low/High Reference	VISIT 1
Blood Chemistry			
AST/SGOT	U/L	10.000/40.000	43.0H
CREATINE PHOSPHOKINASE	U/L	94.000/499.000	
Urinalysis			
UA-SPECIFIC GRAVITY	NO UNITS	1.010/1.034	

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 19
Patient Number: 1924
Treatment Group: Flx

Lab Test	Units	Low/High Reference	VISIT 15
Blood Chemistry			
AST/SGOT	U/L	10.000/40.000	53.0H
CREATINE PHOSPHOKINASE	U/L	94.000/499.000	912H
Urinalysis			
UA-SPECIFIC GRAVITY	NO UNITS	1.010/1.034	1.009L

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 19
Patient Number: 1926
Treatment Group: NON-RAND

Lab Test	Units	Low/High Reference	VISIT 1
Complete Blood Count			
HEMOGLOBIN	mml/L-Fe	6.520/8.380	8.75H
NEUTROPHILS, SEGMENTED	GI/L	4.000/13.500	2.38L
EOSINOPHILS	GI/L	0.000/0.570	0.63H
Blood Chemistry			
TOTAL PROTEIN	g/L	55.000/71.000	74H

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 19
Patient Number: 1927
Treatment Group: Placebo

Lab Test	Units	Low/High Reference	VISIT 1
Complete Blood Count			
NEUTROPHILS, SEGMENTED	GI/L	1.350/8.150	
MONOCYTES	GI/L	0.120/0.920	
Blood Chemistry			
CHOLESTEROL	mmol/L	3.150/5.400	2.95L
Urinalysis			
UA-PROTEIN	NO UNITS		1 A
UA-KETONES	NO UNITS		1 A

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 19
Patient Number: 1927
Treatment Group: Placebo

Lab Test	Units	Low/High Reference	VISIT 15
Complete Blood Count			
NEUTROPHILS, SEGMENTED	GI/L	1.350/8.150	8.60H
MONOCYTES	GI/L	0.120/0.920	1.03H
Blood Chemistry			
CHOLESTEROL	mmol/L	3.150/5.400	
Urinalysis			
UA-PROTEIN	NO UNITS		
UA-KETONES	NO UNITS		

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 19
Patient Number: 1928
Treatment Group: NON-RAND

Lab Test	Units	Low/High Reference	VISIT 1
Complete Blood Count			
HEMOGLOBIN	mml/L-Fe	6.520/8.380	8.81H
LEUKOCYTE COUNT	GI/L	6.000/11.000	4.8L
NEUTROPHILS, SEGMENTED	GI/L	4.000/13.500	2.26L
LYMPHOCYTES	GI/L	4.000/12.000	2.11L

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 19
Patient Number: 1929
Treatment Group: NON-RAND

Lab Test	Units	Low/High Reference	VISIT 1
Complete Blood Count			
HEMOGLOBIN	mml/L-Fe	6.520/8.380	9.68H
LEUKOCYTE COUNT	GI/L	6.000/11.000	4.5L
NEUTROPHILS, SEGMENTED	GI/L	4.000/13.500	2.20L
LYMPHOCYTES	GI/L	4.000/12.000	1.91L
PLATELET COUNT	GI/L	200.000/400.000	188L
Thyroids			
THYROXINE, TOTAL-T4	nmol/L	93.000/201.000	80L
UDS			
MARIJUANA (THC)	NO UNITS		POS A

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 19
Patient Number: 1930
Treatment Group: NON-RAND

Lab Test	Units	Low/High Reference	VISIT 1
Complete Blood Count			
LYMPHOCYTES	GI/L	4.000/12.000	2.78L

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 21
Patient Number: 2101
Treatment Group: NON-RAND

Lab Test	Units	Low/High Reference	VISIT 1
Complete Blood Count			
HEMOGLOBIN	mml/L-Fe	6.520/8.380	9.18H
LYMPHOCYTES	GI/L	4.000/12.000	1.74L
Blood Chemistry			
TOTAL PROTEIN	g/L	55.000/71.000	74H
Urinalysis			
UA-RBC	NO UNITS		2 A
UA-OCCULT BLOOD	NO UNITS		3 A

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 22
Patient Number: 2201
Treatment Group: Placebo

Lab Test	Units	Low/High Reference	VISIT 1
Complete Blood Count			
EOSINOPHILS	GI/L	0.000/0.570	0.58H
PLATELET COUNT	GI/L	130.000/394.000	433H
Blood Chemistry			
CREATINE PHOSPHOKINASE	U/L	150.000/489.000	144L

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 22
Patient Number: 2202
Treatment Group: Flx

Lab Test	Units	Low/High Reference	VISIT 1
Complete Blood Count			
LEUKOCYTE COUNT	GI/L	4.350/13.650	3.9L
NEUTROPHILS, SEGMENTED	GI/L	1.350/8.150	1.18L
Urinalysis			
UA-SPECIFIC GRAVITY	NO UNITS	1.010/1.034	

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 22
Patient Number: 2202
Treatment Group: Flx

Lab Test	Units	Low/High Reference	VISIT 14
Complete Blood Count			
LEUKOCYTE COUNT	GI/L	4.350/13.650	
NEUTROPHILS, SEGMENTED	GI/L	1.350/8.150	
Urinalysis			
UA-SPECIFIC GRAVITY	NO UNITS	1.010/1.034	1.009L

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 22
Patient Number: 2203
Treatment Group: Placebo

Lab Test	Units	Low/High Reference	VISIT 1	
Urinalysis				
UA-PROTEIN	NO UNITS		1	A

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 22
Patient Number: 2204
Treatment Group: Flx

Lab Test	Units	Low/High Reference	VISIT 1
Blood Chemistry			
CREATINE PHOSPHOKINASE	U/L	150.000/489.000	147L

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 22
Patient Number: 2204
Treatment Group: Flx

Lab Test	Units	Low/High Reference	VISIT 15
Blood Chemistry			
CREATINE PHOSPHOKINASE	U/L	150.000/489.000	115L

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 22
Patient Number: 2205
Treatment Group: Flx

Lab Test	Units	Low/High Reference	VISIT 1
Complete Blood Count			
EOSINOPHILS	GI/L	0.000/0.570	
Thyroids			
THYROXINE, TOTAL-T4	nmol/L	82.000/171.000	73L

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 22
Patient Number: 2205
Treatment Group: Flx

Lab Test	Units	Low/High Reference	VISIT 15
Complete Blood Count			
EOSINOPHILS	GI/L	0.000/0.570	0.64H
Thyroids			
THYROXINE, TOTAL-T4	nmol/L	82.000/171.000	

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 22
Patient Number: 2206
Treatment Group: Placebo

Lab Test	Units	Low/High Reference	VISIT 1
Blood Chemistry			
CREATINE PHOSPHOKINASE	U/L	150.000/489.000	80L
CHOLESTEROL	mmol/L	3.360/5.280	
Thyroids			
THYROXINE, TOTAL-T4	nmol/L	82.000/171.000	76L

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 22
Patient Number: 2206
Treatment Group: Placebo

Lab Test	Units	Low/High Reference	VISIT 15
Blood Chemistry			
CREATINE PHOSPHOKINASE	U/L	150.000/489.000	82L
CHOLESTEROL	mmol/L	3.360/5.280	3.03L
Thyroids			
THYROXINE, TOTAL-T4	nmol/L	82.000/171.000	

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 22
Patient Number: 2207
Treatment Group: Placebo

Lab Test	Units	Low/High Reference	VISIT 1
Blood Chemistry			
CREATINE PHOSPHOKINASE	U/L	150.000/489.000	91L
BILIRUBIN, TOTAL	umol/L	3.000/21.000	

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 22
Patient Number: 2207
Treatment Group: Placebo

Lab Test	Units	Low/High Reference	VISIT 15
Blood Chemistry			
CREATINE PHOSPHOKINASE	U/L	150.000/489.000	139L
BILIRUBIN, TOTAL	umol/L	3.000/21.000	

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 22
Patient Number: 2208
Treatment Group: Flx

Lab Test	Units	Low/High Reference	VISIT 1	
Complete Blood Count				
MEAN CELL VOLUME (MCV)	fL	76.000/93.000		
ANISOCYTOSIS	NO UNITS			
POLYCHROMIA	NO UNITS			
Blood Chemistry				
CHOLESTEROL	mmol/L	3.360/5.280		
Urinalysis				
UA-SPECIFIC GRAVITY	NO UNITS	1.010/1.034		
UA-PROTEIN	NO UNITS		1	A
UA-KETONES	NO UNITS			

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 22
Patient Number: 2208
Treatment Group: Flx

Lab Test	Units	Low/High Reference	VISIT 15
Complete Blood Count			
MEAN CELL VOLUME (MCV)	fL	76.000/93.000	74L
ANISOCYTOSIS	NO UNITS		1 A
POLYCHROMIA	NO UNITS		1 A
Blood Chemistry			
CHOLESTEROL	mmol/L	3.360/5.280	5.77H
Urinalysis			
UA-SPECIFIC GRAVITY	NO UNITS	1.010/1.034	1.036H
UA-PROTEIN	NO UNITS		1 A
UA-KETONES	NO UNITS		1 A

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 22
Patient Number: 2209
Treatment Group: NON-RAND

Lab Test	Units	Low/High Reference	VISIT 1
Complete Blood Count			
LEUKOCYTE COUNT	GI/L	6.000/11.000	11.5H
MICROCYTOSIS	NO UNITS		1 A
HYPOCHROMIA	NO UNITS		1 A
Blood Chemistry			
TOTAL PROTEIN	g/L	55.000/71.000	80H

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 22
Patient Number: 2210
Treatment Group: Placebo

Lab Test	Units	Low/High Reference	VISIT 1	
Urinalysis				
UA-OCCULT BLOOD	NO UNITS		1	A

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 22
Patient Number: 2211
Treatment Group: NON-RAND

Lab Test	Units	Low/High Reference	VISIT 1
Complete Blood Count			
HEMOGLOBIN	mml/L-Fe	6.520/8.380	9.93H
LEUKOCYTE COUNT	GI/L	6.000/11.000	5.4L
NEUTROPHILS, SEGMENTED	GI/L	4.000/13.500	3.57L
LYMPHOCYTES	GI/L	4.000/12.000	1.46L
PLATELET COUNT	GI/L	200.000/400.000	169L
Blood Chemistry			
TOTAL PROTEIN	g/L	55.000/71.000	74H

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 22
Patient Number: 2212
Treatment Group: Placebo

Lab Test	Units	Low/High Reference	VISIT 1	
Blood Chemistry				
GGT (GGPT/SGGT/YGGT)	U/L	0.000/51.000	66.0H	
UDS				
MARIJUANA (THC)	NO UNITS		POS	A

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 22
Patient Number: 2213
Treatment Group: Placebo

Lab Test	Units	Low/High Reference	VISIT 1
Complete Blood Count			
PLATELET COUNT	GI/L	130.000/394.000	
Blood Chemistry			
CREATINE PHOSPHOKINASE	U/L	91.000/391.000	74L
INORGANIC PHOSPHORUS	mmol/L	1.000/1.940	
Electrolytes			
BICARBONATE, HCO3	mmol/L	17.000/30.600	
Urinalysis			
UA-WBC	NO UNITS		2 A
UA-BACTERIA	NO UNITS		1 A

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 22
Patient Number: 2213
Treatment Group: Placebo

Lab Test	Units	Low/High Reference	VISIT 10
Complete Blood Count			
PLATELET COUNT	GI/L	130.000/394.000	461H
Blood Chemistry			
CREATINE PHOSPHOKINASE	U/L	91.000/391.000	27L
INORGANIC PHOSPHORUS	mmol/L	1.000/1.940	2.03H
Electrolytes			
BICARBONATE, HCO3	mmol/L	17.000/30.600	31.1H
Urinalysis			
UA-WBC	NO UNITS	2	A
UA-BACTERIA	NO UNITS		

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 22
Patient Number: 2214
Treatment Group: Flx

Lab Test	Units	Low/High Reference	VISIT 1
Complete Blood Count			
EOSINOPHILS	GI/L	0.000/0.570	
MEAN CELL VOLUME (MCV)	fL	79.000/96.000	
ANISOCYTOSIS	NO UNITS		
Blood Chemistry			
ALKALINE PHOSPHATASE	U/L	95.000/385.000	445H
CHOLESTEROL	mmol/L	3.360/5.280	2.87L
Urinalysis			
UA-KETONES	NO UNITS		1 A

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 22
Patient Number: 2214
Treatment Group: Flx

Lab Test	Units	Low/High Reference	VISIT 15
Complete Blood Count			
EOSINOPHILS	GI/L	0.000/0.570	0.64H
MEAN CELL VOLUME (MCV)	fL	79.000/96.000	78L
ANISOCYTOSIS	NO UNITS		1 A
Blood Chemistry			
ALKALINE PHOSPHATASE	U/L	95.000/385.000	
CHOLESTEROL	mmol/L	3.360/5.280	3.13L
Urinalysis			
UA-KETONES	NO UNITS		

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 22
Patient Number: 2215
Treatment Group: NON-RAND

Lab Test	Units	Low/High Reference	VISIT 1
Complete Blood Count			
LEUKOCYTE COUNT	GI/L	6.000/11.000	4.0L
NEUTROPHILS, SEGMENTED	GI/L	4.000/13.500	1.80L
LYMPHOCYTES	GI/L	4.000/12.000	1.85L

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 22
Patient Number: 2216
Treatment Group: Flx

Lab Test	Units	Low/High Reference	VISIT 1	
Urinalysis				
UA-BACTERIA	NO UNITS		1	A

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 22
Patient Number: 2217
Treatment Group: Placebo

Lab Test	Units	Low/High Reference	VISIT 1
Complete Blood Count			
EOSINOPHILS	GI/L	0.000/0.570	
MICROCYTOSIS	NO UNITS		
Blood Chemistry			
CREATINE PHOSPHOKINASE	U/L	150.000/489.000	120L

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 22
Patient Number: 2217
Treatment Group: Placebo

Lab Test	Units	Low/High Reference	VISIT 15
Complete Blood Count			
EOSINOPHILS	GI/L	0.000/0.570	0.63H
MICROCYTOSIS	NO UNITS	1	A
Blood Chemistry			
CREATINE PHOSPHOKINASE	U/L	150.000/489.000	83L

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 22
Patient Number: 2218
Treatment Group: Placebo

Lab Test	Units	Low/High Reference	VISIT 1
Blood Chemistry			
ALKALINE PHOSPHATASE	U/L	51.000/300.000	333H
Urinalysis			
UA-SPECIFIC GRAVITY	NO UNITS	1.010/1.034	

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 22
Patient Number: 2218
Treatment Group: Placebo

Lab Test	Units	Low/High Reference	VISIT 15
Blood Chemistry			
ALKALINE PHOSPHATASE	U/L	51.000/300.000	350H
Urinalysis			
UA-SPECIFIC GRAVITY	NO UNITS	1.010/1.034	1.038H

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 22
Patient Number: 2219
Treatment Group: NON-RAND

Lab Test	Units	Low/High Reference	VISIT 1
Complete Blood Count			
NEUTROPHILS, SEGMENTED	GI/L	4.000/13.500	3.46L
LYMPHOCYTES	GI/L	4.000/12.000	2.34L
Thyroids			
THYROXINE, TOTAL-T4	nmol/L	93.000/201.000	91L
THYROID STIM. HORMONE	mU/L	0.320/5.000	27.95H
			24.16H

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 22
Patient Number: 2220
Treatment Group: Flx

Lab Test	Units	Low/High Reference	VISIT 1
Blood Chemistry			
CREATININE	umol/L	35.000/88.000	97H
CHOLESTEROL	mmol/L	3.210/5.610	6.10H
Urinalysis			
UA-SPECIFIC GRAVITY	NO UNITS	1.010/1.034	1.036H

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (continued)

Protocol: B1Y-MC-HCJE
Investigator Number: 22
Patient Number: 2220
Treatment Group: Flx

Lab Test	Units	Low/High Reference	VISIT 14
Blood Chemistry			
CREATININE	umol/L	35.000/88.000	
CHOLESTEROL	mmol/L	3.210/5.610	5.72H
Urinalysis			
UA-SPECIFIC GRAVITY	NO UNITS	1.010/1.034	

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

Table 14.69. Listing of Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-HCJE (concluded)

Protocol: B1Y-MC-HCJE
Investigator Number: 22
Patient Number: 2221
Treatment Group: Placebo

Lab Test	Units	Low/High Reference	VISIT 1	
Urinalysis				
UA-KETONES	NO UNITS		1	A

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3JEAA)
RMP.B1YO.HCJEREP(LAL3JEAA)
XLAL0003

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16. Appendices

16.1.
Study Information

16.1.1 Protocol and Protocol Amendments

16.1.2. Sample Clinical Report Form

16.1.3. List of Investigators and Other Key Individuals

16.1.4. Signature of Investigator
or Sponsor's Responsible Medical Officer

16.1.5. Randomization Scheme and Codes

16.1.6. Documentation of Statistical Methods

16.1.7. Publications Based on the Study

16.1.8. Important Publications Referenced in the Report

16.1.9. Ethical Review Board Information and Protocol-Specific Informed Consent Document

16.1.10. Listing of Patients Receiving Test Drug(s) or Investigational Product(s) From Specific Batches

16.1.11. Audit Certificates

16.1.12. Documentation of Inter-Laboratory
Standardization Methods
and Quality Assurance Procedures if Used

16.1.13. Errors to the Locked Database

16.1.14 Blinding Plan and Data Monitoring Board Information

16.1.15 Pharmacokinetic Dataset

16.1.16 LC/MS Method and Validation for the Determination of Fluoxetine and Norfluoxetine in Human Plasma

16.1.1.
Protocol and Protocol Amendments

Protocol Amendment Summary B1Y-MC-HCJE(a) Fluoxetine Versus Placebo in Childhood/Adolescent Depression

Confidential Information

The information contained in this protocol amendment summary is confidential and is intended for the use of clinical investigators. It is the property of Eli Lilly and Company or its subsidiaries and should not be copied by or distributed to persons not involved in the clinical investigation of fluoxetine hydrochloride (LY110140), unless such persons are bound by a confidentiality agreement with Eli Lilly and Company or its subsidiaries.

Note to Investigators: The new protocol is indicated by Amendment (**a**) Approved by Lilly: **30 June 1998** on the bottom of every page. Amendment (**a**) will be used to conduct the study in place of any preceding version of this protocol.

Overview

The overall changes and rationale for the changes made to this protocol are as follows:

- Section 2.1 and Section 2.2:

  The primary and the first of the secondary objectives have been interchanged.

  The primary objective was originally constructed to compare all doses of fluoxetine (20-60mg/day) allowed in the study with placebo, over a range of treatment durations bound by the minimum and maximum durations of acute treatment allowed in the protocol, 8-19 weeks.

  This inclusive design was chosen to permit efficacy comparisons in the absence of extensive dosing information and in the presence of widely varying findings regarding the minimum "adequate treatment trial" duration required to achieve an antidepressant response in this population.

  A secondary objective was originally constructed to conduct an analysis of fluoxetine vs. placebo in the same format as was conducted in the [redacted] trial, 20mg/day for 8 weeks, in order to attempt to replicate [redacted] findings.

  Following discussion with the Neuropharmacology Division of the FDA regarding the appropriateness of the study design, the Lilly team agreed to accept the principal suggestion regarding the analysis plan which was to reverse the primary and secondary objectives. This will make the primary objective more succinct and the interpretation of the study results less complex. The more inclusive comparison will be preserved as a secondary objective.

- Section 3.1.1

  a) Language in this section has been updated to clarify that separate diagnostic interviewers will be conducting interviews at each of the three initial visits, to specify more clearly which instruments must be done by different raters, and to clarify when instruments must be reviewed rather than re-administered in their entirety.

b) The MAGIC (hard copy), the DICA (hard copy), or the new, electronic version of the DICA (DICA-IV) shall be equally sufficient for the diagnostic interviews.

At the time of original protocol approval, the MAGIC version of the DICA was chosen as the diagnostic instrument for reasons of timeliness and convenience of copyright permission, while awaiting availability of the most recent electronic DICA. Since the time of protocol approval, a validated, newer and more "user friendly" electronic version of the DICA has become available. This amendment will allow for use of either the MAGIC or the DICA, (in hard copy or electronic form). The DICA is the fundamental instrument from which the MAGIC was derived. The principal difference is that the latter includes genetic information of no consequence to the conduct of this study. This should greatly reduce the time required to conduct the first three diagnostic interviews, yet preserve the standardized assessment.

c) Text was added to clarify that although not depicted in the study illustration, the placebo group will go through the same decision tree algorithm as the active treatment group.

- <u>Section 3.1.2.</u>

  Text was added to clarify that Visit 1 is to be used as the baseline visit when assessing placebo response using the CGI-Improvement at Visit 4.

- <u>Section 3.1.5.</u>

Text was added to clarify that the implementation of the optional dose increase to 60mg at Visit 12 is based on clinical judgment.

- <u>Section 3.4.2.2</u>

  Exclusion criterion 26 has been corrected. The method of sampling for antidepressants will be urine screen rather than blood draw.

- Section 3.4.3

  a) Electronic and paper versions of the MAGIC/DICA diagnostic instrument are both allowed. (See rationale of changes in section 3.1.1)

  b) The second paragraph has been corrected. Raters will not be blinded to the findings of the FHRDC.

- Section 3.4.4

  Change was made to reflect the different dosing regimen for the primary analysis and to specify more clearly that the baseline visit is Visit 4 and the endpoint visit is the last measurement taken from Visits 6 through 10.

- Section 3.7

  The first paragraph has been corrected. In order to facilitate consensus diagnosis, separate diagnostic interviewers must not be blinded to one another's findings. The objective is to provide three, separate diagnostic opportunities.

- Section 3.9.3.2.2

  Overdose has been deleted as one of the outcomes listed as a Serious Adverse Event. The change was made to comply with the new guidelines issued by the FDA on what constitutes a serious adverse event.

- Section 4.1

  Patients who have their dose reduced to 10mg will be included in analysis of "all doses" as if they remained on 20mg.

  This clarifies how the patients whose doses were reduced to 10mg/day will be handled in the data analysis. "As if they remained on 20/mg/day" is, in effect, an intent to treat format, since anyone on 10 mg will have been randomized to and have failed to tolerate 20 mg.

- Section 4.4

A clause has been added to clarify that the analysis of covariance is a secondary analysis.

- Section 4.5.1

  Changes were made to reflect the difference in what is considered primary versus secondary. A repeated measures analysis was added to the analysis plan. The models for the ANOVA and logistic regression were clarified.

- Section 4.8

  These changes modify description of the interim analysis plan to be consistent with the above adjustment of primary versus secondary analyses' dose ranges and endpoints.

- Attachment HCJE.1. Schedule of Events

  These corrections reflect use of either the MAGIC or the DICA, hard copy or electronic format are allowable, and that the sample for determination of the presence of antidepressant shall be a urine drug screen instead of a blood draw.

- Attachment HCJE.2.

  This diagram shall be deleted because it has caused undue confusion. Options for staffing in order to provide separate interviewers in the diagnostic phase of the trial was extensively reviewed at the start up meeting and is being monitored by the regional managers and study monitors.

- Minor style, formatting and reference changes throughout the protocol.

Revised Protocol Sections

Note:	**The page numbers listed are the "Document Page" numbers found in the lower left corner of the page in the revised protocol.** All deletions have been identified by ~~strikethroughs~~ All additions have been identified by the use of underscore
Example:	The period of time between Visits 2 and 3 will be 4 to 6~~5~~ months.

2.1. Primary Objective (page 7)

The primary objective of this study is as follows:

- To test the hypothesis that fluoxetine 20 ~~to 60~~ mg is more effective than placebo in the treatment of children (aged 8 to <13 years) and adolescents (aged 13 to <18 years) with DSM-IV major depression as measured by response rates on the Children's Depression Rating Scale-Revised (CDRS-R) after up to 9~~19~~ weeks, defined as a decrease of at least 30% in the CDRS-R score from baseline to endpoint.

2.2. Secondary Objectives (page 7)

The secondary objectives of the study are as follows:

- To compare the efficacy of fluoxetine 20 to 60 mg with placebo in the treatment of childhood/adolescent depression as measured by response rates on the CDRS-R after up to 19 weeks.

3.1. Summary of Study Design (page 9)

This will be a multicenter, randomized, double-blind, two-arm, parallel study. Fluoxetine will be compared with placebo for efficacy and safety in approximately 220 children and adolescents with depression.

The study will have two general phases, an acute treatment phase and a relapse prevention phase. The 19-week acute treatment phase will consist of five study periods. The 32-week relapse prevention phase (not shown in the illustration) was designed to examine relapse prevention and will follow the acute treatment phase. The acute treatment study design is illustrated in Figure HCJE.1. Although not depicted in the study illustration, all the decision processes made throughout the study will be done for both the fluoxetine and placebo therapy groups to maintain the study blind.

Figure HCJE.1. Illustration of Study Design for Protocol B1Y-MC-HCJE (page 10)

Three diagnostic interviews will be conducted during Study Period I, the diagnostic evaluation phase. Patients who meet the inclusion/exclusion criteria will enter Study Period II, a 1-week placebo washout phase. Patients who do not respond to placebo will enter Study Period III, a 1-week adaptation phase. Patients who can tolerate study medication~~fluoxetine 10 mg~~ will enter Study Period IV, an
8-week fixed-dose phase. After 8 weeks of treatment ~~with fluoxetine 20 mg~~, patients will be evaluated for response status. Responders will remain on fluoxetine 20 mg or placebo during Study Period V. Fluoxetine n~~N~~onresponders will be rerandomized to either remain on fluoxetine 20 mg or to receive fluoxetine 40 mg with an option to titrate to 60 mg during this titration phase. Placebo nonresponders will remain on placebo. Patients who respond to treatment will enter Study Period VI, a 32-week relapse prevention phase.

3.1.1. Study Period I: Diagnostic Evaluation Phase (page 11)

Study Period I will be a 2-week diagnostic evaluation period. This period will begin with Visit 1 and end with Visit 3. The visits will be scheduled weekly (6 to 9 days).

Visits 1, 2, and 3 will serve as diagnostic evaluation visits. At least three separate ~~designated~~ diagnostic interviewers will be required at each site. ~~Each interview will be conducted by a different combination of interviewers (see Protocol Attachment HCJE.2).~~

At each diagnostic evaluation visit, the child and parents will be interviewed both separately and together. The family history will be reviewed at each clinical assessment because often more information becomes available with progressive interviews.

At the first interview (Visit 1), the nature of the study will be fully explained to the patients and their parent/legal guardian(s). After written informed consent has been given by the patients and parent/legal guardian(s), each patient will undergo a psychological and a physical examination to determine whether all inclusion/exclusion criteria are met.

The parents will respond to the Missouri Assessment of Genetics Interview for Children (MAGIC) parent version, {The MAGIC was adapted from the Diagnostic Interview for Children and Adolescents (DICA)}or to the Diagnostic Interview for Children and Adolescents (either hard copy or electronic copy will be acceptable), questions regarding significant historical diagnoses and the patient's psychiatric history, the Children's Depression Rating Scale-Revised (CDRS-R) and the modified ~~f~~Family ~~h~~History Research Diagnostic Criteria (FHRDC). The MAGIC or DICA ~~DICA and RDC will be~~ will be conducted/reviewed by a separate interviewers for each of the three diagnostic visits. ~~who will be blinded to the findings of the other~~.

The patient will respond to the MAGIC or DICA ~~DICA~~, the CDRS-R and either the CDI (children), or the BDI (adolescents) based on their age.

The patients and their parent/legal guardian(s) will complete the ~~CDRS-R, CGI,~~ HAMA, and MADRS together.

Results from safety evaluations, including the physical examination, ECG, laboratory tests, ~~measurement of~~ urine screen for fluoxetine/norfluoxetine levels and other antidepressants , and a urine drug screen must be available by Visit 2. The urine drug screen results must be negative before a patient may be enrolled in Study Period II. If the results of the urine drug screen are abnormal, the patient may be retested once. If results of the second urine drug screen are positive, the patient may not be enrolled in the study.

If all entry criteria are met at Visit 1, an additional interview will be scheduled 1 week later.

The second interview (Visit 2) will be conducted by a different ~~another pair of the three~~ interviewers and will be independent from the previous psychiatric assessment. The primary interviewer (different than primary interviewer at Visit 1) will review the MAGIC or DICA ~~DICA~~, significant historical diagnoses, and the patient's psychiatric history. ~~A second independent interviewer will review the modified family history RDC.~~ ~~Parent and~~ P~~p~~atient self-report measures will be repeated and the CDRS-R and the K-SADS will be administered. If all entry criteria are met, an additional interview will be scheduled 1 week later.

The third interview (Visit 3) will be conducted by a different ~~another pair of the three~~ interviewers and will be independent from the two previous psychiatric assessments. Again, the primary interviewer for the visit (different than Visit 1 or Visit 2)will review the MAGIC or DICA ~~DICA~~, significant historical diagnoses, and the patient's psychiatric history. ~~A second independent~~ An interviewer will review the ~~modified family history~~ FHRDC. ~~Parent and~~ P~~p~~atient self-report measures will be repeated and the CDRS-R and the K-SADS will be administered.

3.1.2. Study Period II: Placebo Washout Phase (page 12)

~~.~~…Patients who respond to placebo (defined as a ≥30% decrease in CDRS-R score from Visit 3 to Visit 4 or a CGI-Improvement score of 1 or 2 at Visit 4 as compared to Visit 1) will be discontinued.

3.1.5. Study Period V: Titration Phase (page 13)

Patients who are rerandomized to the fluoxetine 40 mg arm and fail to respond (based on CGI-Improvement score) after 4 weeks of treatment with fluoxetine 40 mg will have the

option to undergo an additional dosage increase to fluoxetine 60 mg. Whether or not the optional dose increase is implemented will be based on a clinical decision made by the investigator.

3.4.2.2. Exclusion Criteria (page 17 and 18)

Patients will be excluded from the study for **any** of the following reasons:

[26] Receipt of fluoxetine within 3 months prior to study entry.
Note: Patients who have detectable levels of fluoxetine, norfluoxetine, or any other antidepressant in their initial urine screen~~blood draw~~ will be discontinued.

[27] Regular use of other psychotropic or centrally-acting drugs, including lithium and the psychostimulants (ie, drugs normally prescribed for depression, mania, anxiety, insomnia, attention deficit disorder, or psychosis) within 2 weeks prior to study entry that would need to be continued during the study. (The list of excluded medications is located in Appendix HCJE.~~3~~2.)

3.4.3. Disease Diagnostic Criteria (page 18)

The MAGIC (Reich and Todd et al. 1997) or DICA (Herjanic and Reich 1982; Welner et al. 1987)~~DICA (Herjanic and Reich 1982; Welner et al. 1987)~~ will be used by each of three independent diagnostic interviewers to establish a diagnosis of major depression and to exclude other psychiatric illnesses. This structured interview is consistent with the DSM-IV diagnostic criteria for major depressive disorder and consists of two separate interviews with different formats for patients and parents.

The F~~f~~amily H~~h~~istory RDC (Endicott and Andreasen et al. 1977) will be used to collect additional information. ~~The interviewer performing the DICA at each diagnostic evaluation visit will be blinded to the findings of the family history RDC.~~

Because the MAGIC or DICA ~~DICA~~ does not assess symptom severity, the depression items from the K-SADS-PL (Kaufman et al. 1996) ~~(Endicott and Spitzer 1978; Puig-Antich and Chambers 1978; Chambers et al. 1985)~~ will be used as a supplemental diagnostic instrument.

3.4.4. Sample Size (page 19)

The total number of randomized patients to be included in this study is approximately 220 patients or 110 patients per arm. The sample size is designed to detect a difference in the proportion of patients responding of 20 percentage points between fluoxetine 20 ~~to 60~~ mg and placebo with approximately 80% power and a 0.05 significance level (two-sided). Response is defined as at least a 30% decrease in the CDRS-R score from baseline (Visit

4) to endpoint (last measurement from Visits 6 through 10) for patients treated at least a week with 20 mg (2 weeks total).

3.5. Patient Assignment (page 19)

…Randomization at Visit 4 will be stratified by gender and age category (child versus adolescent) ~~for each~~ across investigative~~or~~ sites.

3.7. Blinding (page 22)

~~In order to obtain the most rigorous consensus diagnosis, each of the three diagnostic interviewers will be blinded to the findings of the other two during the diagnostic evaluation phase.~~

3.9.2. Pharmacokinetics (page 25)

Formal pharmacokinetic data will not be collected. Baseline fluoxetine serum concentrations will be assayed. Fluoxetine, norfluoxetine, and other antidepressants and their metabolites must be nondetectable by urine screen at baseline for inclusion into the study.

3.9.3.2.2. Serious Adverse Events (page 26)

Study site personnel must report to Lilly immediately, by telephone, any adverse event from this study that includes one of the following criteria:

- Death
- Initial or prolonged inpatient hospitalization
- Is life-threatening
- Severe or permanent disability
- Cancer (other than cancers diagnosed prior to enrollment in studies involving patients with cancer)
- Congenital anomaly
- ~~Overdose~~
- Is significant for other reason.

~~Definition of *overdose*: For a drug under clinical investigation, an overdose is noted when a clinical trial participant takes a higher daily dose of the primary study drug than *either* of the following:~~

- ~~The maximum daily dose specified in the protocol for the study, *or*~~

- ~~The highest daily dose listed in the dosage and administration section of the current clinical investigator's brochure (CIB).~~

~~In the event that a study participant extends the use of a primary study drug at the daily dose specified by the protocol but for *more days* than specified by the protocol, and the individual does not experience any adverse events from the extension, this occurrence usually is noted as a *protocol violation* and not an overdose.~~

3.9.3.4. Other Safety Measures (page 27)

Other safety measures include a medical history, physical examination, 12-lead ECG (an ECG performed within previous 6 months is acceptable if result was normal and if the original is obtained for the patient's records), weight, monitoring of consumptive habits, pulse (sitting) and blood pressure (sitting), pregnancy test, and a urine drug screen at Visit 1; adverse events, drug and protocol compliance monitoring at each visit; and physical examination, weight, vital signs, ECG, and laboratory tests at discontinuation (unless discontinuation occurs at or before Visit 3 and prior to any dispensing of study medication).

3.10.1. Discontinuations (page 28)

…A physical examination will be conducted on all patients who discontinue the study at any point after Visit 3~~2~~. The investigator is responsible for ensuring that any abnormality found at the discontinuation physical examination receives appropriate follow-up.

4.1. General Considerations (page 30)

…Patients who have their dose reduced to 10 mg during the study will be included in all analyses as if they remained on 20 mg. (A summary of the number of patients who do have their dose reduced to 10 mg will be provided.)

4.4. Patient Characteristics (page 31)

…Should there be a difference in any characteristic on random assignment to the treatment period, analysis of covariance will be performed for the primary efficacy measure to check the robustness of the results, but will be considered as a secondary analysis.

4.5.1. Acute Treatment (Study Periods III-V) (page 31)

CDRS-R response rates will be compared between fluoxetine 20 ~~to 60~~ mg and placebo as the primary analysis for the acute treatment periods. A CDRS-R responder for this analysis will be defined as a patient whose CDRS-R score decreased at least 30% from baseline (Visit 4) to the endpoint of Study Periods IV~~-V~~ (last of Visits 6-Visit 10~~15~~). As a

secondary analysis, CDRS-R response rates will be compared between fluoxetine 20 to 60 mg and placebo (endpoint defined as the last of Visits 6-15~~10~~).

… Analyses of remission will include only those patients treated at least 1 week with 20 mg (2 weeks total). A repeated measures analysis on the CDRS-R score will also be performed as a secondary analysis.

…An ANOVA (Type III sums of squares) with the term treatment in the model will be used when comparing change scores or endpoint scores between treatments. As secondary analyses~~If there is strong evidence for the need to stratify by investigator, gender, and/or age category~~, an ANOVA with treatment, investigator, gender, age category, and the treatment-by-investigator interaction in the model~~possibly the interactions with treatment~~ will be used. Analyses will be performed on both the original and the rank-transformed data. The analysis of the original data will be considered primary unless there is evidence to suggest non-normality. Pearson's chi-square test will be used to compare percentages. ~~If there is strong evidence for the need to stratify by investigator, gender, and/or age category,~~ L~~l~~ogistic regression models with treatment, investigator, gender, ~~and/or~~ age category and the treatment-by-investigator interaction~~possibly the interactions with treatment~~ will also be used to compare percentages, but will be considered secondary. The repeated measures analysis will be performed using a mixed model approach with visit as the within-subject factor, treatment as the between-subject factor and a treatment-by-visit interaction, using an unstructured covariance matrix (e.g., PROC MIXED).

4.8. Interim Analyses (page 34)

One interim analysis is planned. The interim analysis will take place after all patients complete Study Period IV~~V~~ (Visit 10~~the end of all acute treatment periods~~). The interim analysis will be conducted in order to obtain and communicate the results from the fixed-dose acute treatment phase in a more timely manner. The results from the fixed-dose acute treatment unblinded at the treatment level may be presented outside the company including to regulatory agencies. Additional interim analyses may take place after all patients complete Study Period V~~IV~~ (the end of all acute treatment periods~~fixed-dose phase~~) and/or after all patients complete Visit 13 (2 weeks with doses up to 60 mg). These interim analyses will only take place if results are needed for decision-making purposes prior to the expected completion of the study~~planned interim analysis~~. The study will not be stopped if evidence of efficacy is observed, thus adjustment of p-values is not required. To minimize the bias for the relapse prevention therapy phase, no one at the study site will be unblinded at the patient level.

Planned interim analyses, and any unplanned interim analyses, will be conducted under the auspices of the data monitoring board assigned to this study. Only the data monitoring board is authorized to review completely unblinded interim efficacy and safety analyses and, if necessary, to disseminate those results. The data monitoring board will disseminate

interim results in a manner that will minimize bias. Study sites will not receive information about interim results unless they need to know for the safety of their patients.

~~Protocol Attachment HCJE.2.~~
~~Interviewer Responsibilities Grid~~

~~Interviewer Responsibilities Grid~~
~~Protocol B1Y-MC-HCJE~~

~~Visit 1~~	~~Interviewer #1~~	~~Interviewer #2~~	~~Interviewer #3~~
~~Child~~	~~History~~ ~~Physical~~ ~~DICA~~ ~~CDI or BDI~~		
~~Parent~~	~~DICA~~ ~~Psychiatric History~~ ~~Historical Diagnoses~~	~~Family History RDC~~	
~~Child and Parent~~		~~CDRS-R~~ ~~CGI~~ ~~HAMA~~ ~~MADRS~~	

~~Visit 2~~	~~Interviewer #1~~	~~Interviewer #2~~	~~Interviewer #3~~
~~Child~~		~~DICA~~ ~~CDI or BDI~~ ~~K-SADS~~	
~~Parent~~		~~DICA~~ ~~Psychiatric History~~ ~~Historical Diagnoses~~	~~Family History RDC~~
~~Child and Parent~~			~~CDRS-R~~ ~~CGI~~ ~~HAMA~~ ~~MADRS~~

~~Visit 3~~	~~Interviewer #1~~	~~Interviewer #2~~	~~Interviewer #3~~
~~Child~~			~~DICA~~ ~~CDI or BDI~~ ~~K-SADS~~
~~Parent~~	~~Family History RDC~~		~~DICA~~ ~~Psychiatric History~~ ~~Historical Diagnoses~~
~~Child and Parent~~	~~CDRS-R~~ ~~CGI~~ ~~HAMA~~ ~~MADRS~~		

Confidential Information

The information contained in this protocol is confidential and is intended for the use of clinical investigators. It is the property of Eli Lilly and Company or its subsidiaries and should not be copied by or distributed to persons not involved in the clinical investigation of fluoxetine hydrochloride (LY110140), unless such persons are bound by a confidentiality agreement with Eli Lilly and Company or its subsidiaries.

Fluoxetine Hydrochloride (LY110140)

Protocol B1Y-MC-HCJE(a)

Fluoxetine Versus Placebo in Childhood/Adolescent Depression

Protocol Approved by Lilly: 17 November 1997
Amendment (a) Approved by Lilly: 30 June 1998

Fluoxetine Versus Placebo in Childhood/Adolescent Depression

1. Introduction

While much has been written regarding the use of antidepressants in children with various mood and anxiety disorders, there have been few well-powered controlled clinical trials within specific diagnostic areas. Controlled studies of the use of tricyclic antidepressants in children and adolescents with depression have failed to produce a replicable pattern of efficacy (Kramer and Feiguine 1981; Petti and Law 1982; Kashani et al. 1984; Puig-Antich et al. 1987; Geller et al. 1990; Boulos et al. 1992).

Recently, the efficacy of fluoxetine in the treatment of pediatric depression was demonstrated in a double-blind, placebo-controlled study (Emslie et al. 1997). This study used a fixed-dose (20 mg/day) strategy that proved fluoxetine to be efficacious and well tolerated. Other researchers have reported that children and adolescents respond to lower doses of fluoxetine treatment, and that a slow titration to therapeutic dosage or lower maintenance dose may be necessary. Still others have reported that children and adolescents respond to fluoxetine doses of >20 mg/day (Simeon et al. 1990; Jain et al. 1992; Colle et al. 1994). A study addressing the efficacy and tolerability of various dosing strategies in depressed children and adolescents is needed to guide treatment.

2. Objectives

2.1. Primary Objective

The primary objective of this study is as follows:

- To test the hypothesis that fluoxetine 20 mg is more effective than placebo in the treatment of children (aged 8 to <13 years) and adolescents (aged 13 to <18 years) with DSM-IV major depression as measured by response rates on the Children's Depression Rating Scale-Revised (CDRS-R) after up to 9 weeks, defined as a decrease of at least 30% in the CDRS-R score from baseline to endpoint.

2.2. Secondary Objectives

The secondary objectives of the study are as follows:

- To compare the efficacy of fluoxetine 20 to 60 mg with placebo in the treatment of childhood/adolescent depression as measured by response rates on the CDRS-R after up to 19 weeks.
- To compare the efficacy of fluoxetine 20 mg and fluoxetine 20 to 60 mg with placebo in the treatment of childhood/adolescent depression as measured by mean scores on the CDRS-R, Clinical Global Impressions of Severity (CGI-Severity), Clinical Global Impressions of Improvement (CGI-Improvement), the Kiddie Schedule for Affective Disorders and Schizophrenia (K-SADS), Montgomery-Asberg Depression Rating Scale (MADRS), Beck Depression Inventory (BDI), and Children's Depression Inventory (CDI). CDRS-R remission rates and CGI response rates are additional analyses to compare efficacy.
- To compare the effects of fluoxetine 20 mg and fluoxetine 20 to 60 mg with placebo on symptoms of anxiety in children and adolescents with depression as measured by changes in mean Hamilton Anxiety Rating Scale (HAMA) scores.
- To compare the safety of fluoxetine 20 mg and fluoxetine 20 to 60 mg with placebo in the treatment of childhood/adolescent depression.
- To compare the efficacy of fluoxetine 20 to 60 mg with placebo in preventing relapse as determined by time to relapse among the responders after the titration period.
- To compare the efficacy of continued fluoxetine 20 mg with fluoxetine 40 to 60 mg among the nonresponders to 20 mg after the fixed-dose period.

- To determine if there are any differences in the efficacy and safety of fluoxetine between two subgroups: children (aged 8 to <13 years) and adolescents (aged 13 to <18 years).
- To examine steady-state serum concentrations of fluoxetine and norfluoxetine in children and adolescents receiving different dosing regimens.

3. Investigational Plan

3.1. Summary of Study Design

This will be a multicenter, randomized, double-blind, two-arm, parallel study. Fluoxetine will be compared with placebo for efficacy and safety in approximately 220 children and adolescents with depression.

The study will have two general phases, an acute treatment phase and a relapse prevention phase. The 19-week acute treatment phase will consist of five study periods. The 32-week relapse prevention phase (not shown in the illustration) was designed to examine relapse prevention and will follow the acute treatment phase. The acute treatment study design is illustrated in Figure HCJE.1. Although not depicted in the study illustration, all the decision processes made throughout the study will be done for both the fluoxetine and placebo therapy groups to maintain the study blind.

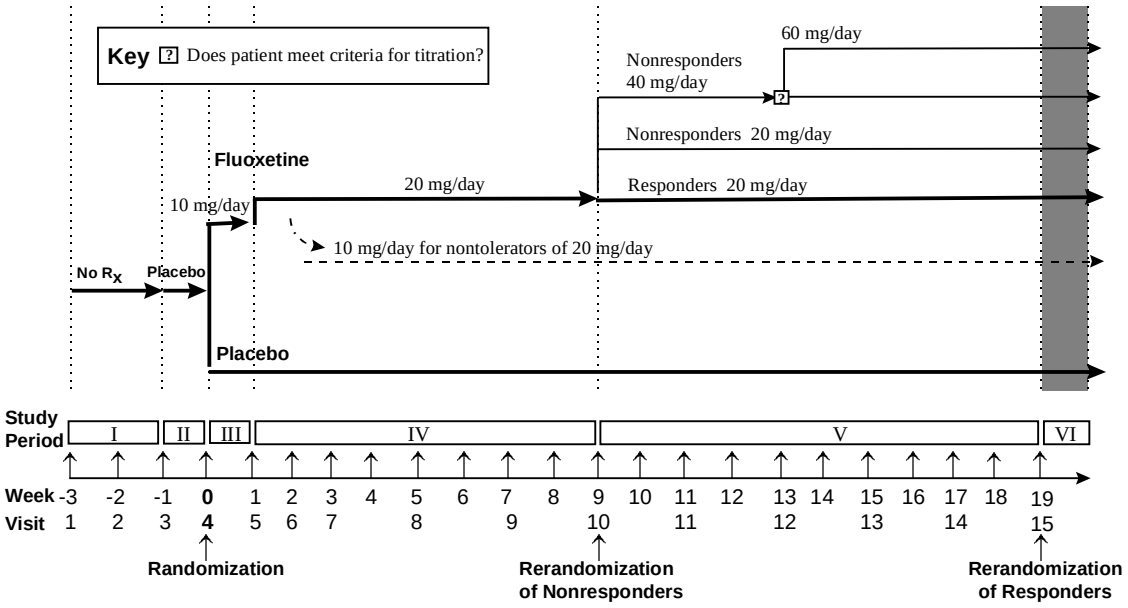

Figure HCJE.1. Illustration of Study Design for Protocol B1Y-MC-HCJE

Three diagnostic interviews will be conducted during Study Period I, the diagnostic evaluation phase. Patients who meet the inclusion/exclusion criteria will enter Study Period II, a 1-week placebo washout phase. Patients who do not respond to placebo will enter Study Period III, a 1-week adaptation phase. Patients who can tolerate study medication will enter Study Period IV, an8-week fixed-dose phase. After 8 weeks of treatment, patients will be evaluated for response status. Responders will remain on fluoxetine 20 mg or placebo during Study Period V. Fluoxetine nonresponders will be rerandomized to either remain on fluoxetine 20 mg or to receive fluoxetine 40 mg with an option to titrate to 60 mg during this titration phase. Placebo nonresponders will remain on placebo. Patients who respond to treatment will enter Study Period VI, a 32-week relapse prevention phase.

3.1.1. Study Period I: Diagnostic Evaluation Phase

Study Period I will be a 2-week diagnostic evaluation period. This period will begin with Visit 1 and end with Visit 3. The visits will be scheduled weekly (6 to 9 days).

Visits 1, 2, and 3 will serve as diagnostic evaluation visits. At least three separate diagnostic interviewers will be required at each site.

At each diagnostic evaluation visit, the child and parents will be interviewed both separately and together. The family history will be reviewed at each clinical assessment because often more information becomes available with progressive interviews.

At the first interview (Visit 1), the nature of the study will be fully explained to the patients and their parent/legal guardian(s). After written informed consent has been given by the patients and parent/legal guardian(s), each patient will undergo a psychological and a physical examination to determine whether all inclusion/exclusion criteria are met.

The parents will respond to the Missouri Assessment of Genetics Interview for Children (MAGIC) parent version, {The MAGIC was adapted from the Diagnostic Interview for Children and Adolescents (DICA)}or to the Diagnostic Interview for Children and Adolescents (either hard copy or electronic copy will be acceptable), questions regarding significant historical diagnoses and the patient's psychiatric history, the Children's Depression Rating Scale-Revised (CDRS-R) and the modified Family History Research Diagnostic Criteria (FHRDC). The MAGIC or DICA will be conducted/reviewed by a separate interviewer for each of the three diagnostic visits. .

The patient will respond to the MAGIC or DICA , the CDRS-R and either the CDI (children), or the BDI (adolescents) based on their age.

The patients and their parent/legal guardian(s) will complete the HAMA, and MADRS together.

Results from safety evaluations, including the physical examination, ECG, laboratory tests, urine screen for fluoxetine/norfluoxetine levels and other antidepressants , and a urine drug screen must be available by Visit 2. The urine drug screen results must be negative before a patient may be enrolled in Study Period II. If the results of the urine drug screen are abnormal, the patient may be retested once. If results of the second urine drug screen are positive, the patient may not be enrolled in the study.

If all entry criteria are met at Visit 1, an additional interview will be scheduled 1 week later.

The second interview (Visit 2) will be conducted by a different interviewer and will be independent from the previous psychiatric assessment. The primary interviewer (different than primary interviewer at Visit 1) will review the MAGIC or DICA , significant historical diagnoses, and the patient's psychiatric history. Patient self-report measures

will be repeated and the CDRS-R and the K-SADS will be administered. If all entry criteria are met, an additional interview will be scheduled 1 week later.

The third interview (Visit 3) will be conducted by a different interviewer and will be independent from the two previous psychiatric assessments. Again, the primary interviewer for the visit (different than Visit 1 or Visit 2)will review the MAGIC or DICA , significant historical diagnoses, and the patient's psychiatric history. An interviewer will review the FHRDC. Patient self-report measures will be repeated and the CDRS-R and the K-SADS will be administered.

Patients who meet the inclusion and exclusion criteria (including laboratory work) at all three interviews, and have a CDRS-R score of >40 at Visit 3, will continue into Study Period II.

3.1.2. Study Period II: Placebo Washout Phase

Study Period II will be a 1-week, single-blind, placebo washout phase. The period will begin at Visit 3 and end at Visit 4. The visits will be scheduled weekly (6 to 9 days).

Patients will be assigned a medication kit and will receive single-blind treatment with placebo. Patients who respond to placebo (defined as a ≥30% decrease in CDRS-R score from Visit 3 to Visit 4 or a CGI-Improvement score of 1 or 2 at Visit 4 as compared to Visit 1) will be discontinued.

3.1.3. Study Period III: Adaptation Phase

Study Period III will be a 1-week adaptation phase. The period will begin at Visit 4 and end at Visit 5. The visits will be scheduled weekly (6 to 9 days).

Patients who continue to meet the inclusion/exclusion criteria at Visit 4 will be randomized to receive either fluoxetine or placebo. Patients in the fluoxetine treatment group will receive fluoxetine 10 mg for the duration of the 1-week period. Patients who adapt readily to study medication will continue into Study Period IV, the fixed-dose phase. Patients who cannot tolerate study drug will be discontinued.

3.1.4. Study Period IV: Fixed-Dose Phase

Study Period IV is an 8-week fixed-dose phase. The period will begin with Visit 5 and end with Visit 10. Visits will be scheduled weekly (6 to 9 days) through Visit 7 and biweekly (13 to 16 days) thereafter.

Patients in the fluoxetine treatment group will undergo a forced titration to fluoxetine 20 mg at Visit 5. Patients who cannot tolerate fluoxetine 20 mg at Visits 6, 7, 8, or 9 may have their dose reduced to 10 mg, but then will not be allowed to increase or decrease their dosage at any subsequent time during the study.

3.1.5. Study Period V: Titration Phase

Study Period V will be a 10-week titration phase. The period will begin at Visit 10 and end at Visit 15. The visits will be scheduled biweekly (13 to 16 days).

At Visit 10, patients who are responding to treatment with fluoxetine 20 mg will remain on fluoxetine 20 mg. To be considered a responder, a patient must have a ≥30% decrease in CDRS-R score from baseline (Visit 4) to Visit 10. Nonresponders will be rerandomized to receive either continued treatment with fluoxetine 20 mg or to receive an increase in dose to fluoxetine 40 mg. Patients who cannot tolerate 40 mg will have the option to drop back to 20 mg, but then will have no further opportunity to increase or decrease their dosage during this study period.

Patients who are rerandomized to the fluoxetine 40 mg arm and fail to respond (based on CGI-Improvement score) after 4 weeks of treatment with fluoxetine 40 mg will have the option to undergo an additional dosage increase to fluoxetine 60 mg. Whether or not the optional dose increase is implemented will be based on a clinical decision made by the investigator. Patients whose dose is increased to 60 mg/day at Visit 12 will have a 2-week window in which their dose can be decreased, if necessary, for reasons of poor tolerability. There will be no further opportunity for a dosage change after Visit 13. The final visit of this study period will occur 4 weeks (26 to 32 days) after Visit 13. This will ensure that all patients will have assessments made following a minimum of 4 weeks at a constant dose.

3.1.6. Study Period VI: Relapse Prevention Phase

Study Period VI will be a 32-week (8-month) double-blind relapse prevention phase. This period will begin at Visit 15 and end at Visit 26. The visits will be scheduled biweekly for the first 3 months and monthly (26 to 32 days) thereafter.

Patients with a CDRS-R score of ≤28 at Visit 15 will be eligible to participate in the relapse prevention phase. Participants will be rerandomized to placebo or to continue their current treatment as of Visit 15. However, both investigators and patients will be blinded to the actual timing of the switch (Visit S) to the new treatment. Patients will be assessed for sustained efficacy of pharmacologic treatment and for continued safety. Investigators must provide a detailed rationale for the decision to stop treatment for any patient.

Relapse during the relapse prevention phase will be defined as a one-time CDRS-R score of >40 in the presence of a history of 2 weeks of clinical deterioration as determined by patient report, parent report, or clinical history.

3.2. Discussion of Design and Control

This study was designed to address the efficacy and tolerability of various dosing strategies and to guide pharmacologic treatment of depressed children and adolescents with fluoxetine.

To obtain the most reliable assessment of a patient's condition, this study incorporates a 2-week diagnostic evaluation phase requiring a consensus diagnosis based on three independent diagnostic interviews conducted by three or more independent interviewers. Furthermore, to eliminate placebo responders and patients who respond simply to intervention, a placebo washout period will follow the extended evaluation period.

Results of prior studies suggest that there is a relationship between rate of dose escalation and susceptibility to adverse events (Riddle et al. 1990/1991). Therefore we have incorporated a 1-week adaptation phase at a dose lower than that used successfully in the Emslie et al. (1997) study or in adult studies.

Data from previous studies and case series suggest that unlike adults, children and adolescents with depressive illnesses respond preferentially to SSRIs. However, it is not known whether the time to onset of therapeutic effect will be different between children and adults. To explore whether 8 weeks is adequate time to achieve a therapeutic response, patients who do not respond to fluoxetine 20 mg after 8 weeks will be rerandomized to either remain on fluoxetine 20 mg for an additional 10 weeks or to receive fluoxetine 40 mg with an option to titrate to 60 mg.

Lastly, postmarketing data suggest that children and adolescents respond over a possibly wider dosage range than do adults with depression. The dosing regimen used in this study was designed with a starting dose of 10 mg/day, an option to gradually titrate the dose to a maximum of 60 mg/day based on response to treatment, and an option to incrementally decrease the dose if not tolerated.

Control will be provided by randomization of patients to fluoxetine or placebo treatment under double-blind conditions.

3.3. Investigator Information

Approximately 10 physicians with training in pediatric psychiatry will participate as investigators in this clinical study.

3.3.1. Final Report Signature

The investigator with the most patients assigned to treatment groups will serve as the final report coordinating investigator.

The final report coordinating investigator will sign the final clinical study report for this study, indicating agreement with the analyses, results, and conclusions of the report.

3.4. Study Population

3.4.1. Entry Procedures

Participation will be voluntary. Potential participants may be screened by phone prior to Visit 1. Visit 1 will serve as the initial diagnostic evaluation visit. Patients must be free of any behavior-altering, centrally-acting, or excluded medication for 7 days prior to Visit 1. At Visit 1, the nature of the study will be fully explained to the patients and their parent/legal guardian(s). An informed consent document will subsequently be signed by the patients and their parent/legal guardian(s) and retained by the investigator. A signed copy will be given to the parent/legal guardian(s).

After obtaining informed consent, each patient will be evaluated to determine whether he or she meets all inclusion/exclusion criteria (as set forth in Sections 3.4.2.1 and 3.4.2.2). Patients who meet entry criteria will enter a 2-week evaluation period. At Visits 2 and 3, patients will again be assessed to determine whether they meet all inclusion/exclusion criteria and for response status. (See Section 3.1.1.)

Those who continue to meet the inclusion/exclusion criteria and have a CDRS-R score >40 at Visit 3 will receive single-blind treatment with placebo for 1 week. Patients who do not respond to placebo will then be randomly assigned to double-blind treatment at Visit 4. (See Section 3.1.2.)

3.4.2. Criteria for Enrollment

For Lilly studies, the following definitions are used:

Screen — The act of determining if an individual meets minimum requirements to become part of a pool of potential candidates for participation in a clinical study.

Screening may involve asking the candidate preliminary questions, such as age and general health status, to determine potential eligibility. In these cases, the screening is not invasive and does not require that screening informed consent be obtained.

Individuals who are screened are not yet considered to be entered into the study and, therefore, do not need to be followed for adverse events.

Enter — The act of obtaining informed consent for participation in a clinical study from individuals deemed potentially eligible to participate in the clinical study. Individuals entered into a study are those for whom informed consent documents for the study have been signed by the potential study participants or their legal representatives.

Adverse events are reported for each individual who has entered the study, even if the individual is never assigned to a treatment group (enrolled).

Enroll — The act of assigning an individual to a treatment group. Individuals who are enrolled in the study are those who have been assigned to a treatment group.

A person who has been entered into the study is potentially eligible to be enrolled in the study, but must meet all criteria for enrollment specified in the protocol before being enrolled (assigned to a treatment group). Individuals who are entered into the study but fail to meet the criteria for enrollment are not eligible to participate in the study and will not be enrolled.

Adverse events are reported for all individuals who have entered the study and all individuals who are enrolled in the study (assigned to treatment groups).

The numbering system used for inclusion and exclusion criteria provides a unique number for each criterion and allows for efficiency in data collection.

3.4.2.1. Inclusion Criteria

Patients may be included in the study **only** if they meet all of the following criteria:

[1] Male and female outpatients.

[2] Children (aged 8 to <13 years) and adolescents (aged 13 to <18 years) at the time of entry into the study.

[3] A primary psychiatric diagnosis of nonpsychotic major depressive disorder (single or recurrent) as defined by the DSM-IV criteria.

[4] Depressive symptoms of at least moderate severity as defined by a CDRS-R score of >40 and a CGI-Severity rating of moderate or greater.

[5] Able to swallow whole medication without difficulty.

[6] No clinically significant laboratory findings in hematology, chemistry, and urinalysis at study entry based on the judgment of the investigator.

[7] ECG without clinically significant abnormalities. The clinical significance will be determined by the investigator and the physician interpreting the ECG.

[8] Educational level and degree of understanding so that the patients and parents can communicate intelligibly with the investigator and study coordinator. Normal intelligence based on the judgment of the investigator.

[9] Patients and parents judged to be reliable who agree to keep appointments for clinic visits and all tests and examinations required by the protocol.

3.4.2.2. Exclusion Criteria

Patients will be excluded from the study for **any** of the following reasons:

[10] Investigators and their immediate families are not permitted to be subjects or patients in Lilly-sponsored trials. Immediate family is defined as the investigator's spouse, parent, child, grandparent, or grandchild.

[11] Persons who have previously completed or withdrawn from this study.

[12] Females who are pregnant or breastfeeding or who are sexually active and are not using medically accepted means of contraception (IUD, birth control pills, barrier devices, or implanted progesterone rods stabilized for at least 3 months).

[13] Serious illness (including cardiac, hepatic, renal, respiratory, endocrinologic, neurologic, or hematologic disease) that is not stabilized so that hospitalization for treatment of that illness is likely within the next 2 months.

[14] Patients with abnormal thyroid function.

[15] Seizure disorder with a seizure occurring within the past 6 months, except for febrile seizures.

[16] Diagnosis of any of the following DSM-IV-defined disorders: bipolar I or II disorder, sleep-wake disorder, psychotic depression (lifetime), anorexia (lifetime), bulimia (lifetime), borderline personality disorder or substance abuse disorder (within the past 6 months).

[17] Patients with one or more first-degree relatives with bipolar I disorder.

[18] Organic brain diseases.

[19] Persons whose illness has previously failed to respond to adequate antidepressant treatment (at least 8 weeks treatment within the typical maximum adult therapeutic range).

[20] Serious suicidal risk.

[21] History of severe allergies, multiple adverse drug reactions, or known allergy to the study drug.

[22] Receipt of an investigational drug within 30 days prior to study entry.

[23] Receipt of any behavior-altering, centrally-acting, or excluded medication within 7 days prior to study entry.

[24] Documented hypersensitivity to fluoxetine.

[25] Prior adequate treatment with fluoxetine (12 weeks on a fixed dose of 20 mg or greater).

[26] Receipt of fluoxetine within 3 months prior to study entry.
Note: Patients who have detectable levels of fluoxetine, norfluoxetine, or any other antidepressant in their initial urine screen will be discontinued.

[27] Regular use of other psychotropic or centrally-acting drugs, including lithium and the psychostimulants (ie, drugs normally prescribed for depression, mania, anxiety, insomnia, attention deficit disorder, or psychosis) within 2 weeks prior to study entry that would need to be continued during the study. (The list of excluded medications is located in Appendix HCJE.2.)

[28] Use of neuroleptics during the 2 weeks prior to study entry or of depot neuroleptics within the 6 weeks prior to study entry.

[29] Use of a monoamine oxidase inhibitor (MAOI) within 2 weeks (14 days) prior to study entry or potential need to use an MAOI within 6 weeks of discontinuation of treatment.

[30] Use of tryptophan, St John's Wort, or melatonin within 2 weeks prior to study entry.

[31] Potential need for the continuation or initiation of other treatments for depression, including cognitive behavioral therapy and behavioral therapy, except for supportive therapy on an individual or family basis.

3.4.2.3. Violation of Criteria for Enrollment

The criteria for enrollment must be followed explicitly. If an individual who does not meet enrollment criteria is inadvertently enrolled, that individual should be discontinued from the study. Such individuals may remain in the study only if there are ethical reasons to have them continue. In such cases, the investigator must obtain approval from the Lilly clinical research physician for the study participant to continue in the study.

3.4.3. Disease Diagnostic Criteria

The MAGIC (Reich and Todd et al. 1997) or DICA (Herjanic and Reich 1982; Welner et al. 1987) will be used by each of three independent diagnostic interviewers to establish a diagnosis of major depression and to exclude other psychiatric illnesses. This structured interview is consistent with the DSM-IV diagnostic criteria for major depressive disorder and consists of two separate interviews with different formats for patients and parents.

The Family History RDC (Endicott and Andreasen et al. 1977) will be used to collect additional information.

Because the MAGIC or DICA does not assess symptom severity, the depression items from the K-SADS-PL (Kaufman et al. 1996) will be used as a supplemental diagnostic instrument. Furthermore, patients must be rated as at least moderately depressed (CDRS-R score of >40 and CGI-Severity rating of moderate or greater) at each of the three evaluation visits. A physical examination including family, psychiatric, and medical histories, laboratory tests, drug screen, and an ECG will be performed at Visit 1 to ensure that patients meet the inclusion/exclusion criteria.

3.4.4. Sample Size

The total number of randomized patients to be included in this study is approximately 220 patients or 110 patients per arm. The sample size is designed to detect a difference in the proportion of patients responding of 20 percentage points between fluoxetine 20 mg and placebo with approximately 80% power and a 0.05 significance level (two-sided). Response is defined as at least a 30% decrease in the CDRS-R score from baseline (Visit 4) to endpoint (last measurement from Visits 6 through 10) for patients treated at least a week with 20 mg (2 weeks total). The calculation assumes the true proportions are 70% for fluoxetine and 50% for placebo and assumes no more than 7 patients in either arm will discontinue prior to the first postrandomization visit with 20 mg (Visit 6). These estimates were based on a previous placebo-controlled trial in depressed children and adolescents (Emslie et al. 1997).

3.5. Patient Assignment

A patient number will be assigned to each patient at the time the informed consent document is signed (Visit 1). Patients who qualify for Study Period III will be randomly assigned to one of the two treatment groups at Visit 4. The treatment group to which the patient is assigned will be determined by a computer-generated randomization sequence. Randomization at Visit 4 will be stratified by gender and age category (child versus adolescent) across investigative sites.

At Visit 10, patients will be evaluated for response status. Responders will remain on fluoxetine 20 mg. Nonresponders will be rerandomized to either fluoxetine 20 mg or fluoxetine 40 to 60 mg as determined by a computer-generated randomization sequence.

Patients with a CDRS-R score of ≤28 at Visit 15 will be eligible to continue into the double-blind relapse prevention phase. This phase will last up to 32 weeks (8 months). Patients will be rerandomized to either continue their current treatment or to placebo at Visit 15; however, the timing of the change in medications will be blinded to the investigator and the patient. Again, the treatment group to which the patient is assigned will be determined by a computer-generated randomization sequence.

3.6. Dosage and Administration

Accountability for the investigational products lies with the investigator. The investigator has the responsibility to explain the correct use of the investigational product(s) to the patient and his or her parent/legal guardian(s) and to check at appropriate intervals to ensure that each study participant is following instructions properly.

3.6.1. Materials and Supplies

Primary study material:	fluoxetine 10-mg capsules fluoxetine 20-mg capsules
Comparator material:	placebo capsules to match fluoxetine.

Medication will be provided in blister packs labeled "Fluoxetine/Placebo in Child/Adolescent Depression."

3.6.2. Dosage Selection and Administration Procedures

Patient kits will be assigned at Visit 3. Patients will be instructed to take three capsules daily, preferably in the morning. If the investigator thinks the patient would benefit from dosing in the evening, the doses may be taken in the evening.

3.6.2.1. Study Period I: Diagnostic Evaluation Phase

No study medications will be dispensed.

3.6.2.2. Study Period II: Placebo Washout Phase

At Visit 3, all patients who have met the inclusion/exclusion criteria will receive single-blind treatment with placebo. All patients will be instructed to take three capsules daily at approximately the same time each day.

3.6.2.3. Study Period III: Adaptation Phase

At Visit 4, patients will be randomized to either the fluoxetine or the placebo treatment group. Patients in the fluoxetine treatment group will receive an initial fluoxetine dose of 10 mg/day. All randomized patients will be instructed to take three capsules daily at approximately the same time each day.

3.6.2.4. Study Period IV: Fixed-Dose Phase

Patients who are able to tolerate their study medication at Visit 5 will enter an 8-week fixed-dose phase. Patients in the fluoxetine treatment group will receive fluoxetine

20 mg/day for 8 weeks. All patients will be instructed to take three capsules daily at approximately the same time each day.

3.6.2.5. Study Period V: Titration Phase

All patients will continue to take three capsules once daily at approximately the same time each day, unless otherwise instructed by the investigator.

At Visit 10, patients who respond to treatment with fluoxetine 20 mg will remain on fluoxetine 20 mg. To be considered a responder, a patient must have a ≥30% decrease in CDRS-R score from baseline (Visit 4) to Visit 10.

Nonresponders will be rerandomized to receive either continued treatment with fluoxetine 20 mg or an increase in dose to fluoxetine 40 mg. Patients who cannot tolerate 40 mg will have the option to drop back to 20 mg, but will have no further opportunity to increase their dosage during this study period.

Patients who are rerandomized to the fluoxetine 40 mg arm and fail to respond after 4 weeks of treatment with fluoxetine 40 mg will undergo an additional dosage increase to fluoxetine 60 mg at Visit 12. Increases in dosage may occur if the patient's CGI-Improvement score is between 3 and 7. Increases in dosage will be prohibited if the patient's CGI-Improvement score is 1 or 2. The investigator may decline to implement a dose increase. The reason must be documented in the clinical report form. Patients whose dose is increased to 60 mg/day at Visit 12 will have a 2-week window in which their dose can be decreased to fluoxetine 40 mg, if necessary, for reasons of poor tolerability. There will be no further opportunity for a dosage change after Visit 13.

Decreases in dosage for safety reasons may occur at any scheduled or unscheduled visit at any time between Visits 10 and 13. Only one dosage reduction will be allowed during a given visit interval. Of course, the clinician always retains the responsibility to discontinue a patient if clinically warranted.

Note: If a patient's dosage is reduced because of any adverse event, significant laboratory abnormality, inadequate response to treatment, or any other reason, study site personnel must report and clearly document the circumstances and data leading to the dosage reduction using the clinical report form (Section 3.9.3.2.1).

3.6.2.6. Study Period VI: Relapse Prevention Phase

Patients with a CDRS-R score of ≤28 at Visit 15 will be enrolled in a 32-week, double-blind relapse prevention phase. Patients will be rerandomized to either placebo or to continue their current treatment at Visit 15. However, the change in medications will take place at a point during the relapse prevention phase (blinded to the investigator and the patient) designated as Visit S. Patients will be instructed to continue taking their study medication as prescribed at the last acute treatment visit. Additional dosage adjustments

will not be allowed during the relapse prevention phase. All patients will take three capsules daily.

3.7. Blinding

To avoid introducing bias, investigators and patients will be blinded to the treatment group assignment given to nonresponders at Visit 10. Furthermore, investigators and patients will be blinded to the *timing* of the change in medications for the relapse prevention phase.

In order to preserve the blinding of the study, only a minimal number of Lilly personnel will see the randomization table and codes before the study is complete.

Emergency codes, generated by a computer drug-labeling system, will be available to the investigator. These codes, which reveal the patient's treatment group when opened, may be opened during the study only if the choice of follow-up treatment depends on the patient's therapy assignment.

The investigator should make every effort to contact the clinical research physician prior to unblinding a patient's therapy assignment. If a patient's therapy assignment is unblinded, Lilly must be notified immediately by telephone. After the study, the investigator must return all sealed and any opened codes.

If an investigator, site personnel performing assessments, or patient is unblinded, the patient must be discontinued from the study unless there are ethical reasons to have the patient remain in the study. In these special cases, the investigator must obtain specific approval from a Lilly clinical research physician for the patient to continue in the study.

3.8. Concomitant Therapy

All nonstudy medication being taken during the study must be recorded on the clinical report form. Patients will be instructed to consult with the investigator or study coordinator at the site before taking any new medications or supplements.

3.8.1. Excluded Medications

A list of medications excluded by the protocol is located in Protocol Attachment HCJE.2. Other treatments for depression, including cognitive behavioral therapy and behavioral therapy are also excluded, with the exception of supportive therapy on an individual or family basis. Patients requiring excluded concomitant medication or therapy will be discontinued from the study.

Warning: Monoamine oxidase inhibitors (MAOIs) should not be used for 14 days prior to study entry, during the study period, nor for 5 weeks after study discontinuation.

3.8.2. Permitted Medications

Patients may take over-the-counter or prescription medications not specifically excluded by the protocol. Acceptable over-the-counter medications include Tylenol®, cold preparations, birth control pills, vitamins, and so forth. A patient may be given chloral hydrate up to 1.0 g/day as needed at bedtime for sleep. Ambien® may also be prescribed for the short-term treatment of insomnia. Use should be limited to no more than 5 days within a 4-week time period.

3.9. Efficacy, Pharmacokinetic, and Safety Evaluations

The efficacy and safety evaluations to be performed are outlined below. For the timing of assessments, see Protocol Attachment HCJE.1, Schedule of Events.

3.9.1. Efficacy

3.9.1.1. Efficacy Measures

The following efficacy measures will be collected at the times shown in Attachment HCJE.1, Schedule of Events.

- **Children's Depression Rating Scale-Revised (CDRS-R):**
  The CDRS-R (Poznanski et al. 1984; 1985) is modeled after the Hamilton Depression Rating Scale (HAMD) for adults, but also includes questions about school. This is a clinician-rated instrument that measures presence and severity of depression. The scale consists of 17 items scored on a 1 to 5 or 1 to 7 scale. A rating of 1 indicates normal, thus the minimum score is 17. The maximum score is 113. In general, scores below 20 indicate an absence of depression, 20 to 30, borderline depression, 40 to 60, moderate depression.

- **Kiddie Schedule for Affective Disorders and Schizophrenia- Present and Lifetime (K-SADS-PL):**
  The K-SADS-PL (Kaufman et al. 1996) was adapted from the K-SADS (Puig-Antich and Chambers 1978; Chambers et al. 1985) which was adapted for use with children and adolescents from the Schedule for Affective Disorders and Schizophrenia (Endicott and Spitzer 1978). This clinician-rated instrument assesses the extent of depressive symptoms and allows for rating the worst part of an episode as well as for the past week. This instrument will be used in this study as both a supplementary diagnostic instrument and a measure of efficacy.

- **Clinical Global Impression of Severity (CGI-Severity):**
  The CGI-Severity scale (Guy 1976) has previously been used to assess both adults and children. This is a clinician-rated instrument that measures the severity of the patient's depression. It is a 7-point scale where 1 = normal and 7 = extremely severe case of depression.

- **Clinical Global Impression of Improvement (CGI-Improvement):**
  The CGI-Improvement scale (Guy 1976) has previously been used to assess both adults and children. This is a clinician-rated instrument that measures the improvement of the patient's depression. It is a 7-point scale where 1 = very much improved, 4 = no change, and 7 = very much worse.

- **Montgomery-Asberg Depression Rating Scale (MADRS):**
  The MADRS (Montgomery and Asberg 1979) is a clinician-rated instrument that measures the presence and severity of depression. This instrument consists of a 10-symptom scale, namely, apparent sadness, reported sadness, inner tension, reduced sleep, reduced appetite, concentration difficulties, lassitude, inability to feel, pessimistic thoughts, and suicidal ideation. Each symptom is rated on a defined step scale (0 to 6). A high numeric rating shows a greater degree of symptom severity.

- **Beck Depression Inventory (BDI):**
  The BDI (Beck and Steer 1984) has been used extensively with both adults and adolescents in research studies. This patient-rated scale assesses the major symptom categories associated with depression. The higher the total score (range, 0 to 62) the more severe the depression. The BDI scale will be completed by adolescents (patients aged 13 to <18 years).

- **Hamilton Anxiety Rating Scale (HAMA):**
  The HAMA will be administered to assess severity of anxiety, its improvement during the course of treatment, and the timing of such improvement (Riskind et al. 1987). This instrument is completed by the clinician based on his or her assessment of the patient.

- **Children's Depression Inventory (CDI):**
  The CDI was developed from the BDI (Kovacs 1985). Like the BDI, the higher the total score (range, 0 to 54) the more severe the depression. The CDI will be completed by children (patients aged 8 to <13 years).

3.9.1.2. Efficacy Criteria

CDRS-R response rates will be considered primary. Secondary measures will include changes in the CDRS-R, K-SADS, CGI-Severity, CGI-Improvement, MADRS, CDI, and the BDI. CDRS-R remission rates and CGI response rates will be additional criteria for efficacy.

3.9.2. Pharmacokinetics

Formal pharmacokinetic data will not be collected. Baseline fluoxetine serum concentrations will be assayed. Fluoxetine, norfluoxetine, and other antidepressants and their metabolites must be nondetectable by urine screen at baseline for inclusion into the study. Steady-state serum concentrations of fluoxetine and norfluoxetine will be collected as indicated in the Schedule of Events (Protocol Attachment HCJE.1).

3.9.3. Safety

Investigators are responsible for monitoring the safety of patients who have entered this study and for alerting Lilly to any event that seems unusual, even if this event may be considered an unanticipated benefit to the patient. See Section 3.9.3.2.1.

3.9.3.1. Safety Measures

3.9.3.2. Clinical Adverse Events

Lilly has standards for reporting adverse events that are to be followed, regardless of applicable regulatory requirements that are less stringent. For purposes of collecting and evaluating *all* information about Lilly drugs used in clinical trials, a clinical trial adverse event is any undesirable experience, unanticipated benefit (see Section 3.9.3.2.1), or pregnancy that occurs after informed consent has been obtained without regard to the possibility of a causal relationship, without regard to treatment group assignment, even if no study drug has been taken. Lack of drug effect is not an adverse event in clinical trials, because the purpose of the clinical trial is to establish drug effect.

At the first visit, study site personnel will question each patient and will note the occurrence and nature of presenting condition(s) and any preexisting condition(s). At subsequent visits, site personnel will again question the patient and will note any change in the presenting condition(s), any change in the preexisting condition(s), and/or the occurrence and nature of any adverse events.

Reports of spontaneous adverse events will be recorded at the beginning of each visit. A Side Effects Checklist will be administered at the end of each visit.

3.9.3.2.1. Adverse Event Reporting Requirements

All adverse events must be reported to Lilly by clinical report form.

Study site personnel must report to Lilly immediately, by telephone, any **serious** adverse event (see Section 3.9.3.2.2 below) or if the investigator **unblinds** a patient's treatment group assignment because of an adverse event or for any other reason. Remember that **all**

adverse events must be reported by clinical report form, even if a telephone report has been made.

If a patient's dosage is reduced or if a patient is discontinued from the study because of any significant laboratory abnormality, inadequate response to treatment, or any other reason, study site personnel must report and clearly document the circumstances and data leading to any such dosage reduction or discontinuation, using designated data transmission methods clinical report form.

In cases where the investigator notices an unanticipated benefit to the patient, study site personnel should enter "unanticipated benefit" along with the actual event term on the clinical report form (eg, the complete actual term would be "unanticipated benefit—sleeping longer").

3.9.3.2.2. Serious Adverse Events

Study site personnel must report to Lilly immediately, by telephone, any adverse event from this study that includes one of the following criteria:

- Death
- Initial or prolonged inpatient hospitalization
- Is life-threatening
- Severe or permanent disability
- Cancer (other than cancers diagnosed prior to enrollment in studies involving patients with cancer)
- Congenital anomaly
- Is significant for other reason.

3.9.3.3. Clinical Laboratory Tests

The clinical laboratory tests specified in Table HCJE.1 will be performed at the times indicated in the Schedule of Events (Protocol Attachment HCJE.1).

Table HCJE.1. Clinical Laboratory Tests

Hematology:	**Clinical Chemistry -**
Hemoglobin	**Serum Concentrations of:**
Hematocrit	Sodium
Erythrocyte count (RBC)	Potassium
Mean cell volume (MCV)	Bicarbonate
Mean cell hemoglobin (MCH)	Chloride
Mean cell hemoglobin concentration (MCHC)	Total bilirubin
Leukocytes (WBC)	Alkaline phosphatase
Neutrophils, segmented	Gamma-glutamyl transferase (GGT)
Neutrophils, juvenile (bands)	Alanine transaminase (ALT/SGPT)
Lymphocytes	Aspartate transaminase (AST/SGOT)
Monocytes	Blood urea nitrogen (BUN)
Eosinophils	Serum creatinine
Basophils	Uric acid
Platelets	Phosphorus
Cell morphology	Calcium
	Glucose, nonfasting
Urinalysis:	Total protein
Color	Albumin
Specific gravity	Cholesterol
pH	Creatine kinase (CK)
Protein	
Glucose	**Thyroid Function Test:**
Ketones	Free thyroid index
Bilirubin	T_3
Urobilinogen	Thyroid-stimulating hormone (TSH)
Blood	
Nitrite	**Pregnancy Test**
Microscopic examination of sediment	(females only, based on menarchal status)

Laboratory values that fall outside a clinically accepted reference range or values that differ significantly from previous values must be evaluated and commented on by the investigator by marking each value CS (clinically significant) or NCS (not clinically significant). Any clinically significant laboratory value that is outside a clinically acceptable range or that differs importantly from a previous value should be further explained on the clinical report form Comments page.

3.9.3.4. Other Safety Measures

Other safety measures include a medical history, physical examination, 12-lead ECG (an ECG performed within previous 6 months is acceptable if result was normal and if the original is obtained for the patient's records), weight, monitoring of consumptive habits, pulse (sitting) and blood pressure (sitting), pregnancy test, and a urine drug screen at Visit

1; adverse events, drug and protocol compliance monitoring at each visit; and physical examination, weight, vital signs, ECG, and laboratory tests at discontinuation (unless discontinuation occurs at or before Visit 3 and prior to any dispensing of study medication).

3.9.4. Safety Monitoring

The Lilly clinical research physician will monitor safety data (some of which may be partially unblinded) throughout the course of the study.

In the event that safety monitoring uncovers an issue that needs to be addressed by unblinding at the group level, only members of the data monitoring board (an advisory group for this study formed to protect the integrity of data when unblinding for interim analyses must occur; see Section 4.8) can conduct additional analyses of the safety data.

3.9.5. Appropriateness and Consistency of Measurements

All efficacy and safety assessments have been well documented and are generally regarded as reliable, accurate, and relevant.

3.10. Patient Disposition Criteria

3.10.1. Discontinuations

Possible reasons for discontinuation from the study include the following:

- In the opinion of the investigator, a serious adverse event or a significant change in a laboratory value occurs. In this case, the study drug is discontinued and appropriate measures are taken. The sponsor is notified immediately.
- The patient, guardian or attending physician requests, or the investigator decides, that the patient should be withdrawn from the study.
- The patient, for any reason, requires treatment with another therapeutic agent that has been demonstrated to be effective for treatment of the study indication. In this case, discontinuation from the study occurs immediately upon introduction of the new agent.
- The investigator or Lilly, for any reason, stops the study or stops the patient's participation in the study.

A physical examination will be conducted on all patients who discontinue the study at any point after Visit 3. The investigator is responsible for ensuring that any abnormality found at the discontinuation physical examination receives appropriate follow-up.

3.11. Compliance

Study medication will be distributed by qualified personnel at the study site at each visit and recorded on designated worksheets. Compliance to protocol and treatment will be assessed by direct questioning and counting returned medication. All unused medication will be returned to the sponsor at the end of the study. Patients who miss their medication for 3 consecutive days at any time during Study Periods III through V, or for 7 consecutive days in Study Period VI will be deemed noncompliant and will be discontinued from the study.

Patients who fail to cooperate in tests or examinations or do not attend visits within the stated periods may be deemed noncompliant and subsequently discontinued from the study.

3.12. Quality Assurance

To ensure the safety of participants in the study and to ensure accurate, complete, and reliable data, Lilly or its representatives will do the following:

- Provide instructional material to the study sites, as appropriate.
- Sponsor a start-up training session to instruct the investigators and study coordinators. This session will give instruction on the protocol, the completion of the clinical report forms, and study procedures.
- Make periodic visits to the study site.
- Be available for consultation and stay in contact with the study site personnel by mail, telephone, and/or fax.
- Review and evaluate clinical report form data and use standard computer edits to detect errors in data collection.

To ensure the safety of participants in the study and to ensure accurate, complete, and reliable data, the investigator will do the following:

- Keep records of laboratory tests, clinical notes, and patient medical records in the patient files as original source documents for the study.

Lilly or its representatives may periodically check a sample of the patient data recorded against source documents at the study site. The study may be audited by Lilly Medical Quality Assurance (MQA) and/or regulatory agencies at any time. Investigators will be given notice before an MQA audit occurs.

4. Data Analysis Methods

4.1. General Considerations

The total number of randomized patients to be included in this study is approximately 220 patients or 110 patients per arm. The distribution of patients across investigators is expected to be approximately equal. Investigators who enroll no patients into one or more treatment groups will be pooled together for the purpose of statistical analyses when assessing treatment-by-investigator interactions.

Analyses will be done on an intent-to-treat basis unless otherwise specified. An intent-to-treat analysis is an analysis of data by the groups to which patients are assigned by random allocation, even if the patient does not take the assigned treatment, does not receive the correct treatment, or otherwise does not follow the protocol. Patients who have their dose reduced to 10 mg during the study will be included in all analyses as if they remained on 20 mg. (A summary of the number of patients who do have their dose reduced to 10 mg will be provided.)

Additional exploratory analyses of the data will be conducted as deemed appropriate. Statistical analysis of this study will be the responsibility of Eli Lilly and Company. All tests of hypotheses will be considered statistically significant if the two-sided p-value is less than 0.05. No adjustments for multiple comparisons will be made.

4.2. Data to be Analyzed

All patients with a randomization (Visit 4) and at least one postrandomization visit will be included in the analyses of efficacy from Study Periods III through V. All randomly assigned patients will be included in the analyses of safety data from Study Periods III through V. All patients with a Study Period VI baseline visit (Visit S) and at least one visit beyond baseline will be included in the analyses of efficacy from Study Period VI. All patients remaining in the Study Period VI at Visit S will be included in the analyses of safety from Study Period VI.

4.3. Patient Disposition

The reasons for discontinuation during this study will be summarized across all study periods. The percentages of patients discontinuing for lack of efficacy, adverse event, and for any reason will be compared between treatment groups using Pearson's chi-square test with 2 degrees of freedom for Study Periods III through IV and Study Periods III through V.

4.4. Patient Characteristics

The patient characteristics that will be collected include demographics (age, gender, origin) and psychiatric history. Baseline patient characteristics will be summarized for all patients enrolled in this study. Mean ages will be compared between the treatment groups using a t-test. The gender, origin, and psychiatric history distributions will be compared using Pearson's chi-square test. Since randomization will be stratified by gender and age category (childhood/adolescent), no differences between age and gender are expected. Should there be a difference in any characteristic on random assignment to the treatment period, analysis of covariance will be performed for the primary efficacy measure to check the robustness of the results, but will be considered as a secondary analysis.

4.5. Efficacy Analyses

The primary efficacy measure will be the CDRS-R. Secondary efficacy measures include the CGI-Severity, CGI-Improvement, K-SADS, MADRS, CDI, and BDI.

4.5.1. Acute Treatment (Study Periods III-V)

CDRS-R response rates will be compared between fluoxetine 20 mg and placebo as the primary analysis for the acute treatment periods. A CDRS-R responder for this analysis will be defined as a patient whose CDRS-R score decreased at least 30% from baseline (Visit 4) to the endpoint of Study Period IV (last of Visits 6-Visit 10). As a secondary analysis, CDRS-R response rates will be compared between fluoxetine 20 to 60 mg and placebo (endpoint defined as the last of Visits 6-15).

The above analyses include only patients treated at least one week with 20 mg (2 weeks total). Change in the CDRS-R score from baseline (Visit 4) to Study Periods III through IV endpoint (last measurement from Visits 5 through 10) and from baseline to Study Periods III through V endpoint (last measurement from Visits 5 through Visit 15) will be compared between fluoxetine and placebo as secondary efficacy analyses. Change in CDRS-R scores from baseline (Visit 4) to each subsequent visit (Visits 5 through Visit 15) and CDRS-R remission rates (using both the Study Period IV endpoint and Study Periods IV through V endpoint) will be compared between treatment groups as additional secondary analyses on the CDRS-R score. The by-visit analyses will be performed 1) by including only patients active in the study at the visit of interest and 2) by including all patients with at least one postrandomization measure using a last-observation-carried-forward approach. A CDRS-R remitter will be defined as a patient who has an endpoint CDRS-R score ≤28. Analyses of remission will include only those patients treated at least 1 week with 20 mg (2 weeks total). A repeated measures analysis on the CDRS-R score will also be performed as a secondary analysis.

Analyses on change from baseline (Visit 4) to Study Periods III through IV endpoint (last measurement from Visits 5 through 10) and Study Periods III through V endpoint (last of

measurement from Visit 5 through Visit 15) will be performed for the secondary efficacy measures, which includes the CGI-Severity, CGI-Improvement, K-SADS, MADRS, CDI, BDI, HAMA. For the analysis of CGI-Improvement, an ANOVA will be performed only on endpoint values, since this scale inherently measures total improvement in direct comparison to the patient's condition at enrollment. CGI-defined response rates will also be compared between treatment groups. A CGI responder will be defined as a patient whose endpoint CGI-improvement score was 1 or 2. All patients with at least one postrandomization measure will be included in the analysis.

To address the clinical question of whether nonresponders to fluoxetine 20 mg for 8 weeks would respond if the dosage was increased to 40-60 mg or maintained at 20 mg for a longer period of time, CDRS-R response rates will be compared between the nonresponders randomized to fluoxetine 20 mg and the nonresponders randomized to fluoxetine 40-60 mg (using Visit 4 as baseline). In addition, mean change in the CDRS-R, CGI-Severity, CDI, and BDI from the Study Period V baseline (Visit 10) to the Study Period V endpoint (last of Visits 11 through Visit 15) and endpoint CGI-Improvement will be compared.

An ANOVA (Type III sums of squares) with the term treatment in the model will be used when comparing change scores or endpoint scores between treatments. As secondary analyses, an ANOVA with treatment, investigator, gender, age category, and the treatment-by-investigator interaction in the model will be used. Analyses will be performed on both the original and the rank-transformed data. The analysis of the original data will be considered primary unless there is evidence to suggest non-normality. Pearson's chi-square test will be used to compare percentages. Logistic regression models with treatment, investigator, gender, age category and the treatment-by-investigator interaction will also be used to compare percentages, but will be considered secondary. The repeated measures analysis will be performed using a mixed model approach with visit as the within-subject factor, treatment as the between-subject factor and a treatment-by-visit interaction, using an unstructured covariance matrix (e.g., PROC MIXED).

4.5.2. Relapse Prevention Phase (Study Period VI)

Time to relapse during the relapse prevention phase will be compared between fluoxetine (10-60 mg) and placebo. A relapser will be defined as a patient whose CDRS-R score increased to over 40 at any one time during the relapse prevention phase in the presence of a history of 2 weeks of clinical deterioration as determined by patient report, parent report, or clinical history. If the physician feels patients have experienced relapse sufficient enough to discontinue the patient from the study but have not met criteria for relapse, the patient will also be considered a relapser for the primary analysis of relapse. As a secondary analysis of relapse, only those patients meeting the protocol-defined criteria will be considered a relapser. Time to relapse will be analyzed using Kaplan-Meier survival curves (log-rank test). Change in CDRS-R, CGI-Severity, CGI-Improvement,

K-SADS, MADRS, CDI, and BDI scores from baseline (Visit S) to each visit during the relapse prevention therapy phase (Visits S through 26) will be summarized between fluoxetine and placebo by 1) including only patients active in the study at the visit of interest and 2) by including all patients with at least one measure beyond Visit 17 using a last-observation-carried-forward approach. The same statistical methods described in Section 4.5.1 will be used for these analyses.

4.6. Safety Analyses

4.6.1. Acute Treatment (Study Periods III-IV)

Adverse events will be analyzed by comparing the incidence of treatment-emergent adverse events between treatment groups during Study Period III through IV and again for Study Period III through V using Study Periods I and II as baseline for the spontaneously collected adverse events. Treatment-emergent adverse events will also be compared between treatments using Study Period II as baseline for events collected by the Side Effect Checklist. (The Side Effect Checklist is not collected during Study Period I.) An event is considered treatment-emergent if it first occurs or worsens from baseline.

To compare the impact of titration to 40-60 mg, the incidence of treatment-emergent adverse events during Study Period V will be compared between the nonresponders randomized to fluoxetine 20 mg and the nonresponders randomized to fluoxetine 40-60 mg. Study Periods I through IV will be used as baseline for this analysis.

Change from baseline (last measurement from Visits 1 through 4) to Study Period III through V endpoint (last measurement from Visits 5 through Visit 15) in vital signs and continuous laboratory analytes will be compared between treatment groups. Note that since laboratory analytes will not be collected routinely at Visits 2 through Visit 15, laboratory baseline values will be those collected at Visit 1 and laboratory endpoint values will be those collected at Visit 15 or the visit of discontinuation if discontinued prior to Visit 15 for most, if not all patients. The incidence of treatment-emergent extreme values during Study Period III through V will also be compared between treatments for continuous laboratory analytes. Specifically, percentages of patients whose values changed from normal or low during Study Period I and II to high at any time during Study Period III through V will be compared between treatment groups among patients with normal or low values during Study Period I and II. Similarly, percentages of patients whose values changed from normal or high during Study Period I and II to low at any time during Study Period III through V will be compared between treatment groups for categorical laboratory analytes. That is, the percentages of patients whose values changed from normal during Study Periods I and II to abnormal at anytime during Study Period III through V will be compared between treatment groups among patients with normal values during Study Period I and II.

The same statistical methods described in Section 4.5.1 will be used for these analyses.

4.6.2. Relapse Prevention Phase (Study Period VI)

Adverse events will be analyzed by comparing the incidence of treatment-emergent adverse events between treatment groups during Study Period VI (after Visit S) using Study Periods I through V (and up through Visit S) as baseline for the spontaneously collected adverse events. Treatment-emergent adverse events during Study Period VI (after Visit S) will also be compared between treatments using Study Period II through V (and up through Visit S) as baseline for events collected by the Side Effect Checklist. (The Side Effect Checklist is not collected during Study Period I.)

The same statistical methods described in Section 4.5.1 will be used for these analyses.

4.7. Subgroup Analyses

Efficacy analyses of the CDRS-R and CGI and treatment-emergent adverse events will be performed for children and adolescents separately, males and females separately, and for children with a family history of depression.

4.8. Interim Analyses

One interim analysis is planned. The interim analysis will take place after all patients complete Study Period IV (Visit 10). The interim analysis will be conducted in order to obtain and communicate the results from the fixed-dose acute treatment phase in a more timely manner. The results from the fixed-dose acute treatment unblinded at the treatment level may be presented outside the company including to regulatory agencies. Additional interim analyses may take place after all patients complete Study Period V (the end of all acute treatment periods) and/or after all patients complete Visit 13 (2 weeks with doses up to 60 mg). These interim analyses will only take place if results are needed for decision-making purposes prior to the expected completion of the study. The study will not be stopped if evidence of efficacy is observed, thus adjustment of p-values is not required. To minimize the bias for the relapse prevention therapy phase, no one at the study site will be unblinded at the patient level.

Planned interim analyses, and any unplanned interim analyses, will be conducted under the auspices of the data monitoring board assigned to this study. Only the data monitoring board is authorized to review completely unblinded interim efficacy and safety analyses and, if necessary, to disseminate those results. The data monitoring board will disseminate interim results in a manner that will minimize bias. Study sites will not receive information about interim results unless they need to know for the safety of their patients.

4.9. Pharmacokinetic/Pharmacodynamic Analyses

Up to four blood samples from each patient (see Protocol Attachment HCJE.1) will be collected. The concentrations of fluoxetine and norfluoxetine will be measured from these samples. Samples will be collected at baseline and during periods of constant-dose study drug administration (steady-state concentration). The analysis will incorporate steady-state daily dose, time since the last dose of active study drug, and the influence of covariates such as gender or age. The relationship between plasma concentration and treatment-emergent adverse events may also be assessed.

5. Informed Consent, Ethical Review, and Regulatory Considerations

5.1. Informed Consent

The informed consent document will be used to explain in simple terms, before the patient is entered into the study, the risks and benefits to the patient. The informed consent document must contain a statement that the consent is freely given, that the patient is aware of the risks and benefits of entering the study, and that the patient is free to withdraw from the study at any time.

The investigator is responsible to see that informed consent is obtained from each patient or legal representative and for obtaining the appropriate signatures and dates on the informed consent document prior to the performance of any protocol procedures and prior to the administration of study drug.

A parent or legal representative must give informed consent for a child to participate in this study. In addition, the child may be required to give assent to participate in the study, if the ethical review board determines that the child is capable of providing such assent.

If the ethical review board opts to waive the requirement for the assent provision, the investigator must document the waiver and send a copy of that documentation to Lilly.

As used in this protocol, the term "informed consent" includes all consent and/or assent given by subjects, patients, or their legal representatives.

5.2. Ethical Review

The investigator will provide Lilly with documentation of ethical review board approval of the protocol and the informed consent document *before* the study may begin at the site or sites concerned. The ethical review board(s) will review the protocol as required.

The investigator is to supply the following to the study site's ethical review board(s):

- the current CIB
- all updates to the CIB during the course of the study
- relevant curricula vitae.

The investigator must provide the following documentation:

- The ethical review board's annual reapproval of the protocol
- The ethical review board's approvals of any revisions to the informed consent document or amendments to the protocol.

5.3. Regulatory Considerations

This study will be conducted in accordance with the ethical principles stated in the most recent version of the Declaration of Helsinki or the applicable guidelines on good clinical practice, whichever represents the greater protection of the individual.

After reading the protocol, each investigator will sign two protocol signature pages and return one of the signed pages to a Lilly representative (see Protocol Attachment HCJE.3).

This study is being conducted under a US Investigational New Drug (IND) application. The US IND number is 12274.

6. References

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Protocol Attachment HCJE.1.
Schedule of Events

Schedule of Events, Protocol B1Y-MC-HCJE, Study Periods I through IV

Study Period	I			II	III	IV						
Visit (Week) / Activity	V1 (-3)	V2 (-2)	V3 (-1)	V4 (0)	V5 (1)	V6 (2)	V7 (3)	V8 (5)	V9 (7)	V10 (9)	Unsched Visit	Early D/C
Patient informed consent	x											
Parent informed consent	x											
MAGIC or DICA (Patient Version)	x	R	R									
MAGIC or DICA (Parent Version)	x	R	R									
K-SADS		x	x	x						x		x
Historical diagnosis	x	R	R									
Psychiatric history / Previous therapy	x	R	R									
Modified Family History RDC	x	R	R									
Urine Drug Screen	x											
Urine Antidepressant Screen	x											
Laboratory tests[a]	x											x
Fluoxetine/norfluoxetine levels	x									x		x
Consumptive habits	x											
Demographics	x											
Physical examination	x											x
Weight	x											x
Height	x											
ECG	x											x
Vitals	x	x	x	x	x	x	x	x	x	x	x	x
Secondary conditions	x											
Adverse events		x	x	x	x	x	x	x	x	x	x	x
Side Effects Checklist				x	x	x	x	x	x	x		x
Dosage adjustment[b]				x↑	x↑	x↓				x↑		
Concomitant medications	x	x	x	x	x	x	x	x	x	x	x	x
CDRS-R	x	x	x	x	x	x	x	x	x	x	x	x
CGI-Severity	x	x	x	x	x	x	x	x	x	x	x	x
CGI-Improvement		x	x	x	x	x	x	x	x	x	x	x
MADRS	x	x	x	x	x	x	x	x	x	x	x	x
CDI (aged 8 to <13 only)	x	x	x	x				x		x		x
BDI (aged 13 to <18 only)	x	x	x	x				x		x		x
HAMA	x	x	x	x				x		x		x
Patient summary												x

Abbreviations: BDI = Beck Depression Inventory; CDI = Children's Depression Inventory; CDRS-R = Childhood Depression Rating Scale-Revised; CGI-Severity = Clinical Global Impressions of Severity; CGI-Improvement = Clinical Global Impressions of Improvement; MAGIC= Missouri Assessment of Genetics Interview for Children; DICA= Diagnostic Interview for Children and Adolescents; ECG = electrocardiogram; HAMA = Hamilton Anxiety Rating Scale; K-SADS-PL = Kiddie Schedule for Affective Disorders and Schizophrenia- Present and Lifetime; MADRS = Montgomery-Asberg Depression Rating Scale; R = reviewed at this visit; x = performed at this visit.

a Specified in Section 3.9.3.3, Table HCJE.1, Clinical Laboratory Tests.

b Arrows indicate the direction of dosage adjustments. All fluoxetine-treated patients will have their dosage increased to fluoxetine 20 mg at Visit 5. Patients who cannot tolerate fluoxetine 20 mg at Visits 6, 7, 8, or 9 may have their dose decreased to fluoxetine 10 mg, but must remain on 10 mg for the remainder of the study. Nonresponders will rerandomized to 20 or 40 mg at Visit 10.

Schedule of Events, Protocol B1Y-MC-HCJE Acute Phase, Study Period V

Study Period	IV	V						
Visit	V10	V11	V12	V13	V14	V15	Unsched Visit	Early D/C
Activity (Week)	(9)	(11)	(13)	(15)	(17)	(19)		
K-SADS	x					x		x
Laboratory tests[a]						x		x
Fluoxetine/norfluoxetine levels	x					x		x
Physical examination						x		x
Weight						x		x
Height						x		
ECG						x		x
Vitals	x	x	x	x	x	x	x	x
Adverse events	x	x	x	x	x	x	x	x
Side Effects Checklist	x	x	x	x	x	x		x
Dosage adjustment[b]	x↑	x↑	x↓					
Concomitant medications	x	x	x	x	x	x	x	x
CDRS-R	x	x	x	x	x	x	x	x
CGI-Severity	x	x	x	x	x	x	x	x
CGI-Improvement	x	x	x	x	x	x	x	x
MADRS	x	x	x	x	x	x	x	x
CDI (aged 8 to <13 only)	x	x		x		x		x
BDI (aged 13 to <18 only)	x	x		x		x		x
HAMA	x	x		x		x		x
Patient summary								x

Abbreviations: BDI = Beck Depression Inventory; CDI = Children's Depression Inventory; CDRS-R = Childhood Depression Rating Scale-Revised; CGI-Severity = Clinical Global Impressions of Severity; CGI-Improvement = Clinical Global Impressions of Improvement; ECG = electrocardiogram; HAMA = Hamilton Anxiety Rating Scale; K-SADS-PL = Kiddie Schedule for Affective Disorders and Schizophrenia- Present and Lifetime; MADRS = Montgomery-Asberg Depression Rating Scale; x = performed at this visit.

a Specified in Section 3.9.3.3, Table HCJE.1, Clinical Laboratory Tests.

b Nonresponders will rerandomized to 20 or 40 mg at Visit 10. Dosage decreases for safety purposes can be made at any scheduled or unscheduled visit between Visits 10 and 13. After Visit 13, no further dosage adjustments may be made during Study Period V.

Schedule of Events, Protocol B1Y-MC-HCJE Relapse Prevention Phase, Study Period VI

Study Period	V	VI												
Visit (Week) / Activity	V15 (19)	V16 (21)	V17 (23)	V18 (25)	V19 (27)	V20 (29)	V21 (31)	V22 (35)	V23 (39)	V24 (43)	V25 (47)	V26 (51)	Unsched Visit	Early D/C
K-SADS	x											x		x
Laboratory tests[a]	x											x		x
Fluoxetine/norfluoxetine levels	x											x		x
Physical examination	x											x		x
Weight	x											x		x
Height	x											x		x
ECG	x											x		x
Vitals	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Adverse events	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Side Effects Checklist	x	x	x	x	x	x	x	x	x	x	x	x		x
Dosage adjustment[b]														
Concomitant medications	x	x	x	x	x	x	x	x	x	x	x	x	x	x
CDRS-R	x	x	x	x	x	x	x	x	x	x	x	x	x	x
CGI-Severity	x	x	x	x	x	x	x	x	x	x	x	x	x	x
CGI-Improvement	x	x	x	x	x	x	x	x	x	x	x	x	x	x
MADRS	x	x	x	x	x	x	x	x	x	x	x	x	x	x
CDI (aged 8 to <13 only)	x		x		x		x	x		x		x		x
BDI (aged 13 to <18 only)	x		x		x		x	x		x		x		x
HAMA	x		x		x		x	x		x		x		x
Patient summary												x		x

Abbreviations: BDI = Beck Depression Inventory; CDI = Children's Depression Inventory; CDRS-R = Childhood Depression Rating Scale-Revised; CGI = Clinical Global Impressions; ECG = electrocardiogram; HAMA = Hamilton Anxiety Rating Scale; K-SADS-PL = Kiddie Schedule for Affective Disorders and Schizophrenia- Present and lifetime; MADRS = Montgomery-Asberg Depression Rating Scale; x = performed at this visit.

a Specified in Section 3.9.3.3, Table HCJE.1, Clinical Laboratory Tests.

b Patients will remain on the last dosage prescribed during the titration phase; additional dosage adjustments will not be allowed during the relapse prevention phase.

Protocol Attachment HCJE.2.
Excluded Medications

Excluded Medications
Protocol B1Y-MC-HCJE

This is not an exhaustive list. Included are the most often prescribed medications in each category. However, there may be other unlisted drugs within these categories that also should not be given to the patient during this study. If in doubt, consult with the global clinical research administrator and/or clinical research physician.

Antidepressants
amitriptyline
amoxapine
benactyzine
bupropion
clomipramine
desipramine
doxepin
fluoxetine
fluvoxamine
imipramine
maprotiline
nortriptyline
paroxetine
protriptyline
sertraline
trazodone
trimipramine
venlafaxine
St. Johns Wort (OTC)

MAOIs
furazolidone
phenelzine
procarbazine
selegiline
tranylcypromine

CNS Stimulants
amphetamine
dextroamphetamine
methamphetamine
methylphenidate
pemoline

Anxiolytics
alprazolam
buspirone
chlordiazepoxide
chlormezanone
clorazepam
clorazepate
diazepam
doxepin
halazepam
hydroxyzine
lorazepam
meprobamate
oxazepam
prazepam

Antipsychotics
acetophenazine
chlorpromazine
chlorprothixene
clozapine
fluphenazine
haloperidol
loxapine
mesoridazine
molindone
perphenazine
pimozide
prochlorperazine
promazine
thioridazine
thiothixene
trifluoperazine
triflupromazine

Antimigraine Compounds
dihydroergotamine
ergotamine (and derivatives)
isometheptene/dichloralphen
methysergide
sumatriptan

Sedative-Hypnotics/Sleep Aids
acetylcarbromal
amobarbital
aprobarbital
butabarbital
doxylamine (OTC)
estazolamine
ethchlorvynol
ethinamate
flurazepam
glutethimide
melatonin (OTC)
mephobarbital
metharbital
methyprylon
paraldehyde
pentobarbital
phenobarbital
propiomazine
pyrilamine (OTC)
quazepam
secobarbital
temazepam
triazolam
tryptophan (including OTC)
zolpidem

Antimanic
lithium

Xanthine Bronchodilators
aminophylline
theophylline

Pain Medications
alfentanil
buprenorphine
butalbital
butorphanol
codeine
dezocine
fentanyl
hydrocodone
hydromorphone
levorphanol
meperidine
methadone
methotrimeprazine
morphone
nalbuphine
opium
oxycodone
oxymorphone
pentazocine
propoxyphene
sufentanil
tramadol

Decongestants
phenylephrine
phenylpropanolamine

Antihistamines
chlorpheniramine (OTC)
Note: We will allow Allegra
Clariton, & Tavist (OTC)

Cardiovascular Medications
acebutolol
atenolol
clonidine
doxazsin
guanabenz
guanadrel
guanethidine
guanfacine
hydralazine
labetalol
mecamylamine
methyldopa
metoprolol
metyrosine
minoxidil
nadolol
nisoldipine
nitrendipine
penbutolol
phenoxybenzamine
phentalomine
pindolol
prazosin
propanolol
reserpine
terazosin
timolol

Other
all muscle relaxants
all anorexiants

Any Illicit Drugs

Protocol Attachment HCJE.3.
Protocol Signatures

Protocol Signatures
Protocol B1Y-MC-HCJE(a)

I confirm that I have read this protocol, I understand it, and I will work according to this protocol and to the ethical principles stated in the latest version of the Declaration of Helsinki, the applicable guidelines for good clinical practices, or the applicable laws and regulations of the country of the study site for which I am responsible, whichever provides the greater protection of the individual. I will accept the monitor's overseeing of the study. I will abide by the publication plan set forth in my agreement with Eli Lilly and Company (or subsidiary).

Instructions to the investigator--Please SIGN and DATE both copies of this signature page. PRINT your name, title, and the name of the facility in which the study will be conducted on both copies. Return one of the signed copies to Lilly.

Signature of Investigator | Date

Signature of Representative of
Eli Lilly and Company (or Subsidiary) | Date

[redacted]
Lilly Corporate Center

Instructions to the investigator: Please print or type remaining information.

Investigator Name

Investigator Title

Name of Facility

Location of Facility
(City, State (if applicable), Country)

Protocol Signatures
Protocol B1Y-MC-HCJE(a)

I confirm that I have read this protocol, I understand it, and I will work according to this protocol and to the ethical principles stated in the latest version of the Declaration of Helsinki, the applicable guidelines for good clinical practices, or the applicable laws and regulations of the country of the study site for which I am responsible, whichever provides the greater protection of the individual. I will accept the monitor's overseeing of the study. I will abide by the publication plan set forth in my agreement with Eli Lilly and Company (or subsidiary).

Instructions to the investigator: Please SIGN and DATE both copies of this signature page. PRINT your name, title, and the name of the facility in which the study will be conducted on both copies. Return one of the signed copies to Lilly.

Signature of Investigator

Date

Signature of Representative of
Eli Lilly and Company (or Subsidiary)

Date

[redacted]
Lilly Corporate Center

Instructions to the investigator: Please print or type remaining information.

Investigator Name

Investigator Title

Name of Facility

Location of Facility
(City, State (if applicable), Country)

16.1.2.
Sample Clinical Report Form

Clinical Report Form
Fluoxetine Versus Placebo in Childhood/Adolescent Depression
B1Y-MC-HCJE

PATIENT AND VISIT IDENTIFICATION

Patient initials _____ _____ _____
First Middle Last

Visit date _____/_____/_____
MM DD YY

INFORMED CONSENT : PATIENT (CHILD)

Date patient (child) signed the consent document _____/_____/_____
MM DD YY

INFORMED CONSENT : PARENT/GUARDIAN

Date parent/guardian signed the consent document _____/_____/_____
MM DD YY

REMINDER

Record the patient's pre-existing conditions on the Pre-existing Conditions and Study Adverse Events pages.

Record all medications the patient is currently taking on the Concomitant Medication pages.

Initials
Date Verified
Initials
Date Keyed
Date Received at Lilly
Reviewed
Inspected
Date

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DEMOGRAPHICS

Date of birth _____/_____/__ __ __ __
MM DD Y Y Y Y

Sex ☐F Female ☐M Male

Origin
☐CA Caucasian (European, Mediterranean, Middle Eastern)
☐AF African Descent (Black)
☐EA East/Southeast Asian (Burmese, Chinese, Japanese, Korean, Mongolian, Vietnamese)
☐AS Western Asian (Pakistani, Indian Sub-continent)
☐HP Hispanic (Mexican-American, Mexico, Central and South America)
☐O Other (Mixed-racial parentage, American Indian, Eskimo)

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Clinical Report Form
Fluoxetine Versus Placebo in Childhood/Adolescent Depression
B1Y-MC-HCJE

SIGNIFICANT HISTORICAL DIAGNOSES

NO SIGNIFICANT HISTORICAL DIAGNOSES ☐

List each clinically significant (at the discretion of the investigator) historical diagnosis that is **NO LONGER PRESENT** (no longer clinically active). If exact date is unknown, enter month and year. A year MUST be entered.

	Historical Diagnosis	Date Recovered MM	DD	YY
0.				
1.				
2.				
3.				
4.				
5.				
6.				
7.				
8.				
9.				
10.				
11.				
12.				
13.				
14.				
15.				
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Clinical Report Form
Fluoxetine Versus Placebo in Childhood/Adolescent Depression
B1Y-MC-HCJE

PSYCHIATRIC HISTORY : MAJOR DEPRESSION

INFORMATION NOT OBTAINED ☐

Use whole numbers only.

1. What was the age of the patient at the first MDD episode? ____ years
2. What is the duration of the current MDD episode? ____ weeks
3. Has the patient had one or more previous episodes of MDD? ☐ 1 Yes ☐ 2 No

4. What was the number of previous episodes of MDD? ____ episodes
5. What was the duration of the last MDD episode? ____ weeks
6. What is the time interval between the start of the current MDD episode and remission of the last MDD episode? ____ weeks
7. If there have been 3 or more previous MDD episodes, was there a seasonal pattern for those episodes? ☐ 1 Yes ☐ 2 No ☐ 96 Not Applicable

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FAMILY HISTORY : PSYCHIATRIC

INFORMATION NOT OBTAINED ☐

1. Is there a history of depression in the following *biological* family members:

Mother	☐ 1 Yes	☐ 2 No	☐ 97 Unknown	
Father	☐ 1 Yes	☐ 2 No	☐ 97 Unknown	
Siblings (brother, sister)	☐ 1 Yes	☐ 2 No	☐ 97 Unknown	☐ 96 Not Applicable

If yes, enter number of siblings with depression _____

2. Is there a history of manic depression (bipolar) in the following *biological* family members:

Mother	☐ 1 Yes	☐ 2 No	☐ 97 Unknown	
Father	☐ 1 Yes	☐ 2 No	☐ 97 Unknown	
Siblings (brother, sister)	☐ 1 Yes	☐ 2 No	☐ 97 Unknown	☐ 96 Not Applicable

If yes, enter number of siblings with manic depression (bipolar) disorder _____

3. Is there a history of anxiety disorders (i.e., OCD, panic disorder, generalized) in the following *biological* family members:

Mother	☐ 1 Yes	☐ 2 No	☐ 97 Unknown	
Father	☐ 1 Yes	☐ 2 No	☐ 97 Unknown	
Siblings (brother, sister)	☐ 1 Yes	☐ 2 No	☐ 97 Unknown	☐ 96 Not Applicable

If yes, enter number of siblings with anxiety disorder _____

RATER'S IDENTIFICATION : DICA ADMINISTRATION

Rater's initials _____ _____ _____
First Middle Last

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PHYSICIAN CHECK LIST

INFORMATION NOT OBTAINED ☐

Answer the following questioning concerning the circumstances in the patient's life.

1. Attending school ☐1 Yes ☐2 No
2. Change to special classes/school ☐1 Yes ☐2 No
3. School difficulties ☐1 Yes ☐2 No
4. Other therapy ☐1 Yes ☐2 No
5. Vacation ☐1 Yes ☐2 No
6. Illness ☐1 Yes ☐2 No
7. Sexual activity ☐1 Yes ☐2 No
8. Change in family mental status ☐1 Yes ☐2 No
9. Change in family status (divorce, death, grandparent illentss, etc) ☐1 Yes ☐2 No
10. Family move ☐1 Yes ☐2 No
11. Death of friend or close family member ☐1 Yes ☐2 No
12. Sexual abuse ☐1 Yes ☐2 No
13. Physical abuse ☐1 Yes ☐2 No
14. Mental abuse ☐1 Yes ☐2 No
15. Other _____
    Specify

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B1Y-MC-HCJE

PSYCHIATRIC DIAGNOSTIC SURVEY

INFORMATION NOT OBTAINED ☐

DISORDER	LIFETIME				CURRENT (within past 1 month)		
	Absent	Sub-Threshold	Threshold	Unknown	Absent	Sub-Threshold	Threshold
A. Bipolar I Disorder							
1. Single manic episode	☐ 1	☐ 2	☐ 3	☐ 97	☐ 4	☐ 8	☐ 9
2. Recurrent manic episode	☐ 1	☐ 2	☐ 3	☐ 97	☐ 4	☐ 8	☐ 9
3. Single depressed episode	☐ 1	☐ 2	☐ 3	☐ 97	☐ 4	☐ 8	☐ 9
4. Recurrent depressed episode	☐ 1	☐ 2	☐ 3	☐ 97	☐ 4	☐ 8	☐ 9
5. Mixed episode	☐ 1	☐ 2	☐ 3	☐ 97	☐ 4	☐ 8	☐ 9
B. Bipolar II Disorder	☐ 1	☐ 2	☐ 3	☐ 97	☐ 4	☐ 8	☐ 9

C. Substance Use Disorder	Absent	Abuse	Dependence	Absent	Present
1. Alcohol	☐ 1	☐ 6	☐ 7	☐ 4	☐ 5
2. Sedative/hypnotic/ Anxiolytic	☐ 1	☐ 6	☐ 7	☐ 4	☐ 5
3. Cannabis	☐ 1	☐ 6	☐ 7	☐ 4	☐ 5
4. Stimulants (nonprescribed)	☐ 1	☐ 6	☐ 7	☐ 4	☐ 5
5. Opioid	☐ 1	☐ 6	☐ 7	☐ 4	☐ 5
6. Cocaine	☐ 1	☐ 6	☐ 7	☐ 4	☐ 5
7. Hallucinogen/PCP	☐ 1	☐ 6	☐ 7	☐ 4	☐ 5
8. Other	☐ 1	☐ 6	☐ 7	☐ 4	☐ 5

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PSYCHIATRIC DIAGNOSTIC SURVEY

DISORDER	LIFETIME				CURRENT (within past 1 month)		
	Absent	Sub-Threshold	Threshold	Unknown	Absent	Sub-Threshold	Threshold
D. Attention Deficit Disorder	☐ 1	☐ 2	☐ 3	☐ 97	☐ 4	☐ 8	☐ 9
E. Oppositional Disorder	☐ 1	☐ 2	☐ 3	☐ 97	☐ 4	☐ 8	☐ 9
F. Conduct Disorder	☐ 1	☐ 2	☐ 3	☐ 97	☐ 4	☐ 8	☐ 9
G. Major Depressive Disorder	☐ 1	☐ 2	☐ 3	☐ 97	☐ 4	☐ 8	☐ 9
H. Mania	☐ 1	☐ 2	☐ 3	☐ 97	☐ 4	☐ 8	☐ 9
I. Dysthymic Disorder	☐ 1	☐ 2	☐ 3	☐ 97	☐ 4	☐ 8	☐ 9
J. Separation Anxiety Disorder	☐ 1	☐ 2	☐ 3	☐ 97	☐ 4	☐ 8	☐ 9
K. Overanxious Disorder	☐ 1	☐ 2	☐ 3	☐ 97	☐ 4	☐ 8	☐ 9
L. Simple Phobia	☐ 1	☐ 2	☐ 3	☐ 97	☐ 4	☐ 8	☐ 9
M. Obsessive Compulsive Disorder	☐ 1	☐ 2	☐ 3	☐ 97	☐ 4	☐ 8	☐ 9
N. Compulsions	☐ 1	☐ 2	☐ 3	☐ 97	☐ 4	☐ 8	☐ 9
O. Avoidant Disorder	☐ 1	☐ 2	☐ 3	☐ 97	☐ 4	☐ 8	☐ 9
P. Post-Traumatic Stress Disorder	☐ 1	☐ 2	☐ 3	☐ 97	☐ 4	☐ 8	☐ 9
Q. Anorexia Nervosa	☐ 1	☐ 2	☐ 3	☐ 97	☐ 4	☐ 8	☐ 9
R. Bulimia	☐ 1	☐ 2	☐ 3	☐ 97	☐ 4	☐ 8	☐ 9
S. Somatization	☐ 1	☐ 2	☐ 3	☐ 97	☐ 4	☐ 8	☐ 9
T. Enuresis	☐ 1	☐ 2	☐ 3	☐ 97	☐ 4	☐ 8	☐ 9
U. Encopresis	☐ 1	☐ 2	☐ 3	☐ 97	☐ 4	☐ 8	☐ 9
V. Gender Identity	☐ 1	☐ 2	☐ 3	☐ 97	☐ 4	☐ 8	☐ 9
W. Psychotic Symptoms	☐ 1	☐ 2	☐ 3	☐ 97	☐ 4	☐ 8	☐ 9

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HABITS : SMOKING

INFORMATION NOT OBTAINED ☐

Enter the average current daily use
0 = None
L = Less than one *(eg, cigar or pipe smoker who smokes only 1 or 2x a week)*
1, 2, 3, etc = Whole numbers ONLY

Number of cigarettes _____

Number of cigars _____

Number of pipesful _____

Enter the number of years (past or current) patient has smoked. If patient has never smoked, enter 0. _____ years

HABITS : SMOKELESS TOBACCO

INFORMATION NOT OBTAINED ☐

Does the patient currently use smokeless tobacco? ☐ 1 Yes ☐ 2 No

HABITS : ALCOHOL

INFORMATION NOT OBTAINED ☐

Enter the average current weekly consumption
0 = None
L = Less than one
1, 2, 3, etc = Whole numbers ONLY

Number of beers or wine coolers/spritzers _____

Number of glasses of wine _____

Number of drinks containing distilled spirits _____

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HABITS : CAFFEINE

INFORMATION NOT OBTAINED ☐

Enter the average current daily consumption
0 = None
L = Less than one
1, 2, 3, etc = Whole numbers ONLY

Number of cups of *caffeinated* coffee _____

Number of cups of *caffeinated* tea _____

Number of *caffeinated* colas _____

PROCEDURE : PHYSICAL EXAM

NOTE: A physical exam must be performed for entry into the study.

Was a physical exam performed? ☐1 Yes ☐2 No

WEIGHT

INFORMATION NOT OBTAINED ☐

Measure with shoes off. Round up or down to the nearest whole pound.

Weight ___ ___ ___ (lb)

HEIGHT

INFORMATION NOT OBTAINED ☐

Measure with shoes off. Round up or down to the nearest whole inch.

Height ___ ___ ___ (in)

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VITAL SIGNS : BLOOD PRESSURE AND HEART RATE

INFORMATION NOT OBTAINED ☐

Position
SI = Sitting

Position	Blood Pressure (mm Hg) Systolic/Diastolic	Heart Rate (bpm)
SI	/	

VITAL SIGNS: TEMPERATURE

INFORMATION NOT OBTAINED ☐

Temperature ___ ___ ___ . ___

Unit of measure (F) Fahrenheit

Method (E) Ear

MENSTRUAL CYCLE

INFORMATION NOT OBTAINED ☐

1. Does the patient menstruate? ☐ 1 Yes ☐ 2 No ☐ 96 Not Applicable (males)

2. First day of last menstrual cycle _____/_____/_____ (MM DD YY)

3. Are cycles regular? ☐ 1 Yes ☐ 2 No

4. Number of days in cycle _____ (days)

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CONTRACEPTION

INFORMATION NOT OBTAINED ☐

Contraception is ensured through:

- ☐ 13 Prepubertal status
- ☐ 9 Strict abstinence
- ☐ 7 Use of condom and spermicidal foam
- ☐ 4 Use of oral contraceptives
- ☐ 6 Use of contraceptive implant
- ☐ 5 Use of intra-uterine device (IUD)
- ☐ 11 Depo-Provera©
- ☐ 10 Solitary partner who is vasectomized
- ☐ 8 Homosexual lifestyle
- ☐ 1 Surgical sterilization
- ☐ 2 Radiation-induced sterilization
- ☐ 96 Not applicable (applies to male patients)

Note: If a female patient is not using one of the above methods of contraception, she cannot be entered into this phase of the study.

ELECTROCARDIOGRAM

INFORMATION NOT OBTAINED ☐

Electrocardiogram date _____/_____/_____
MM DD YY

Electrocardiogram result ☐ 12 Acceptable ☐ 13 Not Acceptable

Insert the ECG (original) in the envelope provided.

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B1Y-MC-HCJE

PREVIOUS DRUG THERAPY

NO PREVIOUS DRUG THERAPY ☐

Enter any previous medications and non-drug therapies (eg, electroconvulsive therapy, photo-therapy) for the treatment of any neuropsychiatric or behavior conditions that were discontinued within the last year.

Stop Code
59 = Noncompliance
79 = To enter this trial
52 = Inadequate response
3 = Adverse event
33 = Adequate response
99 = Other

	Brand or Trade Name (Enter generic if trade unknown)	Dose	Unit	Fre-quency	Route	Start Date MM DD YY	Stop Date MM DD YY	Stop Code
0.								
1.								
2.								
3.								
4.								
5.								
6.								
7.								
8.								
9.								
10.								

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B1Y-MC-HCJE

CHILDRENS DEPRESSION RATING SCALE - REVISED

INFORMATION NOT OBTAINED ☐

CHECK THE NUMERIC CODE which best describes the patient.

1. **SCHOOLWORK**:

☐ 1 Performance consistent with ability
☐ 2
☐ 3 Decrease in school performance
☐ 4
☐ 5 Major interference in most subjects
☐ 6
☐ 7 No motivation to perform

2. **CAPACITY TO HAVE FUN**

☐ 1 Interest and activities realistically appropriate for age, personality, and social environment. Shows no appreciable change with present illness.
☐ 2
☐ 3 Describes some activities realistically available several times a week but not on a daily basis. Shows interest but not enthusiasm.
☐ 4
☐ 5 Is easily bored. Complains of "nothing to do." Participates in structured activities with a "going through the motions" attitude. May express interest primarily in activities that are (realistically) unavailable on a daily or weekly basis.
☐ 6
☐ 7 Has no initiative to become involved in any activities. Primarily passive. Watches others play or watches TV but shows little interest. Requires coaxing and/or pushing to get involved in activity. Shows no enthusiasm or real interest. Has difficulty naming activities.

3. **SOCIAL WITHDRAWAL**

☐ 1 Enjoys friendships with peers at school and home
☐ 2
☐ 3 May not actively seek out friendships but waits for others to initiate a relationship or may occasionally reject opportunities to play without a describable alternative
☐ 4
☐ 5 Frequently avoids or refuses opportunities for desirable interaction with others and/or sets up situations where rejection is inevitable.
☐ 6
☐ 7 Does not currently relate to other children. States he or she has "no friends" or actively rejects new or former friends.

4. **SLEEP**

☐ 1 No (or occasional) difficulty. (Goes to sleep within 1/2 hour or less.)
☐ 2
☐ 3 Frequently has mild difficulty with sleep
☐ 4
☐ 5 Moderate difficulty with sleep nearly every night.

5. **APPETITE OR EATING PATTERNS**

☐ 1 No problems or change in eating pattern
☐ 2
☐ 3 Mild change from usual eating habits within onset of current behavioral problem
☐ 4
☐ 5 Is not hungry most of the time or has excessive food intake since onset of current behavioral problems or marked increase in appetite

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CHILDRENS DEPRESSION RATING SCALE - REVISED

CHECK THE NUMERIC CODE which best describes the patient.

6. **EXCESSIVE FATIGUE**

- ☐ 1 No unusual complaints of "feeling tired" during the day
- ☐ 2
- ☐ 3 Complaints of fatigue which seem somewhat excessive and not related to boredom
- ☐ 4
- ☐ 5 Daily complaints of feeling tired
- ☐ 6
- ☐ 7 Complains of feeling tired most of the day. May voluntarily take long naps without feeling refreshed. Interferes with play activities.

7. **PHYSICAL COMPLAINTS**:

- ☐ 1 Occasional complaints
- ☐ 2
- ☐ 3 Complaints appear mildly excessive
- ☐ 4
- ☐ 5 Complains daily. Some interference with the ability of the child to function
- ☐ 6
- ☐ 7 Preoccupied with aches and pains; interferes with play activities several times a week

8. **IRRITABILITY**

- ☐ 1 Rare
- ☐ 2 Occasional
- ☐ 3 Several times a week for short periods
- ☐ 4
- ☐ 5 Several times a week for longer periods
- ☐ 6
- ☐ 7 Constant

9. **GUILT**

- ☐ 1 Does not express any undue feeling of guilt. Appears appropriate to precipitating event.
- ☐ 2
- ☐ 3 Exaggerates guilt and/or shame out of proportion to the event described.
- ☐ 4
- ☐ 5 Feels guilty over things not under his or her control. Guilt is definitely pathological.
- ☐ 6
- ☐ 7 Severe delusions of guilt

10. **SELF-ESTEEM**

- ☐ 1 Describes self in primarily positive terms
- ☐ 2
- ☐ 3 Describes self with one important area where the child feels deficit
- ☐ 4
- ☐ 5 Describes self in preponderance of negative terms or gives bland answers to questions
- ☐ 6
- ☐ 7 Refers to self in derogatory terms. Reports that other children refer to him/her frequently by using derogatory nicknames and child puts self down

11. **DEPRESSED FEELINGS**

- ☐ 1 Occasional feelings of unhappiness which quickly disappear
- ☐ 2
- ☐ 3 Describes sustained periods of unhappiness which appear excessive for events described
- ☐ 4
- ☐ 5 Feels unhappy most of the time without a major precipitating cause
- ☐ 6
- ☐ 7 Feels unhappy all of the time. Accompanied by psychic pain (e.g., "I can't stand it").

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B1Y-MC-HCJE

CHILDRENS DEPRESSION RATING SCALE - REVISED

CHECK THE NUMERIC CODE which best describes the patient.

12. **MORBID IDEATION**

- ☐ 1 None
- ☐ 2
- ☐ 3 Has some morbid thought, all of which relate to a reality event but seem excessive.
- ☐ 4
- ☐ 5 Preoccupied with morbid thoughts several times a week. Morbid thoughts extend beyond external reality
- ☐ 6
- ☐ 7 Preoccupied with death themes or morbid thoughts that are elaborate, extensive or bizarre on a daily basis

13. **SUICIDAL IDEATION**

- ☐ 1 Understands the word "suicide" but does not apply term to self
- ☐ 2 Sharp denial of suicidal thoughts
- ☐ 3 Has thoughts about suicide, usually when angry.
- ☐ 4
- ☐ 5 Has recurrent thoughts of suicide
- ☐ 6
- ☐ 7 Has made suicide attempt within the last month or is actively suicidal

14. **WEEPING**:

- ☐ 1 Normal for age.
- ☐ 2 Suggestive statements that child cries, or feels like crying, more frequently than peers.
- ☐ 3 Child cries slightly more than peers.
- ☐ 4
- ☐ 5 Cries or feels like crying frequently (several times a week). Admits to crying without knowing reason why.
- ☐ 6
- ☐ 7 Cries nearly every day.

15. **DEPRESSED AFFECT:**

- ☐ 1 Definitely not depressed. Facial expression and voice animated during interview.
- ☐ 2 Mild suppression of affect. Some loss of spontaneity.
- ☐ 3 Overall loss of spontaneity. Looks distinctly unhappy during parts of the interview. May still be able to smile when discussing non-threatening areas.
- ☐ 4
- ☐ 5 Moderate restriction of affect throughout most of interview. Has longer and frequent periods of looking distinctly unhappy.
- ☐ 6
- ☐ 7 Severe. Looks sad, withdrawn. Minimal verbal interaction throughout interview. Cries or may appear tearful.

16. **TEMPO OF SPEECH:**

- ☐ 1 Normal
- ☐ 2 Slow
- ☐ 3 Slow: delays interview.
- ☐ 4
- ☐ 5 Severe. Low; marked interference with interview.

17. **HYPOACTIVITY:**

- ☐ 1 None
- ☐ 2
- ☐ 3 Mild. Some body movements.
- ☐ 4
- ☐ 5 Moderate. Definite motor retardation.
- ☐ 6
- ☐ 7 Severe. Motionless throughout interview.

(DNDE)

Total of 1 - 17 _____

Evaluator's initials _____ _____ _____
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CLINICAL GLOBAL IMPRESSION: SEVERITY

INFORMATION NOT OBTAINED ☐

Considering your total clinical experience with this particular population, how mentally ill is the patient at this time?

- ☐ 1 Normal, not at all ill
- ☐ 2 Borderline ill
- ☐ 3 Mildly ill
- ☐ 4 Moderately ill
- ☐ 5 Markedly ill
- ☐ 6 Severely ill
- ☐ 7 Among the most extremely ill patients

Evaluator's initials _____ _____ _____
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MONTGOMERY - ASBERG DEPRESSION RATING SCALE (MADRS)

INFORMATION NOT OBTAINED ☐

The rating should be based on a clinical interview moving from broadly phrased questions about symptoms to more detailed ones which allow a precise rating of severity. The rater must decide whether the rating lies on the defined scale steps (0, 2, 4, 6) or between them (1, 3, 5).

Check the box (number) that best characterizes the patient at this time

1. **APPARENT SADNESS**
   Representing despondency, gloom, and despair (more than just ordinary transient low spirits), reflected in speech, facial expression, and posture. Rate by depth and inability to brighten up.

   ☐ 0 No sadness.
   ☐ 1
   ☐ 2 Looks dispirited but does brighten up without difficulty.
   ☐ 3
   ☐ 4 Appears sad and unhappy most of the time.
   ☐ 5
   ☐ 6 Looks miserable all the time. Extremely despondent.

2. **REPORTED SADNESS**
   Represented by reports of depressed mood, regardless of whether it is reflected in appearance or not. Includes low spirits, despondency, or the feeling of being beyond help and without hope. Rate according to intensity, duration, and the extent to which the mood is reported to be influenced by events.

   ☐ 0 Occasional sadness in keeping with the circumstances.
   ☐ 1
   ☐ 2 Sad or low but brightens up without difficulty.
   ☐ 3
   ☐ 4 Pervasive feelings of sadness or gloominess. The mood is still influenced by external circumstances.
   ☐ 5
   ☐ 6 Continuous unvarying sadness, misery or despondency.

3. **INNER TENSION**
   Representing feelings of ill-defined discomfort, edginess, inner turmoil, mental tension mounting to either panic, dread, or anguish. Rate according to intensity, frequency, duration, and the extent of reassurance called for.

   ☐ 0 Placid. Only fleeting inner tension.
   ☐ 1
   ☐ 2 Occasional feelings of edginess and ill-defined discomfort.
   ☐ 3
   ☐ 4 Continuous feelings of inner tension or intermittent panic which the patient can only master with some difficulty.
   ☐ 5
   ☐ 6 Unrelenting dread or anguish. Overwhelming panic.

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MONTGOMERY - ASBERG DEPRESSION RATING SCALE (MADRS)

4. **REDUCED SLEEP**
Representing the experience of reduced duration or depth of sleep compared to the subject's own pattern when well.

- ☐ 0 Sleeps as usual.
- ☐ 1
- ☐ 2 Slight difficulty dropping off to sleep or slightly reduced, light or fitful sleep.
- ☐ 3
- ☐ 4 Sleep reduced or broken by at least two hours.
- ☐ 5
- ☐ 6 Less than two or three hours sleep.

5. **REDUCED APPETITE**
Representing the feeling of a loss of appetite compared with when well. Rate by loss of desire for food or the need to force oneself to eat.

- ☐ 0 Normal or increased appetite
- ☐ 1
- ☐ 2 Slightly reduced appetite.
- ☐ 3
- ☐ 4 No appetite. Food is tasteless.
- ☐ 5
- ☐ 6 Needs persuasion to eat at all.

6. **CONCENTRATION DIFFICULTIES**
Representing difficulties in collecting one's thoughts mounting to incapacitating lack of concentration.

- ☐ 0 No difficulties in concentrating.
- ☐ 1
- ☐ 2 Occasional difficulties in collecting one's thoughts.
- ☐ 3
- ☐ 4 Difficulties in concentrating and sustaining thought which reduces ability to read or hold a conversation.
- ☐ 5
- ☐ 6 Unable to read or converse without great difficulty.

7. **LASSITUDE**
Representing a difficulty getting started or slowness initiating and performing everyday activities.

- ☐ 0 Hardly any difficulty in getting started. No sluggishness.
- ☐ 1
- ☐ 2 Difficulties in starting activities
- ☐ 3
- ☐ 4 Difficulties in starting simple routine activities which are carried out with effort.
- ☐ 5
- ☐ 6 Complete lassitude. Unable to do anything without help.

8. **INABILITY TO FEEL**
Representing the subjective experience of reduced interest in the surroundings, or activities that normally give pleasure. The ability to react with adequate emotion to circumstances or people is reduced.

- ☐ 0 Normal interest in the surroundings and other people.
- ☐ 1
- ☐ 2 Reduced ability to enjoy usual interests.
- ☐ 3
- ☐ 4 Loss of interest in the surroundings. Loss of feelings for friends and acquaintances.
- ☐ 5
- ☐ 6 The experience of being emotionally paralyzed, inability to feel anger, grief, or pleasure and a complete or even painful failure to feel for close relatives and friends.

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Fluoxetine Versus Placebo in Childhood/Adolescent Depression
B1Y-MC-HCJE

MONTGOMERY - ASBERG DEPRESSION RATING SCALE (MADRS)

9. **PESSIMISTIC THOUGHTS**
Representing thoughts of guilt, inferiority, self-reproach, sinfulness, remorse, and ruin

- ☐ 0 No pessimistic thoughts.
- ☐ 1
- ☐ 2 Fluctuating ideas of failure, self-reproach, or self-depreciation.
- ☐ 3
- ☐ 4 Persistent self-accusations, or definite but still rational ideas of guilt, or sin. Increasingly pessimistic about the future.
- ☐ 5
- ☐ 6 Delusions of ruin, remorse, or unredeemable sin. Self-accusations which are absurd and unshakable.

10. **SUICIDAL THOUGHTS**
Representing the feeling that life is not worth living, that a natural death would be welcome, suicidal thoughts, and preparations for suicide. Suicidal attempts should not in themselves influence the rating.

- ☐ 0 Enjoys life or takes it as it comes.
- ☐ 1
- ☐ 2 Weary of life. Only fleeting suicidal thoughts.
- ☐ 3
- ☐ 4 Probably better off dead. Suicidal thoughts are common, and suicide is considered as a possible solution, but without specific plans or intention.
- ☐ 5
- ☐ 6 Explicit plans for suicide when there is an opportunity. Active preparations for suicide.

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B1Y-MC-HCJE

CHILDREN'S DEPRESSION INDEX (CDI)

NOTE: Only complete if patient was 8 to 12 years old at Visit 1. If patient was not 8 to 12 years old, check the Information Not Obtained box.

INFORMATION NOT OBTAINED ☐

This lists the feelings and ideas in groups. From each group of three sentences, pick one sentence that describes you **best** for the past two weeks. After you pick a sentence from the first group, go on to the next group. There is no right answer or wrong answer. Just pick the sentence that best describes the way you have been recently. Put an "X" in the box next to your answer.
Remember: pick out the sentences that describe you best **in the past two weeks**.

Item 1

- ☐ 0 I am sad once in a while.
- ☐ 1 I am sad many times.
- ☐ 2 I am sad all the time.

Item 2

- ☐ 2 Nothing will ever work out for me.
- ☐ 1 I am not sure if things will work out for me.
- ☐ 0 Things will work out for me O.K.

Item 3

- ☐ 0 I do most things O.K.
- ☐ 1 I do many things wrong.
- ☐ 2 I do everything wrong.

Item 4

- ☐ 0 I have fun in many things.
- ☐ 1 I have fun in some things.
- ☐ 2 Nothing is fun at all.

Item 5

- ☐ 2 I am bad all the time.
- ☐ 1 I am bad many times.
- ☐ 0 I am bad once in a while.

Item 6

- ☐ 0 I think about bad things happening to me once in a while.
- ☐ 1 I worry that bad things will happen to me.
- ☐ 2 I am sure that terrible things will happen to me.

Item 7

- ☐ 2 I hate myself.
- ☐ 1 I do not like myself.
- ☐ 0 I like myself.

Item 8

- ☐ 2 All bad things are my fault.
- ☐ 1 Many bad things are my fault.
- ☐ 0 Bad things are not usually my fault.

Item 9

- ☐ 0 I do not think about killing myself.
- ☐ 1 I think about killing myself but I would not do it.
- ☐ 2 I want to kill myself.

Item 10

- ☐ 2 I feel like crying every day.
- ☐ 1 I feel like crying many days.
- ☐ 0 I feel like crying once in a while.

Item 11

- ☐ 2 Things bother me all the time.
- ☐ 1 Things bother me many times.
- ☐ 0 Things bother me once in a while.

Item 12

- ☐ 0 I like being with people.
- ☐ 1 I do not like being with people many times.
- ☐ 2 I do not want to be with people at all.

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CHILDREN'S DEPRESSION INDEX (CDI)

Item 13

- ☐ 2 I cannot make up my mind about things.
- ☐ 1 It is hard to make up my mind about things.
- ☐ 0 I make up my mind about things easily.

Item 14

- ☐ 0 I look O.K.
- ☐ 1 There are some bad things about my looks.
- ☐ 2 I look ugly.

Item 15

- ☐ 2 I have to push myself all the time to do my schoolwork.
- ☐ 1 I have to push myself many times to do my schoolwork.
- ☐ 0 Doing schoolwork is not a big problem.

Item 16

- ☐ 2 I have trouble sleeping every night.
- ☐ 1 I have trouble sleeping many nights.
- ☐ 0 I sleep pretty well.

Item 17

- ☐ 0 I am tired once in a while.
- ☐ 1 I am tired many days.
- ☐ 2 I am tired all the time.

Item 18

- ☐ 2 Most days I do not feel like eating.
- ☐ 1 Many days I do not feel like eating.
- ☐ 0 I eat pretty well.

Item 19

- ☐ 0 I do not worry about aches and pains.
- ☐ 1 I worry about aches and pains many times.
- ☐ 2 I worry about aches and pains all the time.

Item 20

- ☐ 0 I do not feel alone.
- ☐ 1 I feel alone many times.
- ☐ 2 I feel alone all the time.

Item 21

- ☐ 2 I never have fun at school.
- ☐ 1 I have fun at school only once in a while.
- ☐ 0 I have fun at school many times.

Item 22

- ☐ 0 I have plenty of friends.
- ☐ 1 I have some friends but I wish I had more.
- ☐ 2 I do not have any friends.

Item 23

- ☐ 0 My schoolwork is alright.
- ☐ 1 My schoolwork is not as good as before.
- ☐ 2 I do very badly in subjects I used to be good in.

Item 24

- ☐ 2 I can never be as good as other kids.
- ☐ 1 I can be as good as other kids if I want to.
- ☐ 0 I am just as good as other kids.

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CHILDREN'S DEPRESSION INDEX (CDI)

Item 25

- ☐ 2 Nobody really loves me.
- ☐ 1 I am not sure if anybody loves me.
- ☐ 0 I am sure that somebody loves me.

Item 26

- ☐ 0 I usually do what I am told.
- ☐ 1 I do not do what I am told most times.
- ☐ 2 I never do what I am told.

Item 27

- ☐ 0 I get along with people.
- ☐ 1 I get into fights many times.
- ☐ 2 I get into fights all the time.

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BECK DEPRESSION INVENTORY

NOTE: Only complete if patient was 13 to 17 years old at Visit 1. If patient was not 13 to 17 years old, check the Information Not Obtained box.

INFORMATION NOT OBTAINED ☐

This questionnaire consists of 21 groups of statements. After reading each group of statements carefully circle the number (0, 1, 2, 3) next to the one statement in each group which best describes the way you have been feeling **the past week, including today**. If several statements within a group seem to apply equally well, circle each one. Be sure to read all the statements in each group before making your choice.

1

0 I do not feel sad.
1 I feel sad.
2 I am sad all the time and I can't snap out of it.
3 I am so sad or unhappy that I can't stand it.

2

0 I am not particularly discouraged about the future.
1 I feel discouraged about the future.
2 I feel I have nothing to look forward to.
3 I feel that the future is hopeless and that things cannot improve.

3

0 I do not feel like a failure.
1 I feel I have failed more than the average person.
2 As I look back on my life, all I can see is a lot of failures.
3 I feel I am a complete failure as a person.

4

0 I get as much satisfaction out of things as I used to.
1 I don't enjoy things the way I used to.
2 I don't get real satisfaction out of anything anymore.
3 I am dissatisfied or bored with everything.

5

0 I don't feel particularly guilty.
1 I feel guilty a good part of the time.
2 I feel quite guilty most of the time.
3 I feel guilty all of the time.

6

0 I don't feel I am being punished.
1 I feel I may be punished.
2 I expect to be punished.
3 I feel I am being punished.

7

0 I don't feel disappointed in myself.
1 I am disappointed in myself.
2 I am disgusted with myself.
3 I hate myself.

8

0 I don't feel I am any worse than anybody else.
1 I am critical of myself for my weaknesses or mistakes.
2 I blame myself all the time for my faults.
3 I blame myself for everything bad that happens.

9

0 I don't have any thoughts of killing myself.
1 I have thoughts of killing myself, but I would not carry them out.
2 I would like to kill myself.
3 I would kill myself if I had the chance.

10

0 I don't cry any more than usual.
1 I cry more now than I used to.
2 I cry all the time now.
3 I used to be able to cry, but now I can't cry even though I want to.

11

0 I am no more irritated now than I ever am.
1 I get annoyed or irritated more easily than I used to.
2 I feel irritated all the time now.
3 I don't get irritated at all by the things that used to irritate me.

12

0 I have not lost interest in other people.
1 I am less interested in other people than I used to be.
2 I have lost most of my interest in other people.
3 I have lost all of my interest in other people.

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BECK DEPRESSION INVENTORY

13

0 I make decisions about as well as I ever could.
1 I put off making decisions more than I used to.
2 I have greater difficulty in making decisions than before.
3 I can't make decisions at all anymore.

14

0 I don't feel I look any worse than I used to.
1 I am worried that I am looking old or unattractive.
2 I feel that there are permanent changes in my appearance that make me look unattractive.
3 I believe that I look ugly.

15

0 I can work about as well as before.
1 It takes an extra effort to get started at doing something.
2 I have to push myself very hard to do anything.
3 I can't do any work at all.

16

0 I can sleep as well as usual.
1 I don't sleep as well as I used to.
2 I wake up 1-2 hours earlier than usual and find it hard to get back to sleep.
3 I wake up several hours earlier than I used to and cannot get back to sleep.

17

0 I don't get more tired than usual.
1 I get tired more easily than I used to.
2 I get tired from doing almost anything.
3 I am too tired to do anything.

18

0 My appetite is no worse than usual.
1 My appetite is not as good as it used to be.
2 My appetite is much worse now.
3 I have no appetite at all anymore.

19

0 I haven't lost much weight, if any, lately.
1 I have lost more than 5 pounds.
2 I have lost more than 10 pounds.
3 I have lost more than 15 pounds.

19a

I am purposely trying to lose weight by eating less.
1 Yes
2 No

20

0 I am no more worried about my health than usual.
1 I am worried about physical problems such as aches and pains; or upset stomach or constipation.
2 I am very worried about physical problems and it's hard to think of much else.
3 I am so worried about my physical problems that I cannot think about anything else.

21

0 I have not noticed any recent change in my interest in sex.
1 I am less interested in sex than I used to be.
2 I am much less interested in sex now.
3 I have lost interest in sex completely.

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HAMILTON ANXIETY SCALE

INFORMATION NOT OBTAINED ☐

For each of the items below, **CHECK ONE BOX** that best describes the patient.

1. **ANXIOUS MOOD:** Worries, anticipation of the worst, fearful anticipation, irritability

   ☐ 0 Not present
   ☐ 1 Mild
   ☐ 2 Moderate
   ☐ 3 Severe
   ☐ 4 Very severe

2. **TENSION**: Feelings of tension, fatigability, startle response, moved to tears easily, trembling, feeling of restlessness, inability to relax

   ☐ 0 Not present
   ☐ 1 Mild
   ☐ 2 Moderate
   ☐ 3 Severe
   ☐ 4 Very severe

3. **FEARS**: Of dark, of strangers, of being alone, of animals, of traffic, of crowds

   ☐ 0 Not present
   ☐ 1 Mild
   ☐ 2 Moderate
   ☐ 3 Severe
   ☐ 4 Very severe

4. **INSOMNIA**: Difficulty in falling asleep, broken sleep, unsatisfying sleep and fatigue on waking, dreams, nightmares, night terrors

   ☐ 0 Not present
   ☐ 1 Mild
   ☐ 2 Moderate
   ☐ 3 Severe
   ☐ 4 Very severe

5. **INTELLECTUAL (COGNITIVE)**: Difficulty in concentration, poor memory

   ☐ 0 Not present
   ☐ 1 Mild
   ☐ 2 Moderate
   ☐ 3 Severe
   ☐ 4 Very severe

6. **DEPRESSED MOOD**: Loss of interest, lack of pleasure in hobbies, depression, early waking, diurnal swing

   ☐ 0 Not present
   ☐ 1 Mild
   ☐ 2 Moderate
   ☐ 3 Severe
   ☐ 4 Very severe

7. **SOMATIC (MUSCULAR)**: Pains and aches, twitchings, stiffness, myoclonic jerks, grinding of teeth, unsteady voice, increased muscular tone

   ☐ 0 Not present
   ☐ 1 Mild
   ☐ 2 Moderate
   ☐ 3 Severe
   ☐ 4 Very severe

8. **SOMATIC (SENSORY)**: Tinnitus, blurring of vision, hot and cold flushes, feeling of weakness, pricking sensation

   ☐ 0 Not present
   ☐ 1 Mild
   ☐ 2 Moderate
   ☐ 3 Severe
   ☐ 4 Very severe

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HAMILTON ANXIETY SCALE

9. **CARDIOVASCULAR SYMPTOMS:** Tachycardia, palpitations, pain in chest, throbbing of vessels, fainting feelings, missing beat

- ☐ 0 Not present
- ☐ 1 Mild
- ☐ 2 Moderate
- ☐ 3 Severe
- ☐ 4 Very severe

10. **RESPIRATORY SYMPTOMS:** Pressure or constriction in chest, choking feelings, sighing, dyspnea

- ☐ 0 Not present
- ☐ 1 Mild
- ☐ 2 Moderate
- ☐ 3 Severe
- ☐ 4 Very severe

11. **GASTROINTESTINAL SYMPTOMS:** Difficulty in swallowing, wind, abdominal pain, burning sensations, abdominal fullness, nausea, vomiting, borborygmi, looseness of bowels, loss of weight, constipation

- ☐ 0 Not present
- ☐ 1 Mild
- ☐ 2 Moderate
- ☐ 3 Severe
- ☐ 4 Very severe

12. **GENITOURINARY SYMPTOMS:** Frequency of micturition, urgency of micturition, amenorrhea, menorrhagia, development of frigidity, premature ejaculation, loss of libido, impotence

- ☐ 0 Not present
- ☐ 1 Mild
- ☐ 2 Moderate
- ☐ 3 Severe
- ☐ 4 Very severe

13. **AUTONOMIC SYMPTOMS:** Dry mouth, flushing, pallor, tendency to sweat, giddiness, tension headache, raising of hair

- ☐ 0 Not present
- ☐ 1 Mild
- ☐ 2 Moderate
- ☐ 3 Severe
- ☐ 4 Very severe

14. **BEHAVIOR AT INTERVIEW:** Fidgeting, restlessness or pacing, tremor of hands, furrowed brow, strained face, sighing or rapid respiration, facial pallor, swallowing, belching, brisk tendon jerks, dilated pupils, exophthalmos

- ☐ 0 Not present
- ☐ 1 Mild
- ☐ 2 Moderate
- ☐ 3 Severe
- ☐ 4 Very severe

Evaluator's Initials _____ _____ _____
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B1Y-MC-HCJE

COMMENTS : VISIT

NO COMMENTS ☐

Comments should address any clinical report form items that require further explanation. Repeating information from the clinical report form is discouraged.

Comment on all clinically significant lab values that are outside a clinically accepted reference range or clinically significant values that differ importantly from previous values.

If the patient is ending participation in the study at this visit, enter only comments that apply to this visit; then complete the Patient Summary and Study Summary Comments pages.

Print legibly and do not use abbreviations or symbols.

The information reported for this visit is accurate and complete.

_____ _____/_____/_____
Signature MM DD YY

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PATIENT AND VISIT IDENTIFICATION

Patient initials _____ _____ _____
First Middle Last

Visit date _____/_____/_____
MM DD YY

K-SADS : AFFECTIVE DISORDERS

INFORMATION NOT OBTAINED ☐

Check the appropriate boxes.

Depressive Disorders - Current	☐ 1 Yes	☐ 2 No
Depressive Disorders - Past	☐ 1 Yes	☐ 2 No
Mania - Current	☐ 1 Yes	☐ 2 No
Mania -Past	☐ 1 Yes	☐ 2 No

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First Middle Last

Initials
Date Verified
Initials
Date Keyed
Date Received at Lilly
Reviewed
Inspected
Date

REMINDER

On the Pre-existing Conditions and Study Adverse Events pages, record new events that occurred since the previous visit and re-evaluate any on-going conditions or events.

On the Concomitant Medication pages, record new medications the patient has taken since the previous visit, any changes to ongoing medications, and a stop date for any medication the patient is no longer taking.

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B1Y-MC-HCJE

GLOBAL ASSESSMENT OF FUNCTIONING SCALE (GAF SCALE)

INFORMATION NOT OBTAINED ☐

Enter the number (between 1 and 90) that best represents the patient's:

1. **Current** level of functioning _____
2. **Highest** level of functioning in *past year* _____

Level of Functioning Definitions	
90 – 81	Absent or minimal symptoms, good functioning in all areas, interested and involved in a wide range of activities, socially effective, generally satisfied with life, no more than everyday problems or concerns.
80 – 71	If symptoms are present, they are transient and expectable reactions to psychosocial stressors; no more than slight impairment in social, occupational, or school functioning.
70 – 61	Some mild symptoms OR some difficulty in social, occupational, or school functioning, but generally functioning pretty well, has some meaningful interpersonal relationships.
60 – 51	Moderate symptoms OR any moderate difficulty in social, occupational, or school functioning.
50 – 41	Serious symptoms OR any serious impairment in social, occupational, or school functioning.
40 – 31	Some impairment in reality testing or communication OR major impairment in several areas, such as work or school, family relations, judgment, thinking, or mood.
30 – 21	Behavior is considered influenced by delusions or hallucinations OR serious impairment in communications or judgment OR inability to function in almost all areas.
20 – 11	Some danger of hurting self or other OR occasionally fails to maintain minimal personal hygiene OR gross impairment in communication.
10 – 1	Persistent danger of severely hurting self or others OR persistent inability to maintain minimum personal hygiene OR serious suicidal act with clear expectation of death.

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VITAL SIGNS : BLOOD PRESSURE AND HEART RATE

INFORMATION NOT OBTAINED ☐

Position
SI = Sitting

Position	Blood Pressure (mm Hg) Systolic/Diastolic	Heart Rate (bpm)
SI	/	

VITAL SIGNS: TEMPERATURE

INFORMATION NOT OBTAINED ☐

Temperature ___ ___ ___ . ___

Unit of measure (F) Fahrenheit

Method (E) Ear

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B1Y-MC-HCJE

Visit 2
Page 4 of 18

CHILDRENS DEPRESSION RATING SCALE - REVISED

INFORMATION NOT OBTAINED ☐

CHECK THE NUMERIC CODE which best describes the patient.

1. **SCHOOLWORK**:

☐ 1 Performance consistent with ability
☐ 2
☐ 3 Decrease in school performance
☐ 4
☐ 5 Major interference in most subjects
☐ 6
☐ 7 No motivation to perform

2. **CAPACITY TO HAVE FUN**

☐ 1 Interest and activities realistically appropriate for age, personality, and social environment. Shows no appreciable change with present illness.
☐ 2
☐ 3 Describes some activities realistically available several times a week but not on a daily basis. Shows interest but not enthusiasm.
☐ 4
☐ 5 Is easily bored. Complains of "nothing to do." Participates in structured activities with a "going through the motions" attitude. May express interest primarily in activities that are (realistically) unavailable on a daily or weekly basis.
☐ 6
☐ 7 Has no initiative to become involved in any activities. Primarily passive. Watches others play or watches TV but shows little interest. Requires coaxing and/or pushing to get involved in activity. Shows no enthusiasm or real interest. Has difficulty naming activities.

3. **SOCIAL WITHDRAWAL**

☐ 1 Enjoys friendships with peers at school and home
☐ 2
☐ 3 May not actively seek out friendships but waits for others to initiate a relationship or may occasionally reject opportunities to play without a describable alternative
☐ 4
☐ 5 Frequently avoids or refuses opportunities for desirable interaction with others and/or sets up situations where rejection is inevitable.
☐ 6
☐ 7 Does not currently relate to other children. States he or she has "no friends" or actively rejects new or former friends.

4. **SLEEP**

☐ 1 No (or occasional) difficulty. (Goes to sleep within 1/2 hour or less.)
☐ 2
☐ 3 Frequently has mild difficulty with sleep
☐ 4
☐ 5 Moderate difficulty with sleep nearly every night.

5. **APPETITE OR EATING PATTERNS**

☐ 1 No problems or change in eating pattern
☐ 2
☐ 3 Mild change from usual eating habits within onset of current behavioral problem
☐ 4
☐ 5 Is not hungry most of the time or has excessive food intake since onset of current behavioral problems or marked increase in appetite

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B1Y-MC-HCJE

CHILDRENS DEPRESSION RATING SCALE - REVISED

CHECK THE NUMERIC CODE which best describes the patient.

6. **EXCESSIVE FATIGUE**

- ☐ 1 No unusual complaints of "feeling tired" during the day
- ☐ 2
- ☐ 3 Complaints of fatigue which seem somewhat excessive and not related to boredom
- ☐ 4
- ☐ 5 Daily complaints of feeling tired
- ☐ 6
- ☐ 7 Complains of feeling tired most of the day. May voluntarily take long naps without feeling refreshed. Interferes with play activities.

7. **PHYSICAL COMPLAINTS**:

- ☐ 1 Occasional complaints
- ☐ 2
- ☐ 3 Complaints appear mildly excessive
- ☐ 4
- ☐ 5 Complains daily. Some interference with the ability of the child to function
- ☐ 6
- ☐ 7 Preoccupied with aches and pains; interferes with play activities several times a week

8. **IRRITABILITY**

- ☐ 1 Rare
- ☐ 2 Occasional
- ☐ 3 Several times a week for short periods
- ☐ 4
- ☐ 5 Several times a week for longer periods
- ☐ 6
- ☐ 7 Constant

9. **GUILT**

- ☐ 1 Does not express any undue feeling of guilt. Appears appropriate to precipitating event.
- ☐ 2
- ☐ 3 Exaggerates guilt and/or shame out of proportion to the event described.
- ☐ 4
- ☐ 5 Feels guilty over things not under his or her control. Guilt is definitely pathological.
- ☐ 6
- ☐ 7 Severe delusions of guilt

10. **SELF-ESTEEM**

- ☐ 1 Describes self in primarily positive terms
- ☐ 2
- ☐ 3 Describes self with one important area where the child feels deficit
- ☐ 4
- ☐ 5 Describes self in preponderance of negative terms or gives bland answers to questions
- ☐ 6
- ☐ 7 Refers to self in derogatory terms. Reports that other children refer to him/her frequently by using derogatory nicknames and child puts self down

11. **DEPRESSED FEELINGS**

- ☐ 1 Occasional feelings of unhappiness which quickly disappear
- ☐ 2
- ☐ 3 Describes sustained periods of unhappiness which appear excessive for events described
- ☐ 4
- ☐ 5 Feels unhappy most of the time without a major precipitating cause
- ☐ 6
- ☐ 7 Feels unhappy all of the time. Accompanied by psychic pain (e.g., "I can't stand it").

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CHILDRENS DEPRESSION RATING SCALE - REVISED

CHECK THE NUMERIC CODE which best describes the patient.

12. **MORBID IDEATION**

- ☐ 1 None
- ☐ 2
- ☐ 3 Has some morbid thought, all of which relate to a reality event but seem excessive.
- ☐ 4
- ☐ 5 Preoccupied with morbid thoughts several times a week. Morbid thoughts extend beyond external reality
- ☐ 6
- ☐ 7 Preoccupied with death themes or morbid thoughts that are elaborate, extensive or bizarre on a daily basis

13. **SUICIDAL IDEATION**

- ☐ 1 Understands the word "suicide" but does not apply term to self
- ☐ 2 Sharp denial of suicidal thoughts
- ☐ 3 Has thoughts about suicide, usually when angry.
- ☐ 4
- ☐ 5 Has recurrent thoughts of suicide
- ☐ 6
- ☐ 7 Has made suicide attempt within the last month or is actively suicidal

14. **WEEPING**:

- ☐ 1 Normal for age.
- ☐ 2 Suggestive statements that child cries, or feels like crying, more frequently than peers.
- ☐ 3 Child cries slightly more than peers.
- ☐ 4
- ☐ 5 Cries or feels like crying frequently (several times a week). Admits to crying without knowing reason why.
- ☐ 6
- ☐ 7 Cries nearly every day.

15. **DEPRESSED AFFECT:**

- ☐ 1 Definitely not depressed. Facial expression and voice animated during interview.
- ☐ 2 Mild suppression of affect. Some loss of spontaneity.
- ☐ 3 Overall loss of spontaneity. Looks distinctly unhappy during parts of the interview. May still be able to smile when discussing non-threatening areas.
- ☐ 4
- ☐ 5 Moderate restriction of affect throughout most of interview. Has longer and frequent periods of looking distinctly unhappy.
- ☐ 6
- ☐ 7 Severe. Looks sad, withdrawn. Minimal verbal interaction throughout interview. Cries or may appear tearful.

16. **TEMPO OF SPEECH:**

- ☐ 1 Normal
- ☐ 2 Slow
- ☐ 3 Slow: delays interview.
- ☐ 4
- ☐ 5 Severe. Low; marked interference with interview.

17. **HYPOACTIVITY:**

- ☐ 1 None
- ☐ 2
- ☐ 3 Mild. Some body movements.
- ☐ 4
- ☐ 5 Moderate. Definite motor retardation.
- ☐ 6
- ☐ 7 Severe. Motionless throughout interview.

(DNDE)

Total of 1 - 17 _____

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CLINICAL GLOBAL IMPRESSION: SEVERITY

INFORMATION NOT OBTAINED ☐

Considering your total clinical experience with this particular population, how mentally ill is the patient at this time?

- ☐ 1 Normal, not at all ill
- ☐ 2 Borderline ill
- ☐ 3 Mildly ill
- ☐ 4 Moderately ill
- ☐ 5 Markedly ill
- ☐ 6 Severely ill
- ☐ 7 Among the most extremely ill patients

Evaluator's initials _____ _____ _____
First Middle Last

CLINICAL GLOBAL IMPRESSION: IMPROVEMENT

INFORMATION NOT OBTAINED ☐

Rate total improvement, whether or not in your judgement it is due entirely to drug treatment. Compared to the patient's condition at Visit 1, how much has he/she changed?

- ☐ 1 Very much improved
- ☐ 2 Much improved
- ☐ 3 Minimally improved
- ☐ 4 No change
- ☐ 5 Minimally worse
- ☐ 6 Much worse
- ☐ 7 Very much worse

Evaluator's initials _____ _____ _____
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MONTGOMERY - ASBERG DEPRESSION RATING SCALE (MADRS)

INFORMATION NOT OBTAINED ☐

The rating should be based on a clinical interview moving from broadly phrased questions about symptoms to more detailed ones which allow a precise rating of severity. The rater must decide whether the rating lies on the defined scale steps (0, 2, 4, 6) or between them (1, 3, 5).

Check the box (number) that best characterizes the patient at this time

1. **APPARENT SADNESS**
   Representing despondency, gloom, and despair (more than just ordinary transient low spirits), reflected in speech, facial expression, and posture. Rate by depth and inability to brighten up.

   ☐ 0 No sadness.
   ☐ 1
   ☐ 2 Looks dispirited but does brighten up without difficulty.
   ☐ 3
   ☐ 4 Appears sad and unhappy most of the time.
   ☐ 5
   ☐ 6 Looks miserable all the time. Extremely despondent.

2. **REPORTED SADNESS**
   Represented by reports of depressed mood, regardless of whether it is reflected in appearance or not. Includes low spirits, despondency, or the feeling of being beyond help and without hope. Rate according to intensity, duration, and the extent to which the mood is reported to be influenced by events.

   ☐ 0 Occasional sadness in keeping with the circumstances.
   ☐ 1
   ☐ 2 Sad or low but brightens up without difficulty.
   ☐ 3
   ☐ 4 Pervasive feelings of sadness or gloominess. The mood is still influenced by external circumstances.
   ☐ 5
   ☐ 6 Continuous unvarying sadness, misery or despondency.

3. **INNER TENSION**
   Representing feelings of ill-defined discomfort, edginess, inner turmoil, mental tension mounting to either panic, dread, or anguish. Rate according to intensity, frequency, duration, and the extent of reassurance called for.

   ☐ 0 Placid. Only fleeting inner tension.
   ☐ 1
   ☐ 2 Occasional feelings of edginess and ill-defined discomfort.
   ☐ 3
   ☐ 4 Continuous feelings of inner tension or intermittent panic which the patient can only master with some difficulty.
   ☐ 5
   ☐ 6 Unrelenting dread or anguish. Overwhelming panic.

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MONTGOMERY - ASBERG DEPRESSION RATING SCALE (MADRS)

4. **REDUCED SLEEP**
Representing the experience of reduced duration or depth of sleep compared to the subject's own pattern when well.

- ☐ 0 Sleeps as usual.
- ☐ 1
- ☐ 2 Slight difficulty dropping off to sleep or slightly reduced, light or fitful sleep.
- ☐ 3
- ☐ 4 Sleep reduced or broken by at least two hours.
- ☐ 5
- ☐ 6 Less than two or three hours sleep.

5. **REDUCED APPETITE**
Representing the feeling of a loss of appetite compared with when well. Rate by loss of desire for food or the need to force oneself to eat.

- ☐ 0 Normal or increased appetite
- ☐ 1
- ☐ 2 Slightly reduced appetite.
- ☐ 3
- ☐ 4 No appetite. Food is tasteless.
- ☐ 5
- ☐ 6 Needs persuasion to eat at all.

6. **CONCENTRATION DIFFICULTIES**
Representing difficulties in collecting one's thoughts mounting to incapacitating lack of concentration.

- ☐ 0 No difficulties in concentrating.
- ☐ 1
- ☐ 2 Occasional difficulties in collecting one's thoughts.
- ☐ 3
- ☐ 4 Difficulties in concentrating and sustaining thought which reduces ability to read or hold a conversation.
- ☐ 5
- ☐ 6 Unable to read or converse without great difficulty.

7. **LASSITUDE**
Representing a difficulty getting started or slowness initiating and performing everyday activities.

- ☐ 0 Hardly any difficulty in getting started. No sluggishness.
- ☐ 1
- ☐ 2 Difficulties in starting activities
- ☐ 3
- ☐ 4 Difficulties in starting simple routine activities which are carried out with effort.
- ☐ 5
- ☐ 6 Complete lassitude. Unable to do anything without help.

8. **INABILITY TO FEEL**
Representing the subjective experience of reduced interest in the surroundings, or activities that normally give pleasure. The ability to react with adequate emotion to circumstances or people is reduced.

- ☐ 0 Normal interest in the surroundings and other people.
- ☐ 1
- ☐ 2 Reduced ability to enjoy usual interests.
- ☐ 3
- ☐ 4 Loss of interest in the surroundings. Loss of feelings for friends and acquaintances.
- ☐ 5
- ☐ 6 The experience of being emotionally paralyzed, inability to feel anger, grief, or pleasure and a complete or even painful failure to feel for close relatives and friends.

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B1Y-MC-HCJE

MONTGOMERY - ASBERG DEPRESSION RATING SCALE (MADRS)

9. **PESSIMISTIC THOUGHTS**
Representing thoughts of guilt, inferiority, self-reproach, sinfulness, remorse, and ruin

- ☐ 0 No pessimistic thoughts.
- ☐ 1
- ☐ 2 Fluctuating ideas of failure, self-reproach, or self-depreciation.
- ☐ 3
- ☐ 4 Persistent self-accusations, or definite but still rational ideas of guilt, or sin. Increasingly pessimistic about the future.
- ☐ 5
- ☐ 6 Delusions of ruin, remorse, or unredeemable sin. Self-accusations which are absurd and unshakable.

10. **SUICIDAL THOUGHTS**
Representing the feeling that life is not worth living, that a natural death would be welcome, suicidal thoughts, and preparations for suicide. Suicidal attempts should not in themselves influence the rating.

- ☐ 0 Enjoys life or takes it as it comes.
- ☐ 1
- ☐ 2 Weary of life. Only fleeting suicidal thoughts.
- ☐ 3
- ☐ 4 Probably better off dead. Suicidal thoughts are common, and suicide is considered as a possible solution, but without specific plans or intention.
- ☐ 5
- ☐ 6 Explicit plans for suicide when there is an opportunity. Active preparations for suicide.

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CHILDREN'S DEPRESSION INDEX (CDI)

NOTE: Only complete if patient was 8 to 12 years old at Visit 1. If patient was not 8 to 12 years old, check the Information Not Obtained box.

INFORMATION NOT OBTAINED ☐

This lists the feelings and ideas in groups. From each group of three sentences, pick one sentence that describes you **best** for the past two weeks. After you pick a sentence from the first group, go on to the next group. There is no right answer or wrong answer. Just pick the sentence that best describes the way you have been recently. Put an "X" in the box next to your answer.
Remember: pick out the sentences that describe you best **in the past two weeks**.

Item 1

- ☐ 0 I am sad once in a while.
- ☐ 1 I am sad many times.
- ☐ 2 I am sad all the time.

Item 2

- ☐ 2 Nothing will ever work out for me.
- ☐ 1 I am not sure if things will work out for me.
- ☐ 0 Things will work out for me O.K.

Item 3

- ☐ 0 I do most things O.K.
- ☐ 1 I do many things wrong.
- ☐ 2 I do everything wrong.

Item 4

- ☐ 0 I have fun in many things.
- ☐ 1 I have fun in some things.
- ☐ 2 Nothing is fun at all.

Item 5

- ☐ 2 I am bad all the time.
- ☐ 1 I am bad many times.
- ☐ 0 I am bad once in a while.

Item 6

- ☐ 0 I think about bad things happening to me once in a while.
- ☐ 1 I worry that bad things will happen to me.
- ☐ 2 I am sure that terrible things will happen to me.

Item 7

- ☐ 2 I hate myself.
- ☐ 1 I do not like myself.
- ☐ 0 I like myself.

Item 8

- ☐ 2 All bad things are my fault.
- ☐ 1 Many bad things are my fault.
- ☐ 0 Bad things are not usually my fault.

Item 9

- ☐ 0 I do not think about killing myself.
- ☐ 1 I think about killing myself but I would not do it.
- ☐ 2 I want to kill myself.

Item 10

- ☐ 2 I feel like crying every day.
- ☐ 1 I feel like crying many days.
- ☐ 0 I feel like crying once in a while.

Item 11

- ☐ 2 Things bother me all the time.
- ☐ 1 Things bother me many times.
- ☐ 0 Things bother me once in a while.

Item 12

- ☐ 0 I like being with people.
- ☐ 1 I do not like being with people many times.
- ☐ 2 I do not want to be with people at all.

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CHILDREN'S DEPRESSION INDEX (CDI)

Item 13

- ☐ 2 I cannot make up my mind about things.
- ☐ 1 It is hard to make up my mind about things.
- ☐ 0 I make up my mind about things easily.

Item 14

- ☐ 0 I look O.K.
- ☐ 1 There are some bad things about my looks.
- ☐ 2 I look ugly.

Item 15

- ☐ 2 I have to push myself all the time to do my schoolwork.
- ☐ 1 I have to push myself many times to do my schoolwork.
- ☐ 0 Doing schoolwork is not a big problem.

Item 16

- ☐ 2 I have trouble sleeping every night.
- ☐ 1 I have trouble sleeping many nights.
- ☐ 0 I sleep pretty well.

Item 17

- ☐ 0 I am tired once in a while.
- ☐ 1 I am tired many days.
- ☐ 2 I am tired all the time.

Item 18

- ☐ 2 Most days I do not feel like eating.
- ☐ 1 Many days I do not feel like eating.
- ☐ 0 I eat pretty well.

Item 19

- ☐ 0 I do not worry about aches and pains.
- ☐ 1 I worry about aches and pains many times.
- ☐ 2 I worry about aches and pains all the time.

Item 20

- ☐ 0 I do not feel alone.
- ☐ 1 I feel alone many times.
- ☐ 2 I feel alone all the time.

Item 21

- ☐ 2 I never have fun at school.
- ☐ 1 I have fun at school only once in a while.
- ☐ 0 I have fun at school many times.

Item 22

- ☐ 0 I have plenty of friends.
- ☐ 1 I have some friends but I wish I had more.
- ☐ 2 I do not have any friends.

Item 23

- ☐ 0 My schoolwork is alright.
- ☐ 1 My schoolwork is not as good as before.
- ☐ 2 I do very badly in subjects I used to be good in.

Item 24

- ☐ 2 I can never be as good as other kids.
- ☐ 1 I can be as good as other kids if I want to.
- ☐ 0 I am just as good as other kids.

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CHILDREN'S DEPRESSION INDEX (CDI)

Item 25

☐ 2 Nobody really loves me.
☐ 1 I am not sure if anybody loves me.
☐ 0 I am sure that somebody loves me.

Item 26

☐ 0 I usually do what I am told.
☐ 1 I do not do what I am told most times.
☐ 2 I never do what I am told.

Item 27

☐ 0 I get along with people.
☐ 1 I get into fights many times.
☐ 2 I get into fights all the time.

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BECK DEPRESSION INVENTORY

NOTE: Only complete if patient was 13 to 17 years old at Visit 1. If patient was not 13 to 17 years old, check the Information Not Obtained box.

INFORMATION NOT OBTAINED ☐

This questionnaire consists of 21 groups of statements. After reading each group of statements carefully circle the number (0, 1, 2, 3) next to the one statement in each group which best describes the way you have been feeling **the past week, including today**. If several statements within a group seem to apply equally well, circle each one. Be sure to read all the statements in each group before making your choice.

1

0 I do not feel sad.
1 I feel sad.
2 I am sad all the time and I can't snap out of it.
3 I am so sad or unhappy that I can't stand it.

2

0 I am not particularly discouraged about the future.
1 I feel discouraged about the future.
2 I feel I have nothing to look forward to.
3 I feel that the future is hopeless and that things cannot improve.

3

0 I do not feel like a failure.
1 I feel I have failed more than the average person.
2 As I look back on my life, all I can see is a lot of failures.
3 I feel I am a complete failure as a person.

4

0 I get as much satisfaction out of things as I used to.
1 I don't enjoy things the way I used to.
2 I don't get real satisfaction out of anything anymore.
3 I am dissatisfied or bored with everything.

5

0 I don't feel particularly guilty.
1 I feel guilty a good part of the time.
2 I feel quite guilty most of the time.
3 I feel guilty all of the time.

6

0 I don't feel I am being punished.
1 I feel I may be punished.
2 I expect to be punished.
3 I feel I am being punished.

7

0 I don't feel disappointed in myself.
1 I am disappointed in myself.
2 I am disgusted with myself.
3 I hate myself.

8

0 I don't feel I am any worse than anybody else.
1 I am critical of myself for my weaknesses or mistakes.
2 I blame myself all the time for my faults.
3 I blame myself for everything bad that happens.

9

0 I don't have any thoughts of killing myself.
1 I have thoughts of killing myself, but I would not carry them out.
2 I would like to kill myself.
3 I would kill myself if I had the chance.

10

0 I don't cry any more than usual.
1 I cry more now than I used to.
2 I cry all the time now.
3 I used to be able to cry, but now I can't cry even though I want to.

11

0 I am no more irritated now than I ever am.
1 I get annoyed or irritated more easily than I used to.
2 I feel irritated all the time now.
3 I don't get irritated at all by the things that used to irritate me.

12

0 I have not lost interest in other people.
1 I am less interested in other people than I used to be.
2 I have lost most of my interest in other people.
3 I have lost all of my interest in other people.

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BECK DEPRESSION INVENTORY

13

0 I make decisions about as well as I ever could.
1 I put off making decisions more than I used to.
2 I have greater difficulty in making decisions than before.
3 I can't make decisions at all anymore.

14

0 I don't feel I look any worse than I used to.
1 I am worried that I am looking old or unattractive.
2 I feel that there are permanent changes in my appearance that make me look unattractive.
3 I believe that I look ugly.

15

0 I can work about as well as before.
1 It takes an extra effort to get started at doing something.
2 I have to push myself very hard to do anything.
3 I can't do any work at all.

16

0 I can sleep as well as usual.
1 I don't sleep as well as I used to.
2 I wake up 1-2 hours earlier than usual and find it hard to get back to sleep.
3 I wake up several hours earlier than I used to and cannot get back to sleep.

17

0 I don't get more tired than usual.
1 I get tired more easily than I used to.
2 I get tired from doing almost anything.
3 I am too tired to do anything.

18

0 My appetite is no worse than usual.
1 My appetite is not as good as it used to be.
2 My appetite is much worse now.
3 I have no appetite at all anymore.

19

0 I haven't lost much weight, if any, lately.
1 I have lost more than 5 pounds.
2 I have lost more than 10 pounds.
3 I have lost more than 15 pounds.

19a

I am purposely trying to lose weight by eating less.
1 Yes
2 No

20

0 I am no more worried about my health than usual.
1 I am worried about physical problems such as aches and pains; or upset stomach or constipation.
2 I am very worried about physical problems and it's hard to think of much else.
3 I am so worried about my physical problems that I cannot think about anything else.

21

0 I have not noticed any recent change in my interest in sex.
1 I am less interested in sex than I used to be.
2 I am much less interested in sex now.
3 I have lost interest in sex completely.

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HAMILTON ANXIETY SCALE

INFORMATION NOT OBTAINED ☐

For each of the items below, **CHECK ONE BOX** that best describes the patient.

1. **ANXIOUS MOOD:** Worries, anticipation of the worst, fearful anticipation, irritability

   ☐ 0 Not present
   ☐ 1 Mild
   ☐ 2 Moderate
   ☐ 3 Severe
   ☐ 4 Very severe

2. **TENSION**: Feelings of tension, fatigability, startle response, moved to tears easily, trembling, feeling of restlessness, inability to relax

   ☐ 0 Not present
   ☐ 1 Mild
   ☐ 2 Moderate
   ☐ 3 Severe
   ☐ 4 Very severe

3. **FEARS**: Of dark, of strangers, of being alone, of animals, of traffic, of crowds

   ☐ 0 Not present
   ☐ 1 Mild
   ☐ 2 Moderate
   ☐ 3 Severe
   ☐ 4 Very severe

4. **INSOMNIA**: Difficulty in falling asleep, broken sleep, unsatisfying sleep and fatigue on waking, dreams, nightmares, night terrors

   ☐ 0 Not present
   ☐ 1 Mild
   ☐ 2 Moderate
   ☐ 3 Severe
   ☐ 4 Very severe

5. **INTELLECTUAL (COGNITIVE)**: Difficulty in concentration, poor memory

   ☐ 0 Not present
   ☐ 1 Mild
   ☐ 2 Moderate
   ☐ 3 Severe
   ☐ 4 Very severe

6. **DEPRESSED MOOD**: Loss of interest, lack of pleasure in hobbies, depression, early waking, diurnal swing

   ☐ 0 Not present
   ☐ 1 Mild
   ☐ 2 Moderate
   ☐ 3 Severe
   ☐ 4 Very severe

7. **SOMATIC (MUSCULAR)**: Pains and aches, twitchings, stiffness, myoclonic jerks, grinding of teeth, unsteady voice, increased muscular tone

   ☐ 0 Not present
   ☐ 1 Mild
   ☐ 2 Moderate
   ☐ 3 Severe
   ☐ 4 Very severe

8. **SOMATIC (SENSORY)**: Tinnitus, blurring of vision, hot and cold flushes, feeling of weakness, pricking sensation

   ☐ 0 Not present
   ☐ 1 Mild
   ☐ 2 Moderate
   ☐ 3 Severe
   ☐ 4 Very severe

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HAMILTON ANXIETY SCALE

9. **CARDIOVASCULAR SYMPTOMS:** Tachycardia, palpitations, pain in chest, throbbing of vessels, fainting feelings, missing beat

- ☐ 0 Not present
- ☐ 1 Mild
- ☐ 2 Moderate
- ☐ 3 Severe
- ☐ 4 Very severe

10. **RESPIRATORY SYMPTOMS:** Pressure or constriction in chest, choking feelings, sighing, dyspnea

- ☐ 0 Not present
- ☐ 1 Mild
- ☐ 2 Moderate
- ☐ 3 Severe
- ☐ 4 Very severe

11. **GASTROINTESTINAL SYMPTOMS:** Difficulty in swallowing, wind, abdominal pain, burning sensations, abdominal fullness, nausea, vomiting, borborygmi, looseness of bowels, loss of weight, constipation

- ☐ 0 Not present
- ☐ 1 Mild
- ☐ 2 Moderate
- ☐ 3 Severe
- ☐ 4 Very severe

12. **GENITOURINARY SYMPTOMS:** Frequency of micturition, urgency of micturition, amenorrhea, menorrhagia, development of frigidity, premature ejaculation, loss of libido, impotence

- ☐ 0 Not present
- ☐ 1 Mild
- ☐ 2 Moderate
- ☐ 3 Severe
- ☐ 4 Very severe

13. **AUTONOMIC SYMPTOMS:** Dry mouth, flushing, pallor, tendency to sweat, giddiness, tension headache, raising of hair

- ☐ 0 Not present
- ☐ 1 Mild
- ☐ 2 Moderate
- ☐ 3 Severe
- ☐ 4 Very severe

14. **BEHAVIOR AT INTERVIEW:** Fidgeting, restlessness or pacing, tremor of hands, furrowed brow, strained face, sighing or rapid respiration, facial pallor, swallowing, belching, brisk tendon jerks, dilated pupils, exophthalmos

- ☐ 0 Not present
- ☐ 1 Mild
- ☐ 2 Moderate
- ☐ 3 Severe
- ☐ 4 Very severe

Evaluator's Initials _____ _____ _____
First Middle Last

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COMMENTS : VISIT

NO COMMENTS ☐

Comments should address any clinical report form items that require further explanation. Repeating information from the clinical report form is discouraged.

Comment on all clinically significant lab values that are outside a clinically accepted reference range or clinically significant values that differ importantly from previous values.

If the patient is ending participation in the study at this visit, enter only comments that apply to this visit; then complete the Patient Summary and Study Summary Comments pages.

Print legibly and do not use abbreviations or symbols.

The information reported for this visit is accurate and complete.

_____ _____/_____/_____
Signature MM DD YY

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PATIENT AND VISIT IDENTIFICATION

Patient initials _____ _____ _____
First Middle Last

Visit date _____/_____/_____
MM DD YY

K-SADS : AFFECTIVE DISORDERS

INFORMATION NOT OBTAINED ☐

Check the appropriate boxes.

Depressive Disorders - Current	☐ 1 Yes	☐ 2 No
Depressive Disorders - Past	☐ 1 Yes	☐ 2 No
Mania - Current	☐ 1 Yes	☐ 2 No
Mania -Past	☐ 1 Yes	☐ 2 No

Evaluator's initials _____ _____ _____
First Middle Last

Initials
Date Verified
Initials
Date Keyed
Date Received at Lilly
Reviewed
Inspected
Date

REMINDER

On the Pre-existing Conditions and Study Adverse Events pages, record new events that occurred since the previous visit and re-evaluate any on-going conditions or events.

On the Concomitant Medication pages, record new medications the patient has taken since the previous visit, any changes to ongoing medications, and a stop date for any medication the patient is no longer taking.

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B1Y-MC-HCJE

GLOBAL ASSESSMENT OF FUNCTIONING SCALE (GAF SCALE)

INFORMATION NOT OBTAINED ☐

Enter the number (between 1 and 90) that best represents the patient's:

1. **Current** level of functioning _____
2. **Highest** level of functioning in *past year* _____

Level of Functioning Definitions	
90 – 81	Absent or minimal symptoms, good functioning in all areas, interested and involved in a wide range of activities, socially effective, generally satisfied with life, no more than everyday problems or concerns.
80 – 71	If symptoms are present, they are transient and expectable reactions to psychosocial stressors; no more than slight impairment in social, occupational, or school functioning.
70 – 61	Some mild symptoms OR some difficulty in social, occupational, or school functioning, but generally functioning pretty well, has some meaningful interpersonal relationships.
60 – 51	Moderate symptoms OR any moderate difficulty in social, occupational, or school functioning.
50 – 41	Serious symptoms OR any serious impairment in social, occupational, or school functioning.
40 – 31	Some impairment in reality testing or communication OR major impairment in several areas, such as work or school, family relations, judgment, thinking, or mood.
30 – 21	Behavior is considered influenced by delusions or hallucinations OR serious impairment in communications or judgment OR inability to function in almost all areas.
20 – 11	Some danger of hurting self or other OR occasionally fails to maintain minimal personal hygiene OR gross impairment in communication.
10 – 1	Persistent danger of severely hurting self or others OR persistent inability to maintain minimum personal hygiene OR serious suicidal act with clear expectation of death.

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VITAL SIGNS : BLOOD PRESSURE AND HEART RATE

INFORMATION NOT OBTAINED ☐

Position
SI = Sitting

Position	Blood Pressure (mm Hg) Systolic/Diastolic	Heart Rate (bpm)
SI	/	

VITAL SIGNS: TEMPERATURE

INFORMATION NOT OBTAINED ☐

Temperature ___ ___ ___ . ___

Unit of measure (F) Fahrenheit

Method (E) Ear

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B1Y-MC-HCJE

CHILDRENS DEPRESSION RATING SCALE - REVISED

INFORMATION NOT OBTAINED ☐

CHECK THE NUMERIC CODE which best describes the patient.

1. **SCHOOLWORK**:

☐ 1 Performance consistent with ability
☐ 2
☐ 3 Decrease in school performance
☐ 4
☐ 5 Major interference in most subjects
☐ 6
☐ 7 No motivation to perform

2. **CAPACITY TO HAVE FUN**

☐ 1 Interest and activities realistically appropriate for age, personality, and social environment. Shows no appreciable change with present illness.
☐ 2
☐ 3 Describes some activities realistically available several times a week but not on a daily basis. Shows interest but not enthusiasm.
☐ 4
☐ 5 Is easily bored. Complains of "nothing to do." Participates in structured activities with a "going through the motions" attitude. May express interest primarily in activities that are (realistically) unavailable on a daily or weekly basis.
☐ 6
☐ 7 Has no initiative to become involved in any activities. Primarily passive. Watches others play or watches TV but shows little interest. Requires coaxing and/or pushing to get involved in activity. Shows no enthusiasm or real interest. Has difficulty naming activities.

3. **SOCIAL WITHDRAWAL**

☐ 1 Enjoys friendships with peers at school and home
☐ 2
☐ 3 May not actively seek out friendships but waits for others to initiate a relationship or may occasionally reject opportunities to play without a describable alternative
☐ 4
☐ 5 Frequently avoids or refuses opportunities for desirable interaction with others and/or sets up situations where rejection is inevitable.
☐ 6
☐ 7 Does not currently relate to other children. States he or she has "no friends" or actively rejects new or former friends.

4. **SLEEP**

☐ 1 No (or occasional) difficulty. (Goes to sleep within 1/2 hour or less.)
☐ 2
☐ 3 Frequently has mild difficulty with sleep
☐ 4
☐ 5 Moderate difficulty with sleep nearly every night.

5. **APPETITE OR EATING PATTERNS**

☐ 1 No problems or change in eating pattern
☐ 2
☐ 3 Mild change from usual eating habits within onset of current behavioral problem
☐ 4
☐ 5 Is not hungry most of the time or has excessive food intake since onset of current behavioral problems or marked increase in appetite

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CHILDRENS DEPRESSION RATING SCALE - REVISED

CHECK THE NUMERIC CODE which best describes the patient.

6. **EXCESSIVE FATIGUE**

- ☐ 1 No unusual complaints of "feeling tired" during the day
- ☐ 2
- ☐ 3 Complaints of fatigue which seem somewhat excessive and not related to boredom
- ☐ 4
- ☐ 5 Daily complaints of feeling tired
- ☐ 6
- ☐ 7 Complains of feeling tired most of the day. May voluntarily take long naps without feeling refreshed. Interferes with play activities.

7. **PHYSICAL COMPLAINTS**:

- ☐ 1 Occasional complaints
- ☐ 2
- ☐ 3 Complaints appear mildly excessive
- ☐ 4
- ☐ 5 Complains daily. Some interference with the ability of the child to function
- ☐ 6
- ☐ 7 Preoccupied with aches and pains; interferes with play activities several times a week

8. **IRRITABILITY**

- ☐ 1 Rare
- ☐ 2 Occasional
- ☐ 3 Several times a week for short periods
- ☐ 4
- ☐ 5 Several times a week for longer periods
- ☐ 6
- ☐ 7 Constant

9. **GUILT**

- ☐ 1 Does not express any undue feeling of guilt. Appears appropriate to precipitating event.
- ☐ 2
- ☐ 3 Exaggerates guilt and/or shame out of proportion to the event described.
- ☐ 4
- ☐ 5 Feels guilty over things not under his or her control. Guilt is definitely pathological.
- ☐ 6
- ☐ 7 Severe delusions of guilt

10. **SELF-ESTEEM**

- ☐ 1 Describes self in primarily positive terms
- ☐ 2
- ☐ 3 Describes self with one important area where the child feels deficit
- ☐ 4
- ☐ 5 Describes self in preponderance of negative terms or gives bland answers to questions
- ☐ 6
- ☐ 7 Refers to self in derogatory terms. Reports that other children refer to him/her frequently by using derogatory nicknames and child puts self down

11. **DEPRESSED FEELINGS**

- ☐ 1 Occasional feelings of unhappiness which quickly disappear
- ☐ 2
- ☐ 3 Describes sustained periods of unhappiness which appear excessive for events described
- ☐ 4
- ☐ 5 Feels unhappy most of the time without a major precipitating cause
- ☐ 6
- ☐ 7 Feels unhappy all of the time. Accompanied by psychic pain (e.g., "I can't stand it").

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B1Y-MC-HCJE

CHILDRENS DEPRESSION RATING SCALE - REVISED

CHECK THE NUMERIC CODE which best describes the patient.

12. **MORBID IDEATION**

- ☐ 1 None
- ☐ 2
- ☐ 3 Has some morbid thought, all of which relate to a reality event but seem excessive.
- ☐ 4
- ☐ 5 Preoccupied with morbid thoughts several times a week. Morbid thoughts extend beyond external reality
- ☐ 6
- ☐ 7 Preoccupied with death themes or morbid thoughts that are elaborate, extensive or bizarre on a daily basis

13. **SUICIDAL IDEATION**

- ☐ 1 Understands the word "suicide" but does not apply term to self
- ☐ 2 Sharp denial of suicidal thoughts
- ☐ 3 Has thoughts about suicide, usually when angry.
- ☐ 4
- ☐ 5 Has recurrent thoughts of suicide
- ☐ 6
- ☐ 7 Has made suicide attempt within the last month or is actively suicidal

14. **WEEPING**:

- ☐ 1 Normal for age.
- ☐ 2 Suggestive statements that child cries, or feels like crying, more frequently than peers.
- ☐ 3 Child cries slightly more than peers.
- ☐ 4
- ☐ 5 Cries or feels like crying frequently (several times a week). Admits to crying without knowing reason why.
- ☐ 6
- ☐ 7 Cries nearly every day.

15. **DEPRESSED AFFECT:**

- ☐ 1 Definitely not depressed. Facial expression and voice animated during interview.
- ☐ 2 Mild suppression of affect. Some loss of spontaneity.
- ☐ 3 Overall loss of spontaneity. Looks distinctly unhappy during parts of the interview. May still be able to smile when discussing non-threatening areas.
- ☐ 4
- ☐ 5 Moderate restriction of affect throughout most of interview. Has longer and frequent periods of looking distinctly unhappy.
- ☐ 6
- ☐ 7 Severe. Looks sad, withdrawn. Minimal verbal interaction throughout interview. Cries or may appear tearful.

16. **TEMPO OF SPEECH:**

- ☐ 1 Normal
- ☐ 2 Slow
- ☐ 3 Slow: delays interview.
- ☐ 4
- ☐ 5 Severe. Low; marked interference with interview.

17. **HYPOACTIVITY:**

- ☐ 1 None
- ☐ 2
- ☐ 3 Mild. Some body movements.
- ☐ 4
- ☐ 5 Moderate. Definite motor retardation.
- ☐ 6
- ☐ 7 Severe. Motionless throughout interview.

(DNDE)

Total of 1 - 17 _____

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Fluoxetine Versus Placebo in Childhood/Adolescent Depression
B1Y-MC-HCJE

CLINICAL GLOBAL IMPRESSION: SEVERITY

INFORMATION NOT OBTAINED ☐

Considering your total clinical experience with this particular population, how mentally ill is the patient at this time?

- ☐ 1 Normal, not at all ill
- ☐ 2 Borderline ill
- ☐ 3 Mildly ill
- ☐ 4 Moderately ill
- ☐ 5 Markedly ill
- ☐ 6 Severely ill
- ☐ 7 Among the most extremely ill patients

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CLINICAL GLOBAL IMPRESSION: IMPROVEMENT

INFORMATION NOT OBTAINED ☐

Rate total improvement, whether or not in your judgement it is due entirely to drug treatment. Compared to the patient's condition at Visit 1, how much has he/she changed?

- ☐ 1 Very much improved
- ☐ 2 Much improved
- ☐ 3 Minimally improved
- ☐ 4 No change
- ☐ 5 Minimally worse
- ☐ 6 Much worse
- ☐ 7 Very much worse

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MONTGOMERY - ASBERG DEPRESSION RATING SCALE (MADRS)

INFORMATION NOT OBTAINED ☐

The rating should be based on a clinical interview moving from broadly phrased questions about symptoms to more detailed ones which allow a precise rating of severity. The rater must decide whether the rating lies on the defined scale steps (0, 2, 4, 6) or between them (1, 3, 5).

Check the box (number) that best characterizes the patient at this time

1. **APPARENT SADNESS**
   Representing despondency, gloom, and despair (more than just ordinary transient low spirits), reflected in speech, facial expression, and posture. Rate by depth and inability to brighten up.

   ☐ 0 No sadness.
   ☐ 1
   ☐ 2 Looks dispirited but does brighten up without difficulty.
   ☐ 3
   ☐ 4 Appears sad and unhappy most of the time.
   ☐ 5
   ☐ 6 Looks miserable all the time. Extremely despondent.

2. **REPORTED SADNESS**
   Represented by reports of depressed mood, regardless of whether it is reflected in appearance or not. Includes low spirits, despondency, or the feeling of being beyond help and without hope. Rate according to intensity, duration, and the extent to which the mood is reported to be influenced by events.

   ☐ 0 Occasional sadness in keeping with the circumstances.
   ☐ 1
   ☐ 2 Sad or low but brightens up without difficulty.
   ☐ 3
   ☐ 4 Pervasive feelings of sadness or gloominess. The mood is still influenced by external circumstances.
   ☐ 5
   ☐ 6 Continuous unvarying sadness, misery or despondency.

3. **INNER TENSION**
   Representing feelings of ill-defined discomfort, edginess, inner turmoil, mental tension mounting to either panic, dread, or anguish. Rate according to intensity, frequency, duration, and the extent of reassurance called for.

   ☐ 0 Placid. Only fleeting inner tension.
   ☐ 1
   ☐ 2 Occasional feelings of edginess and ill-defined discomfort.
   ☐ 3
   ☐ 4 Continuous feelings of inner tension or intermittent panic which the patient can only master with some difficulty.
   ☐ 5
   ☐ 6 Unrelenting dread or anguish. Overwhelming panic.

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MONTGOMERY - ASBERG DEPRESSION RATING SCALE (MADRS)

4. **REDUCED SLEEP**
Representing the experience of reduced duration or depth of sleep compared to the subject's own pattern when well.

- ☐ 0 Sleeps as usual.
- ☐ 1
- ☐ 2 Slight difficulty dropping off to sleep or slightly reduced, light or fitful sleep.
- ☐ 3
- ☐ 4 Sleep reduced or broken by at least two hours.
- ☐ 5
- ☐ 6 Less than two or three hours sleep.

5. **REDUCED APPETITE**
Representing the feeling of a loss of appetite compared with when well. Rate by loss of desire for food or the need to force oneself to eat.

- ☐ 0 Normal or increased appetite
- ☐ 1
- ☐ 2 Slightly reduced appetite.
- ☐ 3
- ☐ 4 No appetite. Food is tasteless.
- ☐ 5
- ☐ 6 Needs persuasion to eat at all.

6. **CONCENTRATION DIFFICULTIES**
Representing difficulties in collecting one's thoughts mounting to incapacitating lack of concentration.

- ☐ 0 No difficulties in concentrating.
- ☐ 1
- ☐ 2 Occasional difficulties in collecting one's thoughts.
- ☐ 3
- ☐ 4 Difficulties in concentrating and sustaining thought which reduces ability to read or hold a conversation.
- ☐ 5
- ☐ 6 Unable to read or converse without great difficulty.

7. **LASSITUDE**
Representing a difficulty getting started or slowness initiating and performing everyday activities.

- ☐ 0 Hardly any difficulty in getting started. No sluggishness.
- ☐ 1
- ☐ 2 Difficulties in starting activities
- ☐ 3
- ☐ 4 Difficulties in starting simple routine activities which are carried out with effort.
- ☐ 5
- ☐ 6 Complete lassitude. Unable to do anything without help.

8. **INABILITY TO FEEL**
Representing the subjective experience of reduced interest in the surroundings, or activities that normally give pleasure. The ability to react with adequate emotion to circumstances or people is reduced.

- ☐ 0 Normal interest in the surroundings and other people.
- ☐ 1
- ☐ 2 Reduced ability to enjoy usual interests.
- ☐ 3
- ☐ 4 Loss of interest in the surroundings. Loss of feelings for friends and acquaintances.
- ☐ 5
- ☐ 6 The experience of being emotionally paralyzed, inability to feel anger, grief, or pleasure and a complete or even painful failure to feel for close relatives and friends.

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MONTGOMERY - ASBERG DEPRESSION RATING SCALE (MADRS)

9. **PESSIMISTIC THOUGHTS**
Representing thoughts of guilt, inferiority, self-reproach, sinfulness, remorse, and ruin

- ☐ 0 No pessimistic thoughts.
- ☐ 1
- ☐ 2 Fluctuating ideas of failure, self-reproach, or self-depreciation.
- ☐ 3
- ☐ 4 Persistent self-accusations, or definite but still rational ideas of guilt, or sin. Increasingly pessimistic about the future.
- ☐ 5
- ☐ 6 Delusions of ruin, remorse, or unredeemable sin. Self-accusations which are absurd and unshakable.

10. **SUICIDAL THOUGHTS**
Representing the feeling that life is not worth living, that a natural death would be welcome, suicidal thoughts, and preparations for suicide. Suicidal attempts should not in themselves influence the rating.

- ☐ 0 Enjoys life or takes it as it comes.
- ☐ 1
- ☐ 2 Weary of life. Only fleeting suicidal thoughts.
- ☐ 3
- ☐ 4 Probably better off dead. Suicidal thoughts are common, and suicide is considered as a possible solution, but without specific plans or intention.
- ☐ 5
- ☐ 6 Explicit plans for suicide when there is an opportunity. Active preparations for suicide.

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CHILDREN'S DEPRESSION INDEX (CDI)

NOTE: Only complete if patient was 8 to 12 years old at Visit 1. If patient was not 8 to 12 years old, check the Information Not Obtained box.

INFORMATION NOT OBTAINED ☐

This lists the feelings and ideas in groups. From each group of three sentences, pick one sentence that describes you **best** for the past two weeks. After you pick a sentence from the first group, go on to the next group. There is no right answer or wrong answer. Just pick the sentence that best describes the way you have been recently. Put an "X" in the box next to your answer.
Remember: pick out the sentences that describe you best **in the past two weeks**.

Item 1

- ☐ 0 I am sad once in a while.
- ☐ 1 I am sad many times.
- ☐ 2 I am sad all the time.

Item 2

- ☐ 2 Nothing will ever work out for me.
- ☐ 1 I am not sure if things will work out for me.
- ☐ 0 Things will work out for me O.K.

Item 3

- ☐ 0 I do most things O.K.
- ☐ 1 I do many things wrong.
- ☐ 2 I do everything wrong.

Item 4

- ☐ 0 I have fun in many things.
- ☐ 1 I have fun in some things.
- ☐ 2 Nothing is fun at all.

Item 5

- ☐ 2 I am bad all the time.
- ☐ 1 I am bad many times.
- ☐ 0 I am bad once in a while.

Item 6

- ☐ 0 I think about bad things happening to me once in a while.
- ☐ 1 I worry that bad things will happen to me.
- ☐ 2 I am sure that terrible things will happen to me.

Item 7

- ☐ 2 I hate myself.
- ☐ 1 I do not like myself.
- ☐ 0 I like myself.

Item 8

- ☐ 2 All bad things are my fault.
- ☐ 1 Many bad things are my fault.
- ☐ 0 Bad things are not usually my fault.

Item 9

- ☐ 0 I do not think about killing myself.
- ☐ 1 I think about killing myself but I would not do it.
- ☐ 2 I want to kill myself.

Item 10

- ☐ 2 I feel like crying every day.
- ☐ 1 I feel like crying many days.
- ☐ 0 I feel like crying once in a while.

Item 11

- ☐ 2 Things bother me all the time.
- ☐ 1 Things bother me many times.
- ☐ 0 Things bother me once in a while.

Item 12

- ☐ 0 I like being with people.
- ☐ 1 I do not like being with people many times.
- ☐ 2 I do not want to be with people at all.

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CHILDREN'S DEPRESSION INDEX (CDI)

Item 13

- ☐ 2 I cannot make up my mind about things.
- ☐ 1 It is hard to make up my mind about things.
- ☐ 0 I make up my mind about things easily.

Item 14

- ☐ 0 I look O.K.
- ☐ 1 There are some bad things about my looks.
- ☐ 2 I look ugly.

Item 15

- ☐ 2 I have to push myself all the time to do my schoolwork.
- ☐ 1 I have to push myself many times to do my schoolwork.
- ☐ 0 Doing schoolwork is not a big problem.

Item 16

- ☐ 2 I have trouble sleeping every night.
- ☐ 1 I have trouble sleeping many nights.
- ☐ 0 I sleep pretty well.

Item 17

- ☐ 0 I am tired once in a while.
- ☐ 1 I am tired many days.
- ☐ 2 I am tired all the time.

Item 18

- ☐ 2 Most days I do not feel like eating.
- ☐ 1 Many days I do not feel like eating.
- ☐ 0 I eat pretty well.

Item 19

- ☐ 0 I do not worry about aches and pains.
- ☐ 1 I worry about aches and pains many times.
- ☐ 2 I worry about aches and pains all the time.

Item 20

- ☐ 0 I do not feel alone.
- ☐ 1 I feel alone many times.
- ☐ 2 I feel alone all the time.

Item 21

- ☐ 2 I never have fun at school.
- ☐ 1 I have fun at school only once in a while.
- ☐ 0 I have fun at school many times.

Item 22

- ☐ 0 I have plenty of friends.
- ☐ 1 I have some friends but I wish I had more.
- ☐ 2 I do not have any friends.

Item 23

- ☐ 0 My schoolwork is alright.
- ☐ 1 My schoolwork is not as good as before.
- ☐ 2 I do very badly in subjects I used to be good in.

Item 24

- ☐ 2 I can never be as good as other kids.
- ☐ 1 I can be as good as other kids if I want to.
- ☐ 0 I am just as good as other kids.

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CHILDREN'S DEPRESSION INDEX (CDI)

Item 25

- ☐ 2 Nobody really loves me.
- ☐ 1 I am not sure if anybody loves me.
- ☐ 0 I am sure that somebody loves me.

Item 26

- ☐ 0 I usually do what I am told.
- ☐ 1 I do not do what I am told most times.
- ☐ 2 I never do what I am told.

Item 27

- ☐ 0 I get along with people.
- ☐ 1 I get into fights many times.
- ☐ 2 I get into fights all the time.

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BECK DEPRESSION INVENTORY

NOTE: Only complete if patient was 13 to 17 years old at Visit 1. If patient was not 13 to 17 years old, check the Information Not Obtained box.

INFORMATION NOT OBTAINED ☐

This questionnaire consists of 21 groups of statements. After reading each group of statements carefully circle the number (0, 1, 2, 3) next to the one statement in each group which best describes the way you have been feeling **the past week, including today**. If several statements within a group seem to apply equally well, circle each one. Be sure to read all the statements in each group before making your choice.

1

0 I do not feel sad.
1 I feel sad.
2 I am sad all the time and I can't snap out of it.
3 I am so sad or unhappy that I can't stand it.

2

0 I am not particularly discouraged about the future.
1 I feel discouraged about the future.
2 I feel I have nothing to look forward to.
3 I feel that the future is hopeless and that things cannot improve.

3

0 I do not feel like a failure.
1 I feel I have failed more than the average person.
2 As I look back on my life, all I can see is a lot of failures.
3 I feel I am a complete failure as a person.

4

0 I get as much satisfaction out of things as I used to.
1 I don't enjoy things the way I used to.
2 I don't get real satisfaction out of anything anymore.
3 I am dissatisfied or bored with everything.

5

0 I don't feel particularly guilty.
1 I feel guilty a good part of the time.
2 I feel quite guilty most of the time.
3 I feel guilty all of the time.

6

0 I don't feel I am being punished.
1 I feel I may be punished.
2 I expect to be punished.
3 I feel I am being punished.

7

0 I don't feel disappointed in myself.
1 I am disappointed in myself.
2 I am disgusted with myself.
3 I hate myself.

8

0 I don't feel I am any worse than anybody else.
1 I am critical of myself for my weaknesses or mistakes.
2 I blame myself all the time for my faults.
3 I blame myself for everything bad that happens.

9

0 I don't have any thoughts of killing myself.
1 I have thoughts of killing myself, but I would not carry them out.
2 I would like to kill myself.
3 I would kill myself if I had the chance.

10

0 I don't cry any more than usual.
1 I cry more now than I used to.
2 I cry all the time now.
3 I used to be able to cry, but now I can't cry even though I want to.

11

0 I am no more irritated now than I ever am.
1 I get annoyed or irritated more easily than I used to.
2 I feel irritated all the time now.
3 I don't get irritated at all by the things that used to irritate me.

12

0 I have not lost interest in other people.
1 I am less interested in other people than I used to be.
2 I have lost most of my interest in other people.
3 I have lost all of my interest in other people.

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BECK DEPRESSION INVENTORY

13

0 I make decisions about as well as I ever could.
1 I put off making decisions more than I used to.
2 I have greater difficulty in making decisions than before.
3 I can't make decisions at all anymore.

14

0 I don't feel I look any worse than I used to.
1 I am worried that I am looking old or unattractive.
2 I feel that there are permanent changes in my appearance that make me look unattractive.
3 I believe that I look ugly.

15

0 I can work about as well as before.
1 It takes an extra effort to get started at doing something.
2 I have to push myself very hard to do anything.
3 I can't do any work at all.

16

0 I can sleep as well as usual.
1 I don't sleep as well as I used to.
2 I wake up 1-2 hours earlier than usual and find it hard to get back to sleep.
3 I wake up several hours earlier than I used to and cannot get back to sleep.

17

0 I don't get more tired than usual.
1 I get tired more easily than I used to.
2 I get tired from doing almost anything.
3 I am too tired to do anything.

18

0 My appetite is no worse than usual.
1 My appetite is not as good as it used to be.
2 My appetite is much worse now.
3 I have no appetite at all anymore.

19

0 I haven't lost much weight, if any, lately.
1 I have lost more than 5 pounds.
2 I have lost more than 10 pounds.
3 I have lost more than 15 pounds.

19a

I am purposely trying to lose weight by eating less.
1 Yes
2 No

20

0 I am no more worried about my health than usual.
1 I am worried about physical problems such as aches and pains; or upset stomach or constipation.
2 I am very worried about physical problems and it's hard to think of much else.
3 I am so worried about my physical problems that I cannot think about anything else.

21

0 I have not noticed any recent change in my interest in sex.
1 I am less interested in sex than I used to be.
2 I am much less interested in sex now.
3 I have lost interest in sex completely.

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HAMILTON ANXIETY SCALE

INFORMATION NOT OBTAINED ☐

For each of the items below, **CHECK ONE BOX** that best describes the patient.

1. **ANXIOUS MOOD:** Worries, anticipation of the worst, fearful anticipation, irritability

   ☐ 0 Not present
   ☐ 1 Mild
   ☐ 2 Moderate
   ☐ 3 Severe
   ☐ 4 Very severe

2. **TENSION**: Feelings of tension, fatigability, startle response, moved to tears easily, trembling, feeling of restlessness, inability to relax

   ☐ 0 Not present
   ☐ 1 Mild
   ☐ 2 Moderate
   ☐ 3 Severe
   ☐ 4 Very severe

3. **FEARS**: Of dark, of strangers, of being alone, of animals, of traffic, of crowds

   ☐ 0 Not present
   ☐ 1 Mild
   ☐ 2 Moderate
   ☐ 3 Severe
   ☐ 4 Very severe

4. **INSOMNIA**: Difficulty in falling asleep, broken sleep, unsatisfying sleep and fatigue on waking, dreams, nightmares, night terrors

   ☐ 0 Not present
   ☐ 1 Mild
   ☐ 2 Moderate
   ☐ 3 Severe
   ☐ 4 Very severe

5. **INTELLECTUAL (COGNITIVE)**: Difficulty in concentration, poor memory

   ☐ 0 Not present
   ☐ 1 Mild
   ☐ 2 Moderate
   ☐ 3 Severe
   ☐ 4 Very severe

6. **DEPRESSED MOOD**: Loss of interest, lack of pleasure in hobbies, depression, early waking, diurnal swing

   ☐ 0 Not present
   ☐ 1 Mild
   ☐ 2 Moderate
   ☐ 3 Severe
   ☐ 4 Very severe

7. **SOMATIC (MUSCULAR)**: Pains and aches, twitchings, stiffness, myoclonic jerks, grinding of teeth, unsteady voice, increased muscular tone

   ☐ 0 Not present
   ☐ 1 Mild
   ☐ 2 Moderate
   ☐ 3 Severe
   ☐ 4 Very severe

8. **SOMATIC (SENSORY)**: Tinnitus, blurring of vision, hot and cold flushes, feeling of weakness, pricking sensation

   ☐ 0 Not present
   ☐ 1 Mild
   ☐ 2 Moderate
   ☐ 3 Severe
   ☐ 4 Very severe

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HAMILTON ANXIETY SCALE

9. **CARDIOVASCULAR SYMPTOMS:** Tachycardia, palpitations, pain in chest, throbbing of vessels, fainting feelings, missing beat

- ☐ 0 Not present
- ☐ 1 Mild
- ☐ 2 Moderate
- ☐ 3 Severe
- ☐ 4 Very severe

10. **RESPIRATORY SYMPTOMS:** Pressure or constriction in chest, choking feelings, sighing, dyspnea

- ☐ 0 Not present
- ☐ 1 Mild
- ☐ 2 Moderate
- ☐ 3 Severe
- ☐ 4 Very severe

11. **GASTROINTESTINAL SYMPTOMS:** Difficulty in swallowing, wind, abdominal pain, burning sensations, abdominal fullness, nausea, vomiting, borborygmi, looseness of bowels, loss of weight, constipation

- ☐ 0 Not present
- ☐ 1 Mild
- ☐ 2 Moderate
- ☐ 3 Severe
- ☐ 4 Very severe

12. **GENITOURINARY SYMPTOMS:** Frequency of micturition, urgency of micturition, amenorrhea, menorrhagia, development of frigidity, premature ejaculation, loss of libido, impotence

- ☐ 0 Not present
- ☐ 1 Mild
- ☐ 2 Moderate
- ☐ 3 Severe
- ☐ 4 Very severe

13. **AUTONOMIC SYMPTOMS:** Dry mouth, flushing, pallor, tendency to sweat, giddiness, tension headache, raising of hair

- ☐ 0 Not present
- ☐ 1 Mild
- ☐ 2 Moderate
- ☐ 3 Severe
- ☐ 4 Very severe

14. **BEHAVIOR AT INTERVIEW:** Fidgeting, restlessness or pacing, tremor of hands, furrowed brow, strained face, sighing or rapid respiration, facial pallor, swallowing, belching, brisk tendon jerks, dilated pupils, exophthalmos

- ☐ 0 Not present
- ☐ 1 Mild
- ☐ 2 Moderate
- ☐ 3 Severe
- ☐ 4 Very severe

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B1Y-MC-HCJE

COMMENTS : VISIT

NO COMMENTS ☐

Comments should address any clinical report form items that require further explanation. Repeating information from the clinical report form is discouraged.

Comment on all clinically significant lab values that are outside a clinically accepted reference range or clinically significant values that differ importantly from previous values.

If the patient is ending participation in the study at this visit, enter only comments that apply to this visit; then complete the Patient Summary and Study Summary Comments pages.

Print legibly and do not use abbreviations or symbols.

The information reported for this visit is accurate and complete.

_____ _____/_____/_____
Signature MM DD YY

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PATIENT AND VISIT IDENTIFICATION

Patient initials _____ _____ _____
First Middle Last

Visit date _____/_____/_____
MM DD YY

K-SADS : AFFECTIVE DISORDERS

INFORMATION NOT OBTAINED ☐

Check the appropriate boxes.

Depressive Disorders - Current	☐ 1 Yes	☐ 2 No
Depressive Disorders - Past	☐ 1 Yes	☐ 2 No
Mania - Current	☐ 1 Yes	☐ 2 No
Mania -Past	☐ 1 Yes	☐ 2 No

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First Middle Last

Initials
Date Verified
Initials
Date Keyed
Date Received at Lilly
Reviewed
Inspected
Date

REMINDER

On the Pre-existing Conditions and Study Adverse Events pages, record new events that occurred since the previous visit and re-evaluate any on-going conditions or events.

On the Concomitant Medication pages, record new medications the patient has taken since the previous visit, any changes to ongoing medications, and a stop date for any medication the patient is no longer taking.

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GLOBAL ASSESSMENT OF FUNCTIONING SCALE (GAF SCALE)

INFORMATION NOT OBTAINED ☐

Enter the number (between 1 and 90) that best represents the patient's:

1. **Current** level of functioning _____
2. **Highest** level of functioning in *past year* _____

Level of Functioning Definitions	
90 – 81	Absent or minimal symptoms, good functioning in all areas, interested and involved in a wide range of activities, socially effective, generally satisfied with life, no more than everyday problems or concerns.
80 – 71	If symptoms are present, they are transient and expectable reactions to psychosocial stressors; no more than slight impairment in social, occupational, or school functioning.
70 – 61	Some mild symptoms OR some difficulty in social, occupational, or school functioning, but generally functioning pretty well, has some meaningful interpersonal relationships.
60 – 51	Moderate symptoms OR any moderate difficulty in social, occupational, or school functioning.
50 – 41	Serious symptoms OR any serious impairment in social, occupational, or school functioning.
40 – 31	Some impairment in reality testing or communication OR major impairment in several areas, such as work or school, family relations, judgment, thinking, or mood.
30 – 21	Behavior is considered influenced by delusions or hallucinations OR serious impairment in communications or judgment OR inability to function in almost all areas.
20 – 11	Some danger of hurting self or other OR occasionally fails to maintain minimal personal hygiene OR gross impairment in communication.
10 – 1	Persistent danger of severely hurting self or others OR persistent inability to maintain minimum personal hygiene OR serious suicidal act with clear expectation of death.

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VITAL SIGNS : BLOOD PRESSURE AND HEART RATE

INFORMATION NOT OBTAINED ☐

Position
SI = Sitting

Position	Blood Pressure (mm Hg) Systolic/Diastolic	Heart Rate (bpm)
SI	/	

VITAL SIGNS: TEMPERATURE

INFORMATION NOT OBTAINED ☐

Temperature ___ ___ ___ . ___

Unit of measure (F) Fahrenheit

Method (E) Ear

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B1Y-MC-HCJE

STUDY DRUG : DATES OF MISSED DOSES

NO MISSED DOSES ☐

Record the date for any day on which the patient missed a full or partial dose of study drug.

	Dates of Missed Doses MM	DD	YY
0.			
1.			
2.			
3.			
4.			
5.			
6.			
7.			
8.			
9.			

NOTE: If the patient has missed 3 or more consecutive days of medication, the patient must be discontinued from the study.

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B1Y-MC-HCJE

SIDE EFFECTS CHECKLIST

INFORMATION NOT OBTAINED ☐

Since your last visit, have you been bothered with or had any trouble with any of the items listed below? Check the box which best tells how much you were bothered.

	Not at all	Just a little	Pretty much	Very much	Don't know
1. Eating?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
2. Drinking?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
3. Dry mouth and lips?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
4. Wetness in mouth?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
5. Constipation?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
6. Diarrhea?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
7. Stomachaches?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
8. Muscle cramps?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
9. Being sick to your stomach?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
10. Wetting the bed?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
11. Urinating?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
12. Itchy or scratchy skin?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
13. Rashes?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
14. Cold or sniffles?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
15. Headache?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4

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B1Y-MC-HCJE

SIDE EFFECTS CHECKLIST

	Not at all	Just a little	Pretty much	Very much	Don't know
16. Dizziness?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
17. Playing sports?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
18. Shakiness?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
19. Pronouncing words?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
20. Doing things with your hands?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
21. Sitting still?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
22. Tiredness?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
23. Feeling sleepy?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
24. Trouble sleeping?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
25. Bad dreams?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
26. Getting along with parents?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
27. Getting along with kids?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
28. Crying?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
29. Getting mad?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
30. Not being happy?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
31. Being sad?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
32. Paying attention?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4

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Fluoxetine Versus Placebo in Childhood/Adolescent Depression
B1Y-MC-HCJE

CHILDRENS DEPRESSION RATING SCALE - REVISED

INFORMATION NOT OBTAINED ☐

CHECK THE NUMERIC CODE which best describes the patient.

1. **SCHOOLWORK**:

☐ 1 Performance consistent with ability
☐ 2
☐ 3 Decrease in school performance
☐ 4
☐ 5 Major interference in most subjects
☐ 6
☐ 7 No motivation to perform

2. **CAPACITY TO HAVE FUN**

☐ 1 Interest and activities realistically appropriate for age, personality, and social environment. Shows no appreciable change with present illness.
☐ 2
☐ 3 Describes some activities realistically available several times a week but not on a daily basis. Shows interest but not enthusiasm.
☐ 4
☐ 5 Is easily bored. Complains of "nothing to do." Participates in structured activities with a "going through the motions" attitude. May express interest primarily in activities that are (realistically) unavailable on a daily or weekly basis.
☐ 6
☐ 7 Has no initiative to become involved in any activities. Primarily passive. Watches others play or watches TV but shows little interest. Requires coaxing and/or pushing to get involved in activity. Shows no enthusiasm or real interest. Has difficulty naming activities.

3. **SOCIAL WITHDRAWAL**

☐ 1 Enjoys friendships with peers at school and home
☐ 2
☐ 3 May not actively seek out friendships but waits for others to initiate a relationship or may occasionally reject opportunities to play without a describable alternative
☐ 4
☐ 5 Frequently avoids or refuses opportunities for desirable interaction with others and/or sets up situations where rejection is inevitable.
☐ 6
☐ 7 Does not currently relate to other children. States he or she has "no friends" or actively rejects new or former friends.

4. **SLEEP**

☐ 1 No (or occasional) difficulty. (Goes to sleep within 1/2 hour or less.)
☐ 2
☐ 3 Frequently has mild difficulty with sleep
☐ 4
☐ 5 Moderate difficulty with sleep nearly every night.

5. **APPETITE OR EATING PATTERNS**

☐ 1 No problems or change in eating pattern
☐ 2
☐ 3 Mild change from usual eating habits within onset of current behavioral problem
☐ 4
☐ 5 Is not hungry most of the time or has excessive food intake since onset of current behavioral problems or marked increase in appetite

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CHILDRENS DEPRESSION RATING SCALE - REVISED

CHECK THE NUMERIC CODE which best describes the patient.

6. **EXCESSIVE FATIGUE**

- ☐ 1 No unusual complaints of "feeling tired" during the day
- ☐ 2
- ☐ 3 Complaints of fatigue which seem somewhat excessive and not related to boredom
- ☐ 4
- ☐ 5 Daily complaints of feeling tired
- ☐ 6
- ☐ 7 Complains of feeling tired most of the day. May voluntarily take long naps without feeling refreshed. Interferes with play activities.

7. **PHYSICAL COMPLAINTS**:

- ☐ 1 Occasional complaints
- ☐ 2
- ☐ 3 Complaints appear mildly excessive
- ☐ 4
- ☐ 5 Complains daily. Some interference with the ability of the child to function
- ☐ 6
- ☐ 7 Preoccupied with aches and pains; interferes with play activities several times a week

8. **IRRITABILITY**

- ☐ 1 Rare
- ☐ 2 Occasional
- ☐ 3 Several times a week for short periods
- ☐ 4
- ☐ 5 Several times a week for longer periods
- ☐ 6
- ☐ 7 Constant

9. **GUILT**

- ☐ 1 Does not express any undue feeling of guilt. Appears appropriate to precipitating event.
- ☐ 2
- ☐ 3 Exaggerates guilt and/or shame out of proportion to the event described.
- ☐ 4
- ☐ 5 Feels guilty over things not under his or her control. Guilt is definitely pathological.
- ☐ 6
- ☐ 7 Severe delusions of guilt

10. **SELF-ESTEEM**

- ☐ 1 Describes self in primarily positive terms
- ☐ 2
- ☐ 3 Describes self with one important area where the child feels deficit
- ☐ 4
- ☐ 5 Describes self in preponderance of negative terms or gives bland answers to questions
- ☐ 6
- ☐ 7 Refers to self in derogatory terms. Reports that other children refer to him/her frequently by using derogatory nicknames and child puts self down

11. **DEPRESSED FEELINGS**

- ☐ 1 Occasional feelings of unhappiness which quickly disappear
- ☐ 2
- ☐ 3 Describes sustained periods of unhappiness which appear excessive for events described
- ☐ 4
- ☐ 5 Feels unhappy most of the time without a major precipitating cause
- ☐ 6
- ☐ 7 Feels unhappy all of the time. Accompanied by psychic pain (e.g., "I can't stand it").

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Fluoxetine Versus Placebo in Childhood/Adolescent Depression
B1Y-MC-HCJE

CHILDRENS DEPRESSION RATING SCALE - REVISED

CHECK THE NUMERIC CODE which best describes the patient.

12. **MORBID IDEATION**

- ☐ 1 None
- ☐ 2
- ☐ 3 Has some morbid thought, all of which relate to a reality event but seem excessive.
- ☐ 4
- ☐ 5 Preoccupied with morbid thoughts several times a week. Morbid thoughts extend beyond external reality
- ☐ 6
- ☐ 7 Preoccupied with death themes or morbid thoughts that are elaborate, extensive or bizarre on a daily basis

13. **SUICIDAL IDEATION**

- ☐ 1 Understands the word "suicide" but does not apply term to self
- ☐ 2 Sharp denial of suicidal thoughts
- ☐ 3 Has thoughts about suicide, usually when angry.
- ☐ 4
- ☐ 5 Has recurrent thoughts of suicide
- ☐ 6
- ☐ 7 Has made suicide attempt within the last month or is actively suicidal

14. **WEEPING**:

- ☐ 1 Normal for age.
- ☐ 2 Suggestive statements that child cries, or feels like crying, more frequently than peers.
- ☐ 3 Child cries slightly more than peers.
- ☐ 4
- ☐ 5 Cries or feels like crying frequently (several times a week). Admits to crying without knowing reason why.
- ☐ 6
- ☐ 7 Cries nearly every day.

15. **DEPRESSED AFFECT:**

- ☐ 1 Definitely not depressed. Facial expression and voice animated during interview.
- ☐ 2 Mild suppression of affect. Some loss of spontaneity.
- ☐ 3 Overall loss of spontaneity. Looks distinctly unhappy during parts of the interview. May still be able to smile when discussing non-threatening areas.
- ☐ 4
- ☐ 5 Moderate restriction of affect throughout most of interview. Has longer and frequent periods of looking distinctly unhappy.
- ☐ 6
- ☐ 7 Severe. Looks sad, withdrawn. Minimal verbal interaction throughout interview. Cries or may appear tearful.

16. **TEMPO OF SPEECH:**

- ☐ 1 Normal
- ☐ 2 Slow
- ☐ 3 Slow: delays interview.
- ☐ 4
- ☐ 5 Severe. Low; marked interference with interview.

17. **HYPOACTIVITY:**

- ☐ 1 None
- ☐ 2
- ☐ 3 Mild. Some body movements.
- ☐ 4
- ☐ 5 Moderate. Definite motor retardation.
- ☐ 6
- ☐ 7 Severe. Motionless throughout interview.

(DNDE)

Total of 1 - 17 _____

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Fluoxetine Versus Placebo in Childhood/Adolescent Depression
B1Y-MC-HCJE

CLINICAL GLOBAL IMPRESSION: EFFICACY INDEX

Using the worksheet below, enter the 2-digit efficacy index rating.

1. Efficacy index rating ___ ___

(DNDE)

EFFICACY INDEX WORKSHEET

Rate this item on the basis of DRUG EFFECT ONLY.

Select the terms that best describe the degrees of therapeutic effect and side effects and record the number from the box where the two items intersect in the blanks above.

THERAPEUTIC EFFECT	SIDE EFFECTS			
	None	Do not significantly interfere with patient's functioning	Significantly interferes with patient's functioning	Outweighs therapeutic effect
MARKED - Vast improvement. Complete or nearly complete remission of all symptoms.	**01**	**02**	**03**	**04**
MODERATE - Decided improvement. Partial remission of symptoms.	**05**	**06**	**07**	**08**
MINIMAL - Slight improvement which doesn't alter status of care of patient.	**09**	**10**	**11**	**12**
UNCHANGED OR WORSE	**13**	**14**	**15**	**16**
Not Assessed = **98**				

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Clinical Report Form
Fluoxetine Versus Placebo in Childhood/Adolescent Depression
B1Y-MC-HCJE

CLINICAL GLOBAL IMPRESSION: SEVERITY

INFORMATION NOT OBTAINED ☐

Considering your total clinical experience with this particular population, how mentally ill is the patient at this time?

- ☐ 1 Normal, not at all ill
- ☐ 2 Borderline ill
- ☐ 3 Mildly ill
- ☐ 4 Moderately ill
- ☐ 5 Markedly ill
- ☐ 6 Severely ill
- ☐ 7 Among the most extremely ill patients

Evaluator's initials _____ _____ _____
First Middle Last

CLINICAL GLOBAL IMPRESSION: IMPROVEMENT

INFORMATION NOT OBTAINED ☐

Rate total improvement, whether or not in your judgement it is due entirely to drug treatment. Compared to the patient's condition at Visit 1, how much has he/she changed?

- ☐ 1 Very much improved
- ☐ 2 Much improved
- ☐ 3 Minimally improved
- ☐ 4 No change
- ☐ 5 Minimally worse
- ☐ 6 Much worse
- ☐ 7 Very much worse

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MONTGOMERY - ASBERG DEPRESSION RATING SCALE (MADRS)

INFORMATION NOT OBTAINED ☐

The rating should be based on a clinical interview moving from broadly phrased questions about symptoms to more detailed ones which allow a precise rating of severity. The rater must decide whether the rating lies on the defined scale steps (0, 2, 4, 6) or between them (1, 3, 5).

Check the box (number) that best characterizes the patient at this time

1. **APPARENT SADNESS**
   Representing despondency, gloom, and despair (more than just ordinary transient low spirits), reflected in speech, facial expression, and posture. Rate by depth and inability to brighten up.

   ☐ 0 No sadness.
   ☐ 1
   ☐ 2 Looks dispirited but does brighten up without difficulty.
   ☐ 3
   ☐ 4 Appears sad and unhappy most of the time.
   ☐ 5
   ☐ 6 Looks miserable all the time. Extremely despondent.

2. **REPORTED SADNESS**
   Represented by reports of depressed mood, regardless of whether it is reflected in appearance or not. Includes low spirits, despondency, or the feeling of being beyond help and without hope. Rate according to intensity, duration, and the extent to which the mood is reported to be influenced by events.

   ☐ 0 Occasional sadness in keeping with the circumstances.
   ☐ 1
   ☐ 2 Sad or low but brightens up without difficulty.
   ☐ 3
   ☐ 4 Pervasive feelings of sadness or gloominess. The mood is still influenced by external circumstances.
   ☐ 5
   ☐ 6 Continuous unvarying sadness, misery or despondency.

3. **INNER TENSION**
   Representing feelings of ill-defined discomfort, edginess, inner turmoil, mental tension mounting to either panic, dread, or anguish. Rate according to intensity, frequency, duration, and the extent of reassurance called for.

   ☐ 0 Placid. Only fleeting inner tension.
   ☐ 1
   ☐ 2 Occasional feelings of edginess and ill-defined discomfort.
   ☐ 3
   ☐ 4 Continuous feelings of inner tension or intermittent panic which the patient can only master with some difficulty.
   ☐ 5
   ☐ 6 Unrelenting dread or anguish. Overwhelming panic.

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MONTGOMERY - ASBERG DEPRESSION RATING SCALE (MADRS)

4. **REDUCED SLEEP**
Representing the experience of reduced duration or depth of sleep compared to the subject's own pattern when well.

- ☐ 0 Sleeps as usual.
- ☐ 1
- ☐ 2 Slight difficulty dropping off to sleep or slightly reduced, light or fitful sleep.
- ☐ 3
- ☐ 4 Sleep reduced or broken by at least two hours.
- ☐ 5
- ☐ 6 Less than two or three hours sleep.

5. **REDUCED APPETITE**
Representing the feeling of a loss of appetite compared with when well. Rate by loss of desire for food or the need to force oneself to eat.

- ☐ 0 Normal or increased appetite
- ☐ 1
- ☐ 2 Slightly reduced appetite.
- ☐ 3
- ☐ 4 No appetite. Food is tasteless.
- ☐ 5
- ☐ 6 Needs persuasion to eat at all.

6. **CONCENTRATION DIFFICULTIES**
Representing difficulties in collecting one's thoughts mounting to incapacitating lack of concentration.

- ☐ 0 No difficulties in concentrating.
- ☐ 1
- ☐ 2 Occasional difficulties in collecting one's thoughts.
- ☐ 3
- ☐ 4 Difficulties in concentrating and sustaining thought which reduces ability to read or hold a conversation.
- ☐ 5
- ☐ 6 Unable to read or converse without great difficulty.

7. **LASSITUDE**
Representing a difficulty getting started or slowness initiating and performing everyday activities.

- ☐ 0 Hardly any difficulty in getting started. No sluggishness.
- ☐ 1
- ☐ 2 Difficulties in starting activities
- ☐ 3
- ☐ 4 Difficulties in starting simple routine activities which are carried out with effort.
- ☐ 5
- ☐ 6 Complete lassitude. Unable to do anything without help.

8. **INABILITY TO FEEL**
Representing the subjective experience of reduced interest in the surroundings, or activities that normally give pleasure. The ability to react with adequate emotion to circumstances or people is reduced.

- ☐ 0 Normal interest in the surroundings and other people.
- ☐ 1
- ☐ 2 Reduced ability to enjoy usual interests.
- ☐ 3
- ☐ 4 Loss of interest in the surroundings. Loss of feelings for friends and acquaintances.
- ☐ 5
- ☐ 6 The experience of being emotionally paralyzed, inability to feel anger, grief, or pleasure and a complete or even painful failure to feel for close relatives and friends.

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B1Y-MC-HCJE

MONTGOMERY - ASBERG DEPRESSION RATING SCALE (MADRS)

9. **PESSIMISTIC THOUGHTS**
Representing thoughts of guilt, inferiority, self-reproach, sinfulness, remorse, and ruin

- ☐ 0 No pessimistic thoughts.
- ☐ 1
- ☐ 2 Fluctuating ideas of failure, self-reproach, or self-depreciation.
- ☐ 3
- ☐ 4 Persistent self-accusations, or definite but still rational ideas of guilt, or sin. Increasingly pessimistic about the future.
- ☐ 5
- ☐ 6 Delusions of ruin, remorse, or unredeemable sin. Self-accusations which are absurd and unshakable.

10. **SUICIDAL THOUGHTS**
Representing the feeling that life is not worth living, that a natural death would be welcome, suicidal thoughts, and preparations for suicide. Suicidal attempts should not in themselves influence the rating.

- ☐ 0 Enjoys life or takes it as it comes.
- ☐ 1
- ☐ 2 Weary of life. Only fleeting suicidal thoughts.
- ☐ 3
- ☐ 4 Probably better off dead. Suicidal thoughts are common, and suicide is considered as a possible solution, but without specific plans or intention.
- ☐ 5
- ☐ 6 Explicit plans for suicide when there is an opportunity. Active preparations for suicide.

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B1Y-MC-HCJE

CHILDREN'S DEPRESSION INDEX (CDI)

NOTE: Only complete if patient was 8 to 12 years old at Visit 1. If patient was not 8 to 12 years old, check the Information Not Obtained box.

INFORMATION NOT OBTAINED ☐

This lists the feelings and ideas in groups. From each group of three sentences, pick one sentence that describes you **best** for the past two weeks. After you pick a sentence from the first group, go on to the next group. There is no right answer or wrong answer. Just pick the sentence that best describes the way you have been recently. Put an "X" in the box next to your answer.
Remember: pick out the sentences that describe you best **in the past two weeks**.

Item 1

- ☐ 0 I am sad once in a while.
- ☐ 1 I am sad many times.
- ☐ 2 I am sad all the time.

Item 2

- ☐ 2 Nothing will ever work out for me.
- ☐ 1 I am not sure if things will work out for me.
- ☐ 0 Things will work out for me O.K.

Item 3

- ☐ 0 I do most things O.K.
- ☐ 1 I do many things wrong.
- ☐ 2 I do everything wrong.

Item 4

- ☐ 0 I have fun in many things.
- ☐ 1 I have fun in some things.
- ☐ 2 Nothing is fun at all.

Item 5

- ☐ 2 I am bad all the time.
- ☐ 1 I am bad many times.
- ☐ 0 I am bad once in a while.

Item 6

- ☐ 0 I think about bad things happening to me once in a while.
- ☐ 1 I worry that bad things will happen to me.
- ☐ 2 I am sure that terrible things will happen to me.

Item 7

- ☐ 2 I hate myself.
- ☐ 1 I do not like myself.
- ☐ 0 I like myself.

Item 8

- ☐ 2 All bad things are my fault.
- ☐ 1 Many bad things are my fault.
- ☐ 0 Bad things are not usually my fault.

Item 9

- ☐ 0 I do not think about killing myself.
- ☐ 1 I think about killing myself but I would not do it.
- ☐ 2 I want to kill myself.

Item 10

- ☐ 2 I feel like crying every day.
- ☐ 1 I feel like crying many days.
- ☐ 0 I feel like crying once in a while.

Item 11

- ☐ 2 Things bother me all the time.
- ☐ 1 Things bother me many times.
- ☐ 0 Things bother me once in a while.

Item 12

- ☐ 0 I like being with people.
- ☐ 1 I do not like being with people many times.
- ☐ 2 I do not want to be with people at all.

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CHILDREN'S DEPRESSION INDEX (CDI)

Item 13

- ☐ 2 I cannot make up my mind about things.
- ☐ 1 It is hard to make up my mind about things.
- ☐ 0 I make up my mind about things easily.

Item 14

- ☐ 0 I look O.K.
- ☐ 1 There are some bad things about my looks.
- ☐ 2 I look ugly.

Item 15

- ☐ 2 I have to push myself all the time to do my schoolwork.
- ☐ 1 I have to push myself many times to do my schoolwork.
- ☐ 0 Doing schoolwork is not a big problem.

Item 16

- ☐ 2 I have trouble sleeping every night.
- ☐ 1 I have trouble sleeping many nights.
- ☐ 0 I sleep pretty well.

Item 17

- ☐ 0 I am tired once in a while.
- ☐ 1 I am tired many days.
- ☐ 2 I am tired all the time.

Item 18

- ☐ 2 Most days I do not feel like eating.
- ☐ 1 Many days I do not feel like eating.
- ☐ 0 I eat pretty well.

Item 19

- ☐ 0 I do not worry about aches and pains.
- ☐ 1 I worry about aches and pains many times.
- ☐ 2 I worry about aches and pains all the time.

Item 20

- ☐ 0 I do not feel alone.
- ☐ 1 I feel alone many times.
- ☐ 2 I feel alone all the time.

Item 21

- ☐ 2 I never have fun at school.
- ☐ 1 I have fun at school only once in a while.
- ☐ 0 I have fun at school many times.

Item 22

- ☐ 0 I have plenty of friends.
- ☐ 1 I have some friends but I wish I had more.
- ☐ 2 I do not have any friends.

Item 23

- ☐ 0 My schoolwork is alright.
- ☐ 1 My schoolwork is not as good as before.
- ☐ 2 I do very badly in subjects I used to be good in.

Item 24

- ☐ 2 I can never be as good as other kids.
- ☐ 1 I can be as good as other kids if I want to.
- ☐ 0 I am just as good as other kids.

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CHILDREN'S DEPRESSION INDEX (CDI)

Item 25

- ☐ 2 Nobody really loves me.
- ☐ 1 I am not sure if anybody loves me.
- ☐ 0 I am sure that somebody loves me.

Item 26

- ☐ 0 I usually do what I am told.
- ☐ 1 I do not do what I am told most times.
- ☐ 2 I never do what I am told.

Item 27

- ☐ 0 I get along with people.
- ☐ 1 I get into fights many times.
- ☐ 2 I get into fights all the time.

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BECK DEPRESSION INVENTORY

NOTE: Only complete if patient was 13 to 17 years old at Visit 1. If patient was not 13 to 17 years old, check the Information Not Obtained box.

INFORMATION NOT OBTAINED ☐

This questionnaire consists of 21 groups of statements. After reading each group of statements carefully circle the number (0, 1, 2, 3) next to the one statement in each group which best describes the way you have been feeling **the past week, including today**. If several statements within a group seem to apply equally well, circle each one. Be sure to read all the statements in each group before making your choice.

1

0 I do not feel sad.
1 I feel sad.
2 I am sad all the time and I can't snap out of it.
3 I am so sad or unhappy that I can't stand it.

2

0 I am not particularly discouraged about the future.
1 I feel discouraged about the future.
2 I feel I have nothing to look forward to.
3 I feel that the future is hopeless and that things cannot improve.

3

0 I do not feel like a failure.
1 I feel I have failed more than the average person.
2 As I look back on my life, all I can see is a lot of failures.
3 I feel I am a complete failure as a person.

4

0 I get as much satisfaction out of things as I used to.
1 I don't enjoy things the way I used to.
2 I don't get real satisfaction out of anything anymore.
3 I am dissatisfied or bored with everything.

5

0 I don't feel particularly guilty.
1 I feel guilty a good part of the time.
2 I feel quite guilty most of the time.
3 I feel guilty all of the time.

6

0 I don't feel I am being punished.
1 I feel I may be punished.
2 I expect to be punished.
3 I feel I am being punished.

7

0 I don't feel disappointed in myself.
1 I am disappointed in myself.
2 I am disgusted with myself.
3 I hate myself.

8

0 I don't feel I am any worse than anybody else.
1 I am critical of myself for my weaknesses or mistakes.
2 I blame myself all the time for my faults.
3 I blame myself for everything bad that happens.

9

0 I don't have any thoughts of killing myself.
1 I have thoughts of killing myself, but I would not carry them out.
2 I would like to kill myself.
3 I would kill myself if I had the chance.

10

0 I don't cry any more than usual.
1 I cry more now than I used to.
2 I cry all the time now.
3 I used to be able to cry, but now I can't cry even though I want to.

11

0 I am no more irritated now than I ever am.
1 I get annoyed or irritated more easily than I used to.
2 I feel irritated all the time now.
3 I don't get irritated at all by the things that used to irritate me.

12

0 I have not lost interest in other people.
1 I am less interested in other people than I used to be.
2 I have lost most of my interest in other people.
3 I have lost all of my interest in other people.

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BECK DEPRESSION INVENTORY

13

0 I make decisions about as well as I ever could.
1 I put off making decisions more than I used to.
2 I have greater difficulty in making decisions than before.
3 I can't make decisions at all anymore.

14

0 I don't feel I look any worse than I used to.
1 I am worried that I am looking old or unattractive.
2 I feel that there are permanent changes in my appearance that make me look unattractive.
3 I believe that I look ugly.

15

0 I can work about as well as before.
1 It takes an extra effort to get started at doing something.
2 I have to push myself very hard to do anything.
3 I can't do any work at all.

16

0 I can sleep as well as usual.
1 I don't sleep as well as I used to.
2 I wake up 1-2 hours earlier than usual and find it hard to get back to sleep.
3 I wake up several hours earlier than I used to and cannot get back to sleep.

17

0 I don't get more tired than usual.
1 I get tired more easily than I used to.
2 I get tired from doing almost anything.
3 I am too tired to do anything.

18

0 My appetite is no worse than usual.
1 My appetite is not as good as it used to be.
2 My appetite is much worse now.
3 I have no appetite at all anymore.

19

0 I haven't lost much weight, if any, lately.
1 I have lost more than 5 pounds.
2 I have lost more than 10 pounds.
3 I have lost more than 15 pounds.

19a

I am purposely trying to lose weight by eating less.
1 Yes
2 No

20

0 I am no more worried about my health than usual.
1 I am worried about physical problems such as aches and pains; or upset stomach or constipation.
2 I am very worried about physical problems and it's hard to think of much else.
3 I am so worried about my physical problems that I cannot think about anything else.

21

0 I have not noticed any recent change in my interest in sex.
1 I am less interested in sex than I used to be.
2 I am much less interested in sex now.
3 I have lost interest in sex completely.

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HAMILTON ANXIETY SCALE

INFORMATION NOT OBTAINED ☐

For each of the items below, **CHECK ONE BOX** that best describes the patient.

1. **ANXIOUS MOOD:** Worries, anticipation of the worst, fearful anticipation, irritability

   ☐ 0 Not present
   ☐ 1 Mild
   ☐ 2 Moderate
   ☐ 3 Severe
   ☐ 4 Very severe

2. **TENSION**: Feelings of tension, fatigability, startle response, moved to tears easily, trembling, feeling of restlessness, inability to relax

   ☐ 0 Not present
   ☐ 1 Mild
   ☐ 2 Moderate
   ☐ 3 Severe
   ☐ 4 Very severe

3. **FEARS**: Of dark, of strangers, of being alone, of animals, of traffic, of crowds

   ☐ 0 Not present
   ☐ 1 Mild
   ☐ 2 Moderate
   ☐ 3 Severe
   ☐ 4 Very severe

4. **INSOMNIA**: Difficulty in falling asleep, broken sleep, unsatisfying sleep and fatigue on waking, dreams, nightmares, night terrors

   ☐ 0 Not present
   ☐ 1 Mild
   ☐ 2 Moderate
   ☐ 3 Severe
   ☐ 4 Very severe

5. **INTELLECTUAL (COGNITIVE)**: Difficulty in concentration, poor memory

   ☐ 0 Not present
   ☐ 1 Mild
   ☐ 2 Moderate
   ☐ 3 Severe
   ☐ 4 Very severe

6. **DEPRESSED MOOD**: Loss of interest, lack of pleasure in hobbies, depression, early waking, diurnal swing

   ☐ 0 Not present
   ☐ 1 Mild
   ☐ 2 Moderate
   ☐ 3 Severe
   ☐ 4 Very severe

7. **SOMATIC (MUSCULAR)**: Pains and aches, twitchings, stiffness, myoclonic jerks, grinding of teeth, unsteady voice, increased muscular tone

   ☐ 0 Not present
   ☐ 1 Mild
   ☐ 2 Moderate
   ☐ 3 Severe
   ☐ 4 Very severe

8. **SOMATIC (SENSORY)**: Tinnitus, blurring of vision, hot and cold flushes, feeling of weakness, pricking sensation

   ☐ 0 Not present
   ☐ 1 Mild
   ☐ 2 Moderate
   ☐ 3 Severe
   ☐ 4 Very severe

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HAMILTON ANXIETY SCALE

9. **CARDIOVASCULAR SYMPTOMS:** Tachycardia, palpitations, pain in chest, throbbing of vessels, fainting feelings, missing beat

- ☐ 0 Not present
- ☐ 1 Mild
- ☐ 2 Moderate
- ☐ 3 Severe
- ☐ 4 Very severe

10. **RESPIRATORY SYMPTOMS:** Pressure or constriction in chest, choking feelings, sighing, dyspnea

- ☐ 0 Not present
- ☐ 1 Mild
- ☐ 2 Moderate
- ☐ 3 Severe
- ☐ 4 Very severe

11. **GASTROINTESTINAL SYMPTOMS:** Difficulty in swallowing, wind, abdominal pain, burning sensations, abdominal fullness, nausea, vomiting, borborygmi, looseness of bowels, loss of weight, constipation

- ☐ 0 Not present
- ☐ 1 Mild
- ☐ 2 Moderate
- ☐ 3 Severe
- ☐ 4 Very severe

12. **GENITOURINARY SYMPTOMS:** Frequency of micturition, urgency of micturition, amenorrhea, menorrhagia, development of frigidity, premature ejaculation, loss of libido, impotence

- ☐ 0 Not present
- ☐ 1 Mild
- ☐ 2 Moderate
- ☐ 3 Severe
- ☐ 4 Very severe

13. **AUTONOMIC SYMPTOMS:** Dry mouth, flushing, pallor, tendency to sweat, giddiness, tension headache, raising of hair

- ☐ 0 Not present
- ☐ 1 Mild
- ☐ 2 Moderate
- ☐ 3 Severe
- ☐ 4 Very severe

14. **BEHAVIOR AT INTERVIEW:** Fidgeting, restlessness or pacing, tremor of hands, furrowed brow, strained face, sighing or rapid respiration, facial pallor, swallowing, belching, brisk tendon jerks, dilated pupils, exophthalmos

- ☐ 0 Not present
- ☐ 1 Mild
- ☐ 2 Moderate
- ☐ 3 Severe
- ☐ 4 Very severe

Evaluator's Initials _____ _____ _____
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Clinical Report Form
Fluoxetine Versus Placebo in Childhood/Adolescent Depression
B1Y-MC-HCJE

COMMENTS : VISIT

NO COMMENTS ☐

Comments should address any clinical report form items that require further explanation. Repeating information from the clinical report form is discouraged.

Comment on all clinically significant lab values that are outside a clinically accepted reference range or clinically significant values that differ importantly from previous values.

If the patient is ending participation in the study at this visit, enter only comments that apply to this visit; then complete the Patient Summary and Study Summary Comments pages.

Print legibly and do not use abbreviations or symbols.

The information reported for this visit is accurate and complete.

_____ _____/_____/_____
Signature MM DD YY

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Clinical Report Form
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B1Y-MC-HCJE

PATIENT AND VISIT IDENTIFICATION

Patient initials _____ _____ _____
First Middle Last

Visit date _____/_____/_____
MM DD YY

VITAL SIGNS : BLOOD PRESSURE AND HEART RATE

INFORMATION NOT OBTAINED ☐

Position
SI = Sitting

Position	Blood Pressure (mm Hg) Systolic/Diastolic	Heart Rate (bpm)
SI	/	

VITAL SIGNS: TEMPERATURE

INFORMATION NOT OBTAINED ☐

Temperature ___ ___ ___ . ___

Unit of measure (F) Fahrenheit

Method (E) Ear

REMINDER

On the Pre-existing Conditions and Study Adverse Events pages, record new events that occurred since the previous visit and re-evaluate any on-going conditions or events.

On the Concomitant Medication pages, record new medications the patient has taken since the previous visit, any changes to ongoing medications, and a stop date for any medication the patient is no longer taking.

Initials
Date Verified
Initials
Date Keyed
Date Received at Lilly
Reviewed
Inspected
Date

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B1Y-MC-HCJE

STUDY DRUG : DATES OF MISSED DOSES

NO MISSED DOSES ☐

Record the date for any day on which the patient missed a full or partial dose of study drug.

	Dates of Missed Doses MM	DD	YY
0.			
1.			
2.			
3.			
4.			
5.			
6.			
7.			
8.			
9.			

NOTE: If the patient has missed 3 or more consecutive days of medication, the patient must be discontinued from the study.

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Fluoxetine Versus Placebo in Childhood/Adolescent Depression
B1Y-MC-HCJE

SIDE EFFECTS CHECKLIST

INFORMATION NOT OBTAINED ☐

Since your last visit, have you been bothered with or had any trouble with any of the items listed below? Check the box which best tells how much you were bothered.

	Not at all	Just a little	Pretty much	Very much	Don't know
1. Eating?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
2. Drinking?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
3. Dry mouth and lips?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
4. Wetness in mouth?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
5. Constipation?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
6. Diarrhea?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
7. Stomachaches?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
8. Muscle cramps?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
9. Being sick to your stomach?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
10. Wetting the bed?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
11. Urinating?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
12. Itchy or scratchy skin?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
13. Rashes?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
14. Cold or sniffles?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
15. Headache?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4

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Fluoxetine Versus Placebo in Childhood/Adolescent Depression
B1Y-MC-HCJE

SIDE EFFECTS CHECKLIST

	Not at all	Just a little	Pretty much	Very much	Don't know
16. Dizziness?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
17. Playing sports?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
18. Shakiness?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
19. Pronouncing words?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
20. Doing things with your hands?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
21. Sitting still?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
22. Tiredness?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
23. Feeling sleepy?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
24. Trouble sleeping?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
25. Bad dreams?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
26. Getting along with parents?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
27. Getting along with kids?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
28. Crying?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
29. Getting mad?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
30. Not being happy?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
31. Being sad?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
32. Paying attention?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4

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B1Y-MC-HCJE

CHILDRENS DEPRESSION RATING SCALE - REVISED

INFORMATION NOT OBTAINED ☐

CHECK THE NUMERIC CODE which best describes the patient.

1. **SCHOOLWORK**:

☐ 1 Performance consistent with ability
☐ 2
☐ 3 Decrease in school performance
☐ 4
☐ 5 Major interference in most subjects
☐ 6
☐ 7 No motivation to perform

2. **CAPACITY TO HAVE FUN**

☐ 1 Interest and activities realistically appropriate for age, personality, and social environment. Shows no appreciable change with present illness.
☐ 2
☐ 3 Describes some activities realistically available several times a week but not on a daily basis. Shows interest but not enthusiasm.
☐ 4
☐ 5 Is easily bored. Complains of "nothing to do." Participates in structured activities with a "going through the motions" attitude. May express interest primarily in activities that are (realistically) unavailable on a daily or weekly basis.
☐ 6
☐ 7 Has no initiative to become involved in any activities. Primarily passive. Watches others play or watches TV but shows little interest. Requires coaxing and/or pushing to get involved in activity. Shows no enthusiasm or real interest. Has difficulty naming activities.

3. **SOCIAL WITHDRAWAL**

☐ 1 Enjoys friendships with peers at school and home
☐ 2
☐ 3 May not actively seek out friendships but waits for others to initiate a relationship or may occasionally reject opportunities to play without a describable alternative
☐ 4
☐ 5 Frequently avoids or refuses opportunities for desirable interaction with others and/or sets up situations where rejection is inevitable.
☐ 6
☐ 7 Does not currently relate to other children. States he or she has "no friends" or actively rejects new or former friends.

4. **SLEEP**

☐ 1 No (or occasional) difficulty. (Goes to sleep within 1/2 hour or less.)
☐ 2
☐ 3 Frequently has mild difficulty with sleep
☐ 4
☐ 5 Moderate difficulty with sleep nearly every night.

5. **APPETITE OR EATING PATTERNS**

☐ 1 No problems or change in eating pattern
☐ 2
☐ 3 Mild change from usual eating habits within onset of current behavioral problem
☐ 4
☐ 5 Is not hungry most of the time or has excessive food intake since onset of current behavioral problems or marked increase in appetite

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Fluoxetine Versus Placebo in Childhood/Adolescent Depression
B1Y-MC-HCJE

CHILDRENS DEPRESSION RATING SCALE - REVISED

CHECK THE NUMERIC CODE which best describes the patient.

6. **EXCESSIVE FATIGUE**

- ☐ 1 No unusual complaints of "feeling tired" during the day
- ☐ 2
- ☐ 3 Complaints of fatigue which seem somewhat excessive and not related to boredom
- ☐ 4
- ☐ 5 Daily complaints of feeling tired
- ☐ 6
- ☐ 7 Complains of feeling tired most of the day. May voluntarily take long naps without feeling refreshed. Interferes with play activities.

7. **PHYSICAL COMPLAINTS**:

- ☐ 1 Occasional complaints
- ☐ 2
- ☐ 3 Complaints appear mildly excessive
- ☐ 4
- ☐ 5 Complains daily. Some interference with the ability of the child to function
- ☐ 6
- ☐ 7 Preoccupied with aches and pains; interferes with play activities several times a week

8. **IRRITABILITY**

- ☐ 1 Rare
- ☐ 2 Occasional
- ☐ 3 Several times a week for short periods
- ☐ 4
- ☐ 5 Several times a week for longer periods
- ☐ 6
- ☐ 7 Constant

9. **GUILT**

- ☐ 1 Does not express any undue feeling of guilt. Appears appropriate to precipitating event.
- ☐ 2
- ☐ 3 Exaggerates guilt and/or shame out of proportion to the event described.
- ☐ 4
- ☐ 5 Feels guilty over things not under his or her control. Guilt is definitely pathological.
- ☐ 6
- ☐ 7 Severe delusions of guilt

10. **SELF-ESTEEM**

- ☐ 1 Describes self in primarily positive terms
- ☐ 2
- ☐ 3 Describes self with one important area where the child feels deficit
- ☐ 4
- ☐ 5 Describes self in preponderance of negative terms or gives bland answers to questions
- ☐ 6
- ☐ 7 Refers to self in derogatory terms. Reports that other children refer to him/her frequently by using derogatory nicknames and child puts self down

11. **DEPRESSED FEELINGS**

- ☐ 1 Occasional feelings of unhappiness which quickly disappear
- ☐ 2
- ☐ 3 Describes sustained periods of unhappiness which appear excessive for events described
- ☐ 4
- ☐ 5 Feels unhappy most of the time without a major precipitating cause
- ☐ 6
- ☐ 7 Feels unhappy all of the time. Accompanied by psychic pain (e.g., "I can't stand it").

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CHILDRENS DEPRESSION RATING SCALE - REVISED

CHECK THE NUMERIC CODE which best describes the patient.

12. **MORBID IDEATION**

- ☐ 1 None
- ☐ 2
- ☐ 3 Has some morbid thought, all of which relate to a reality event but seem excessive.
- ☐ 4
- ☐ 5 Preoccupied with morbid thoughts several times a week. Morbid thoughts extend beyond external reality
- ☐ 6
- ☐ 7 Preoccupied with death themes or morbid thoughts that are elaborate, extensive or bizarre on a daily basis

13. **SUICIDAL IDEATION**

- ☐ 1 Understands the word "suicide" but does not apply term to self
- ☐ 2 Sharp denial of suicidal thoughts
- ☐ 3 Has thoughts about suicide, usually when angry.
- ☐ 4
- ☐ 5 Has recurrent thoughts of suicide
- ☐ 6
- ☐ 7 Has made suicide attempt within the last month or is actively suicidal

14. **WEEPING**:

- ☐ 1 Normal for age.
- ☐ 2 Suggestive statements that child cries, or feels like crying, more frequently than peers.
- ☐ 3 Child cries slightly more than peers.
- ☐ 4
- ☐ 5 Cries or feels like crying frequently (several times a week). Admits to crying without knowing reason why.
- ☐ 6
- ☐ 7 Cries nearly every day.

15. **DEPRESSED AFFECT:**

- ☐ 1 Definitely not depressed. Facial expression and voice animated during interview.
- ☐ 2 Mild suppression of affect. Some loss of spontaneity.
- ☐ 3 Overall loss of spontaneity. Looks distinctly unhappy during parts of the interview. May still be able to smile when discussing non-threatening areas.
- ☐ 4
- ☐ 5 Moderate restriction of affect throughout most of interview. Has longer and frequent periods of looking distinctly unhappy.
- ☐ 6
- ☐ 7 Severe. Looks sad, withdrawn. Minimal verbal interaction throughout interview. Cries or may appear tearful.

16. **TEMPO OF SPEECH:**

- ☐ 1 Normal
- ☐ 2 Slow
- ☐ 3 Slow: delays interview.
- ☐ 4
- ☐ 5 Severe. Low; marked interference with interview.

17. **HYPOACTIVITY:**

- ☐ 1 None
- ☐ 2
- ☐ 3 Mild. Some body movements.
- ☐ 4
- ☐ 5 Moderate. Definite motor retardation.
- ☐ 6
- ☐ 7 Severe. Motionless throughout interview.

(DNDE)

Total of 1 - 17 _____

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CLINICAL GLOBAL IMPRESSION: EFFICACY INDEX

Using the worksheet below, enter the 2-digit efficacy index rating.

1. Efficacy index rating ___ ___

(DNDE)

EFFICACY INDEX WORKSHEET

Rate this item on the basis of DRUG EFFECT ONLY.

Select the terms that best describe the degrees of therapeutic effect and side effects and record the number from the box where the two items intersect in the blanks above.

THERAPEUTIC EFFECT	SIDE EFFECTS			
	None	Do not significantly interfere with patient's functioning	Significantly interferes with patient's functioning	Outweighs therapeutic effect
MARKED - Vast improvement. Complete or nearly complete remission of all symptoms.	**01**	**02**	**03**	**04**
MODERATE - Decided improvement. Partial remission of symptoms.	**05**	**06**	**07**	**08**
MINIMAL - Slight improvement which doesn't alter status of care of patient.	**09**	**10**	**11**	**12**
UNCHANGED OR WORSE	**13**	**14**	**15**	**16**
Not Assessed = **98**				

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Clinical Report Form
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B1Y-MC-HCJE

CLINICAL GLOBAL IMPRESSION: SEVERITY

INFORMATION NOT OBTAINED ☐

Considering your total clinical experience with this particular population, how mentally ill is the patient at this time?

- ☐ 1 Normal, not at all ill
- ☐ 2 Borderline ill
- ☐ 3 Mildly ill
- ☐ 4 Moderately ill
- ☐ 5 Markedly ill
- ☐ 6 Severely ill
- ☐ 7 Among the most extremely ill patients

Evaluator's initials _____ _____ _____
First Middle Last

CLINICAL GLOBAL IMPRESSION: IMPROVEMENT

INFORMATION NOT OBTAINED ☐

Rate total improvement, whether or not in your judgement it is due entirely to drug treatment. Compared to the patient's condition at Visit 1, how much has he/she changed?

- ☐ 1 Very much improved
- ☐ 2 Much improved
- ☐ 3 Minimally improved
- ☐ 4 No change
- ☐ 5 Minimally worse
- ☐ 6 Much worse
- ☐ 7 Very much worse

Evaluator's initials _____ _____ _____
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MONTGOMERY - ASBERG DEPRESSION RATING SCALE (MADRS)

INFORMATION NOT OBTAINED ☐

The rating should be based on a clinical interview moving from broadly phrased questions about symptoms to more detailed ones which allow a precise rating of severity. The rater must decide whether the rating lies on the defined scale steps (0, 2, 4, 6) or between them (1, 3, 5).

Check the box (number) that best characterizes the patient at this time

1. **APPARENT SADNESS**
   Representing despondency, gloom, and despair (more than just ordinary transient low spirits), reflected in speech, facial expression, and posture. Rate by depth and inability to brighten up.

   ☐ 0 No sadness.
   ☐ 1
   ☐ 2 Looks dispirited but does brighten up without difficulty.
   ☐ 3
   ☐ 4 Appears sad and unhappy most of the time.
   ☐ 5
   ☐ 6 Looks miserable all the time. Extremely despondent.

2. **REPORTED SADNESS**
   Represented by reports of depressed mood, regardless of whether it is reflected in appearance or not. Includes low spirits, despondency, or the feeling of being beyond help and without hope. Rate according to intensity, duration, and the extent to which the mood is reported to be influenced by events.

   ☐ 0 Occasional sadness in keeping with the circumstances.
   ☐ 1
   ☐ 2 Sad or low but brightens up without difficulty.
   ☐ 3
   ☐ 4 Pervasive feelings of sadness or gloominess. The mood is still influenced by external circumstances.
   ☐ 5
   ☐ 6 Continuous unvarying sadness, misery or despondency.

3. **INNER TENSION**
   Representing feelings of ill-defined discomfort, edginess, inner turmoil, mental tension mounting to either panic, dread, or anguish. Rate according to intensity, frequency, duration, and the extent of reassurance called for.

   ☐ 0 Placid. Only fleeting inner tension.
   ☐ 1
   ☐ 2 Occasional feelings of edginess and ill-defined discomfort.
   ☐ 3
   ☐ 4 Continuous feelings of inner tension or intermittent panic which the patient can only master with some difficulty.
   ☐ 5
   ☐ 6 Unrelenting dread or anguish. Overwhelming panic.

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MONTGOMERY - ASBERG DEPRESSION RATING SCALE (MADRS)

4. **REDUCED SLEEP**
Representing the experience of reduced duration or depth of sleep compared to the subject's own pattern when well.

- ☐ 0 Sleeps as usual.
- ☐ 1
- ☐ 2 Slight difficulty dropping off to sleep or slightly reduced, light or fitful sleep.
- ☐ 3
- ☐ 4 Sleep reduced or broken by at least two hours.
- ☐ 5
- ☐ 6 Less than two or three hours sleep.

5. **REDUCED APPETITE**
Representing the feeling of a loss of appetite compared with when well. Rate by loss of desire for food or the need to force oneself to eat.

- ☐ 0 Normal or increased appetite
- ☐ 1
- ☐ 2 Slightly reduced appetite.
- ☐ 3
- ☐ 4 No appetite. Food is tasteless.
- ☐ 5
- ☐ 6 Needs persuasion to eat at all.

6. **CONCENTRATION DIFFICULTIES**
Representing difficulties in collecting one's thoughts mounting to incapacitating lack of concentration.

- ☐ 0 No difficulties in concentrating.
- ☐ 1
- ☐ 2 Occasional difficulties in collecting one's thoughts.
- ☐ 3
- ☐ 4 Difficulties in concentrating and sustaining thought which reduces ability to read or hold a conversation.
- ☐ 5
- ☐ 6 Unable to read or converse without great difficulty.

7. **LASSITUDE**
Representing a difficulty getting started or slowness initiating and performing everyday activities.

- ☐ 0 Hardly any difficulty in getting started. No sluggishness.
- ☐ 1
- ☐ 2 Difficulties in starting activities
- ☐ 3
- ☐ 4 Difficulties in starting simple routine activities which are carried out with effort.
- ☐ 5
- ☐ 6 Complete lassitude. Unable to do anything without help.

8. **INABILITY TO FEEL**
Representing the subjective experience of reduced interest in the surroundings, or activities that normally give pleasure. The ability to react with adequate emotion to circumstances or people is reduced.

- ☐ 0 Normal interest in the surroundings and other people.
- ☐ 1
- ☐ 2 Reduced ability to enjoy usual interests.
- ☐ 3
- ☐ 4 Loss of interest in the surroundings. Loss of feelings for friends and acquaintances.
- ☐ 5
- ☐ 6 The experience of being emotionally paralyzed, inability to feel anger, grief, or pleasure and a complete or even painful failure to feel for close relatives and friends.

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B1Y-MC-HCJE

MONTGOMERY - ASBERG DEPRESSION RATING SCALE (MADRS)

9. **PESSIMISTIC THOUGHTS**
Representing thoughts of guilt, inferiority, self-reproach, sinfulness, remorse, and ruin

- ☐ 0 No pessimistic thoughts.
- ☐ 1
- ☐ 2 Fluctuating ideas of failure, self-reproach, or self-depreciation.
- ☐ 3
- ☐ 4 Persistent self-accusations, or definite but still rational ideas of guilt, or sin. Increasingly pessimistic about the future.
- ☐ 5
- ☐ 6 Delusions of ruin, remorse, or unredeemable sin. Self-accusations which are absurd and unshakable.

10. **SUICIDAL THOUGHTS**
Representing the feeling that life is not worth living, that a natural death would be welcome, suicidal thoughts, and preparations for suicide. Suicidal attempts should not in themselves influence the rating.

- ☐ 0 Enjoys life or takes it as it comes.
- ☐ 1
- ☐ 2 Weary of life. Only fleeting suicidal thoughts.
- ☐ 3
- ☐ 4 Probably better off dead. Suicidal thoughts are common, and suicide is considered as a possible solution, but without specific plans or intention.
- ☐ 5
- ☐ 6 Explicit plans for suicide when there is an opportunity. Active preparations for suicide.

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B1Y-MC-HCJE

COMMENTS : VISIT

NO COMMENTS ☐

Comments should address any clinical report form items that require further explanation. Repeating information from the clinical report form is discouraged.

Comment on all clinically significant lab values that are outside a clinically accepted reference range or clinically significant values that differ importantly from previous values.

If the patient is ending participation in the study at this visit, enter only comments that apply to this visit; then complete the Patient Summary and Study Summary Comments pages.

Print legibly and do not use abbreviations or symbols.

The information reported for this visit is accurate and complete.

_____ _____/_____/_____
Signature MM DD YY

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Clinical Report Form
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B1Y-MC-HCJE

PATIENT AND VISIT IDENTIFICATION

Patient initials _____ _____ _____
First Middle Last

Visit date _____/_____/_____
MM DD YY

VITAL SIGNS : BLOOD PRESSURE AND HEART RATE

INFORMATION NOT OBTAINED ☐

Position
SI = Sitting

Position	Blood Pressure (mm Hg) Systolic/Diastolic	Heart Rate (bpm)
SI	/	

VITAL SIGNS: TEMPERATURE

INFORMATION NOT OBTAINED ☐

Temperature ___ ___ ___ . ___

Unit of measure (F) Fahrenheit

Method (E) Ear

REMINDER

On the Pre-existing Conditions and Study Adverse Events pages, record new events that occurred since the previous visit and re-evaluate any on-going conditions or events.

On the Concomitant Medication pages, record new medications the patient has taken since the previous visit, any changes to ongoing medications, and a stop date for any medication the patient is no longer taking.

Initials
Date Verified
Initials
Date Keyed
Date Received at Lilly
Reviewed
Inspected
Date

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B1Y-MC-HCJE

STUDY DRUG : DATES OF MISSED DOSES

NO MISSED DOSES ☐

Record the date for any day on which the patient missed a full or partial dose of study drug.

	Dates of Missed Doses MM	DD	YY
0.			
1.			
2.			
3.			
4.			
5.			
6.			
7.			
8.			
9.			

NOTE: If the patient has missed 3 or more consecutive days of medication, the patient must be discontinued from the study.

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Clinical Report Form
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B1Y-MC-HCJE

SIDE EFFECTS CHECKLIST

INFORMATION NOT OBTAINED ☐

Since your last visit, have you been bothered with or had any trouble with any of the items listed below? Check the box which best tells how much you were bothered.

	Not at all	Just a little	Pretty much	Very much	Don't know
1. Eating?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
2. Drinking?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
3. Dry mouth and lips?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
4. Wetness in mouth?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
5. Constipation?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
6. Diarrhea?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
7. Stomachaches?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
8. Muscle cramps?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
9. Being sick to your stomach?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
10. Wetting the bed?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
11. Urinating?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
12. Itchy or scratchy skin?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
13. Rashes?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
14. Cold or sniffles?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
15. Headache?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4

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Clinical Report Form
Fluoxetine Versus Placebo in Childhood/Adolescent Depression
B1Y-MC-HCJE

SIDE EFFECTS CHECKLIST

	Not at all	Just a little	Pretty much	Very much	Don't know
16. Dizziness?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
17. Playing sports?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
18. Shakiness?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
19. Pronouncing words?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
20. Doing things with your hands?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
21. Sitting still?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
22. Tiredness?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
23. Feeling sleepy?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
24. Trouble sleeping?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
25. Bad dreams?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
26. Getting along with parents?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
27. Getting along with kids?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
28. Crying?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
29. Getting mad?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
30. Not being happy?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
31. Being sad?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
32. Paying attention?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4

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CHILDRENS DEPRESSION RATING SCALE - REVISED

INFORMATION NOT OBTAINED ☐

CHECK THE NUMERIC CODE which best describes the patient.

1. **SCHOOLWORK**:

☐ 1 Performance consistent with ability
☐ 2
☐ 3 Decrease in school performance
☐ 4
☐ 5 Major interference in most subjects
☐ 6
☐ 7 No motivation to perform

2. **CAPACITY TO HAVE FUN**

☐ 1 Interest and activities realistically appropriate for age, personality, and social environment. Shows no appreciable change with present illness.
☐ 2
☐ 3 Describes some activities realistically available several times a week but not on a daily basis. Shows interest but not enthusiasm.
☐ 4
☐ 5 Is easily bored. Complains of "nothing to do." Participates in structured activities with a "going through the motions" attitude. May express interest primarily in activities that are (realistically) unavailable on a daily or weekly basis.
☐ 6
☐ 7 Has no initiative to become involved in any activities. Primarily passive. Watches others play or watches TV but shows little interest. Requires coaxing and/or pushing to get involved in activity. Shows no enthusiasm or real interest. Has difficulty naming activities.

3. **SOCIAL WITHDRAWAL**

☐ 1 Enjoys friendships with peers at school and home
☐ 2
☐ 3 May not actively seek out friendships but waits for others to initiate a relationship or may occasionally reject opportunities to play without a describable alternative
☐ 4
☐ 5 Frequently avoids or refuses opportunities for desirable interaction with others and/or sets up situations where rejection is inevitable.
☐ 6
☐ 7 Does not currently relate to other children. States he or she has "no friends" or actively rejects new or former friends.

4. **SLEEP**

☐ 1 No (or occasional) difficulty. (Goes to sleep within 1/2 hour or less.)
☐ 2
☐ 3 Frequently has mild difficulty with sleep
☐ 4
☐ 5 Moderate difficulty with sleep nearly every night.

5. **APPETITE OR EATING PATTERNS**

☐ 1 No problems or change in eating pattern
☐ 2
☐ 3 Mild change from usual eating habits within onset of current behavioral problem
☐ 4
☐ 5 Is not hungry most of the time or has excessive food intake since onset of current behavioral problems or marked increase in appetite

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B1Y-MC-HCJE

CHILDRENS DEPRESSION RATING SCALE - REVISED

CHECK THE NUMERIC CODE which best describes the patient.

6. **EXCESSIVE FATIGUE**

- ☐ 1 No unusual complaints of "feeling tired" during the day
- ☐ 2
- ☐ 3 Complaints of fatigue which seem somewhat excessive and not related to boredom
- ☐ 4
- ☐ 5 Daily complaints of feeling tired
- ☐ 6
- ☐ 7 Complains of feeling tired most of the day. May voluntarily take long naps without feeling refreshed. Interferes with play activities.

7. **PHYSICAL COMPLAINTS**:

- ☐ 1 Occasional complaints
- ☐ 2
- ☐ 3 Complaints appear mildly excessive
- ☐ 4
- ☐ 5 Complains daily. Some interference with the ability of the child to function
- ☐ 6
- ☐ 7 Preoccupied with aches and pains; interferes with play activities several times a week

8. **IRRITABILITY**

- ☐ 1 Rare
- ☐ 2 Occasional
- ☐ 3 Several times a week for short periods
- ☐ 4
- ☐ 5 Several times a week for longer periods
- ☐ 6
- ☐ 7 Constant

9. **GUILT**

- ☐ 1 Does not express any undue feeling of guilt. Appears appropriate to precipitating event.
- ☐ 2
- ☐ 3 Exaggerates guilt and/or shame out of proportion to the event described.
- ☐ 4
- ☐ 5 Feels guilty over things not under his or her control. Guilt is definitely pathological.
- ☐ 6
- ☐ 7 Severe delusions of guilt

10. **SELF-ESTEEM**

- ☐ 1 Describes self in primarily positive terms
- ☐ 2
- ☐ 3 Describes self with one important area where the child feels deficit
- ☐ 4
- ☐ 5 Describes self in preponderance of negative terms or gives bland answers to questions
- ☐ 6
- ☐ 7 Refers to self in derogatory terms. Reports that other children refer to him/her frequently by using derogatory nicknames and child puts self down

11. **DEPRESSED FEELINGS**

- ☐ 1 Occasional feelings of unhappiness which quickly disappear
- ☐ 2
- ☐ 3 Describes sustained periods of unhappiness which appear excessive for events described
- ☐ 4
- ☐ 5 Feels unhappy most of the time without a major precipitating cause
- ☐ 6
- ☐ 7 Feels unhappy all of the time. Accompanied by psychic pain (e.g., "I can't stand it").

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CHILDRENS DEPRESSION RATING SCALE - REVISED

CHECK THE NUMERIC CODE which best describes the patient.

12. **MORBID IDEATION**

- ☐ 1 None
- ☐ 2
- ☐ 3 Has some morbid thought, all of which relate to a reality event but seem excessive.
- ☐ 4
- ☐ 5 Preoccupied with morbid thoughts several times a week. Morbid thoughts extend beyond external reality
- ☐ 6
- ☐ 7 Preoccupied with death themes or morbid thoughts that are elaborate, extensive or bizarre on a daily basis

13. **SUICIDAL IDEATION**

- ☐ 1 Understands the word "suicide" but does not apply term to self
- ☐ 2 Sharp denial of suicidal thoughts
- ☐ 3 Has thoughts about suicide, usually when angry.
- ☐ 4
- ☐ 5 Has recurrent thoughts of suicide
- ☐ 6
- ☐ 7 Has made suicide attempt within the last month or is actively suicidal

14. **WEEPING**:

- ☐ 1 Normal for age.
- ☐ 2 Suggestive statements that child cries, or feels like crying, more frequently than peers.
- ☐ 3 Child cries slightly more than peers.
- ☐ 4
- ☐ 5 Cries or feels like crying frequently (several times a week). Admits to crying without knowing reason why.
- ☐ 6
- ☐ 7 Cries nearly every day.

15. **DEPRESSED AFFECT:**

- ☐ 1 Definitely not depressed. Facial expression and voice animated during interview.
- ☐ 2 Mild suppression of affect. Some loss of spontaneity.
- ☐ 3 Overall loss of spontaneity. Looks distinctly unhappy during parts of the interview. May still be able to smile when discussing non-threatening areas.
- ☐ 4
- ☐ 5 Moderate restriction of affect throughout most of interview. Has longer and frequent periods of looking distinctly unhappy.
- ☐ 6
- ☐ 7 Severe. Looks sad, withdrawn. Minimal verbal interaction throughout interview. Cries or may appear tearful.

16. **TEMPO OF SPEECH:**

- ☐ 1 Normal
- ☐ 2 Slow
- ☐ 3 Slow: delays interview.
- ☐ 4
- ☐ 5 Severe. Low; marked interference with interview.

17. **HYPOACTIVITY:**

- ☐ 1 None
- ☐ 2
- ☐ 3 Mild. Some body movements.
- ☐ 4
- ☐ 5 Moderate. Definite motor retardation.
- ☐ 6
- ☐ 7 Severe. Motionless throughout interview.

(DNDE)

Total of 1 - 17 _____

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CLINICAL GLOBAL IMPRESSION: EFFICACY INDEX

Using the worksheet below, enter the 2-digit efficacy index rating.

1. Efficacy index rating ___ ___

(DNDE)

EFFICACY INDEX WORKSHEET

Rate this item on the basis of DRUG EFFECT ONLY.

Select the terms that best describe the degrees of therapeutic effect and side effects and record the number from the box where the two items intersect in the blanks above.

THERAPEUTIC EFFECT	SIDE EFFECTS			
	None	Do not significantly interfere with patient's functioning	Significantly interferes with patient's functioning	Outweighs therapeutic effect
MARKED - Vast improvement. Complete or nearly complete remission of all symptoms.	**01**	**02**	**03**	**04**
MODERATE - Decided improvement. Partial remission of symptoms.	**05**	**06**	**07**	**08**
MINIMAL - Slight improvement which doesn't alter status of care of patient.	**09**	**10**	**11**	**12**
UNCHANGED OR WORSE	**13**	**14**	**15**	**16**
Not Assessed = **98**				

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CLINICAL GLOBAL IMPRESSION: SEVERITY

INFORMATION NOT OBTAINED ☐

Considering your total clinical experience with this particular population, how mentally ill is the patient at this time?

- ☐ 1 Normal, not at all ill
- ☐ 2 Borderline ill
- ☐ 3 Mildly ill
- ☐ 4 Moderately ill
- ☐ 5 Markedly ill
- ☐ 6 Severely ill
- ☐ 7 Among the most extremely ill patients

Evaluator's initials _____ _____ _____
First Middle Last

CLINICAL GLOBAL IMPRESSION: IMPROVEMENT

INFORMATION NOT OBTAINED ☐

Rate total improvement, whether or not in your judgement it is due entirely to drug treatment. Compared to the patient's condition at Visit 1, how much has he/she changed?

- ☐ 1 Very much improved
- ☐ 2 Much improved
- ☐ 3 Minimally improved
- ☐ 4 No change
- ☐ 5 Minimally worse
- ☐ 6 Much worse
- ☐ 7 Very much worse

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First Middle Last

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MONTGOMERY - ASBERG DEPRESSION RATING SCALE (MADRS)

INFORMATION NOT OBTAINED ☐

The rating should be based on a clinical interview moving from broadly phrased questions about symptoms to more detailed ones which allow a precise rating of severity. The rater must decide whether the rating lies on the defined scale steps (0, 2, 4, 6) or between them (1, 3, 5).

Check the box (number) that best characterizes the patient at this time

1. **APPARENT SADNESS**
   Representing despondency, gloom, and despair (more than just ordinary transient low spirits), reflected in speech, facial expression, and posture. Rate by depth and inability to brighten up.

   ☐ 0 No sadness.
   ☐ 1
   ☐ 2 Looks dispirited but does brighten up without difficulty.
   ☐ 3
   ☐ 4 Appears sad and unhappy most of the time.
   ☐ 5
   ☐ 6 Looks miserable all the time. Extremely despondent.

2. **REPORTED SADNESS**
   Represented by reports of depressed mood, regardless of whether it is reflected in appearance or not. Includes low spirits, despondency, or the feeling of being beyond help and without hope. Rate according to intensity, duration, and the extent to which the mood is reported to be influenced by events.

   ☐ 0 Occasional sadness in keeping with the circumstances.
   ☐ 1
   ☐ 2 Sad or low but brightens up without difficulty.
   ☐ 3
   ☐ 4 Pervasive feelings of sadness or gloominess. The mood is still influenced by external circumstances.
   ☐ 5
   ☐ 6 Continuous unvarying sadness, misery or despondency.

3. **INNER TENSION**
   Representing feelings of ill-defined discomfort, edginess, inner turmoil, mental tension mounting to either panic, dread, or anguish. Rate according to intensity, frequency, duration, and the extent of reassurance called for.

   ☐ 0 Placid. Only fleeting inner tension.
   ☐ 1
   ☐ 2 Occasional feelings of edginess and ill-defined discomfort.
   ☐ 3
   ☐ 4 Continuous feelings of inner tension or intermittent panic which the patient can only master with some difficulty.
   ☐ 5
   ☐ 6 Unrelenting dread or anguish. Overwhelming panic.

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MONTGOMERY - ASBERG DEPRESSION RATING SCALE (MADRS)

4. **REDUCED SLEEP**
Representing the experience of reduced duration or depth of sleep compared to the subject's own pattern when well.

- ☐ 0 Sleeps as usual.
- ☐ 1
- ☐ 2 Slight difficulty dropping off to sleep or slightly reduced, light or fitful sleep.
- ☐ 3
- ☐ 4 Sleep reduced or broken by at least two hours.
- ☐ 5
- ☐ 6 Less than two or three hours sleep.

5. **REDUCED APPETITE**
Representing the feeling of a loss of appetite compared with when well. Rate by loss of desire for food or the need to force oneself to eat.

- ☐ 0 Normal or increased appetite
- ☐ 1
- ☐ 2 Slightly reduced appetite.
- ☐ 3
- ☐ 4 No appetite. Food is tasteless.
- ☐ 5
- ☐ 6 Needs persuasion to eat at all.

6. **CONCENTRATION DIFFICULTIES**
Representing difficulties in collecting one's thoughts mounting to incapacitating lack of concentration.

- ☐ 0 No difficulties in concentrating.
- ☐ 1
- ☐ 2 Occasional difficulties in collecting one's thoughts.
- ☐ 3
- ☐ 4 Difficulties in concentrating and sustaining thought which reduces ability to read or hold a conversation.
- ☐ 5
- ☐ 6 Unable to read or converse without great difficulty.

7. **LASSITUDE**
Representing a difficulty getting started or slowness initiating and performing everyday activities.

- ☐ 0 Hardly any difficulty in getting started. No sluggishness.
- ☐ 1
- ☐ 2 Difficulties in starting activities
- ☐ 3
- ☐ 4 Difficulties in starting simple routine activities which are carried out with effort.
- ☐ 5
- ☐ 6 Complete lassitude. Unable to do anything without help.

8. **INABILITY TO FEEL**
Representing the subjective experience of reduced interest in the surroundings, or activities that normally give pleasure. The ability to react with adequate emotion to circumstances or people is reduced.

- ☐ 0 Normal interest in the surroundings and other people.
- ☐ 1
- ☐ 2 Reduced ability to enjoy usual interests.
- ☐ 3
- ☐ 4 Loss of interest in the surroundings. Loss of feelings for friends and acquaintances.
- ☐ 5
- ☐ 6 The experience of being emotionally paralyzed, inability to feel anger, grief, or pleasure and a complete or even painful failure to feel for close relatives and friends.

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MONTGOMERY - ASBERG DEPRESSION RATING SCALE (MADRS)

9. **PESSIMISTIC THOUGHTS**
Representing thoughts of guilt, inferiority, self-reproach, sinfulness, remorse, and ruin

- ☐ 0 No pessimistic thoughts.
- ☐ 1
- ☐ 2 Fluctuating ideas of failure, self-reproach, or self-depreciation.
- ☐ 3
- ☐ 4 Persistent self-accusations, or definite but still rational ideas of guilt, or sin. Increasingly pessimistic about the future.
- ☐ 5
- ☐ 6 Delusions of ruin, remorse, or unredeemable sin. Self-accusations which are absurd and unshakable.

10. **SUICIDAL THOUGHTS**
Representing the feeling that life is not worth living, that a natural death would be welcome, suicidal thoughts, and preparations for suicide. Suicidal attempts should not in themselves influence the rating.

- ☐ 0 Enjoys life or takes it as it comes.
- ☐ 1
- ☐ 2 Weary of life. Only fleeting suicidal thoughts.
- ☐ 3
- ☐ 4 Probably better off dead. Suicidal thoughts are common, and suicide is considered as a possible solution, but without specific plans or intention.
- ☐ 5
- ☐ 6 Explicit plans for suicide when there is an opportunity. Active preparations for suicide.

Evaluator's initials _____ _____ _____
First Middle Last

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Fluoxetine Versus Placebo in Childhood/Adolescent Depression
B1Y-MC-HCJE

COMMENTS : VISIT

NO COMMENTS ☐

Comments should address any clinical report form items that require further explanation. Repeating information from the clinical report form is discouraged.

Comment on all clinically significant lab values that are outside a clinically accepted reference range or clinically significant values that differ importantly from previous values.

If the patient is ending participation in the study at this visit, enter only comments that apply to this visit; then complete the Patient Summary and Study Summary Comments pages.

Print legibly and do not use abbreviations or symbols.

The information reported for this visit is accurate and complete.

_____ _____/_____/_____
Signature MM DD YY

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Clinical Report Form
Fluoxetine Versus Placebo in Childhood/Adolescent Depression
B1Y-MC-HCJE

PATIENT AND VISIT IDENTIFICATION

Patient initials _____ _____ _____
First Middle Last

Visit date _____/_____/_____
MM DD YY

VITAL SIGNS : BLOOD PRESSURE AND HEART RATE

INFORMATION NOT OBTAINED ☐

Position
SI = Sitting

Position	Blood Pressure (mm Hg) Systolic/Diastolic	Heart Rate (bpm)
SI	/	

VITAL SIGNS: TEMPERATURE

INFORMATION NOT OBTAINED ☐

Temperature ___ ___ ___ . ___

Unit of measure (F) Fahrenheit

Method (E) Ear

REMINDER

On the Pre-existing Conditions and Study Adverse Events pages, record new events that occurred since the previous visit and re-evaluate any on-going conditions or events.

On the Concomitant Medication pages, record new medications the patient has taken since the previous visit, any changes to ongoing medications, and a stop date for any medication the patient is no longer taking.

Initials
Date Verified
Initials
Date Keyed
Date Received at Lilly
Reviewed
Inspected
Date

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Clinical Report Form
Fluoxetine Versus Placebo in Childhood/Adolescent Depression
B1Y-MC-HCJE

STUDY DRUG : DATES OF MISSED DOSES

NO MISSED DOSES ☐

Record the date for any day on which the patient missed a full or partial dose of study drug.

	Dates of Missed Doses MM	DD	YY
0.			
1.			
2.			
3.			
4.			
5.			
6.			
7.			
8.			
9.			

NOTE: If the patient has missed 3 or more consecutive days of medication, the patient must be discontinued from the study.

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Clinical Report Form
Fluoxetine Versus Placebo in Childhood/Adolescent Depression
B1Y-MC-HCJE

SIDE EFFECTS CHECKLIST

INFORMATION NOT OBTAINED ☐

Since your last visit, have you been bothered with or had any trouble with any of the items listed below? Check the box which best tells how much you were bothered.

	Not at all	Just a little	Pretty much	Very much	Don't know
1. Eating?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
2. Drinking?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
3. Dry mouth and lips?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
4. Wetness in mouth?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
5. Constipation?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
6. Diarrhea?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
7. Stomachaches?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
8. Muscle cramps?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
9. Being sick to your stomach?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
10. Wetting the bed?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
11. Urinating?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
12. Itchy or scratchy skin?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
13. Rashes?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
14. Cold or sniffles?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
15. Headache?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4

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Clinical Report Form
Fluoxetine Versus Placebo in Childhood/Adolescent Depression
B1Y-MC-HCJE

SIDE EFFECTS CHECKLIST

	Not at all	Just a little	Pretty much	Very much	Don't know
16. Dizziness?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
17. Playing sports?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
18. Shakiness?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
19. Pronouncing words?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
20. Doing things with your hands?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
21. Sitting still?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
22. Tiredness?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
23. Feeling sleepy?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
24. Trouble sleeping?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
25. Bad dreams?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
26. Getting along with parents?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
27. Getting along with kids?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
28. Crying?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
29. Getting mad?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
30. Not being happy?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
31. Being sad?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
32. Paying attention?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4

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Clinical Report Form
Fluoxetine Versus Placebo in Childhood/Adolescent Depression
B1Y-MC-HCJE

CHILDRENS DEPRESSION RATING SCALE - REVISED

INFORMATION NOT OBTAINED ☐

CHECK THE NUMERIC CODE which best describes the patient.

1. **SCHOOLWORK**:

☐ 1 Performance consistent with ability
☐ 2
☐ 3 Decrease in school performance
☐ 4
☐ 5 Major interference in most subjects
☐ 6
☐ 7 No motivation to perform

2. **CAPACITY TO HAVE FUN**

☐ 1 Interest and activities realistically appropriate for age, personality, and social environment. Shows no appreciable change with present illness.
☐ 2
☐ 3 Describes some activities realistically available several times a week but not on a daily basis. Shows interest but not enthusiasm.
☐ 4
☐ 5 Is easily bored. Complains of "nothing to do." Participates in structured activities with a "going through the motions" attitude. May express interest primarily in activities that are (realistically) unavailable on a daily or weekly basis.
☐ 6
☐ 7 Has no initiative to become involved in any activities. Primarily passive. Watches others play or watches TV but shows little interest. Requires coaxing and/or pushing to get involved in activity. Shows no enthusiasm or real interest. Has difficulty naming activities.

3. **SOCIAL WITHDRAWAL**

☐ 1 Enjoys friendships with peers at school and home
☐ 2
☐ 3 May not actively seek out friendships but waits for others to initiate a relationship or may occasionally reject opportunities to play without a describable alternative
☐ 4
☐ 5 Frequently avoids or refuses opportunities for desirable interaction with others and/or sets up situations where rejection is inevitable.
☐ 6
☐ 7 Does not currently relate to other children. States he or she has "no friends" or actively rejects new or former friends.

4. **SLEEP**

☐ 1 No (or occasional) difficulty. (Goes to sleep within 1/2 hour or less.)
☐ 2
☐ 3 Frequently has mild difficulty with sleep
☐ 4
☐ 5 Moderate difficulty with sleep nearly every night.

5. **APPETITE OR EATING PATTERNS**

☐ 1 No problems or change in eating pattern
☐ 2
☐ 3 Mild change from usual eating habits within onset of current behavioral problem
☐ 4
☐ 5 Is not hungry most of the time or has excessive food intake since onset of current behavioral problems or marked increase in appetite

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Fluoxetine Versus Placebo in Childhood/Adolescent Depression
B1Y-MC-HCJE

CHILDRENS DEPRESSION RATING SCALE - REVISED

CHECK THE NUMERIC CODE which best describes the patient.

6. **EXCESSIVE FATIGUE**

- ☐ 1 No unusual complaints of "feeling tired" during the day
- ☐ 2
- ☐ 3 Complaints of fatigue which seem somewhat excessive and not related to boredom
- ☐ 4
- ☐ 5 Daily complaints of feeling tired
- ☐ 6
- ☐ 7 Complains of feeling tired most of the day. May voluntarily take long naps without feeling refreshed. Interferes with play activities.

7. **PHYSICAL COMPLAINTS**:

- ☐ 1 Occasional complaints
- ☐ 2
- ☐ 3 Complaints appear mildly excessive
- ☐ 4
- ☐ 5 Complains daily. Some interference with the ability of the child to function
- ☐ 6
- ☐ 7 Preoccupied with aches and pains; interferes with play activities several times a week

8. **IRRITABILITY**

- ☐ 1 Rare
- ☐ 2 Occasional
- ☐ 3 Several times a week for short periods
- ☐ 4
- ☐ 5 Several times a week for longer periods
- ☐ 6
- ☐ 7 Constant

9. **GUILT**

- ☐ 1 Does not express any undue feeling of guilt. Appears appropriate to precipitating event.
- ☐ 2
- ☐ 3 Exaggerates guilt and/or shame out of proportion to the event described.
- ☐ 4
- ☐ 5 Feels guilty over things not under his or her control. Guilt is definitely pathological.
- ☐ 6
- ☐ 7 Severe delusions of guilt

10. **SELF-ESTEEM**

- ☐ 1 Describes self in primarily positive terms
- ☐ 2
- ☐ 3 Describes self with one important area where the child feels deficit
- ☐ 4
- ☐ 5 Describes self in preponderance of negative terms or gives bland answers to questions
- ☐ 6
- ☐ 7 Refers to self in derogatory terms. Reports that other children refer to him/her frequently by using derogatory nicknames and child puts self down

11. **DEPRESSED FEELINGS**

- ☐ 1 Occasional feelings of unhappiness which quickly disappear
- ☐ 2
- ☐ 3 Describes sustained periods of unhappiness which appear excessive for events described
- ☐ 4
- ☐ 5 Feels unhappy most of the time without a major precipitating cause
- ☐ 6
- ☐ 7 Feels unhappy all of the time. Accompanied by psychic pain (e.g., "I can't stand it").

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CHILDRENS DEPRESSION RATING SCALE - REVISED

CHECK THE NUMERIC CODE which best describes the patient.

12. **MORBID IDEATION**

- ☐ 1 None
- ☐ 2
- ☐ 3 Has some morbid thought, all of which relate to a reality event but seem excessive.
- ☐ 4
- ☐ 5 Preoccupied with morbid thoughts several times a week. Morbid thoughts extend beyond external reality
- ☐ 6
- ☐ 7 Preoccupied with death themes or morbid thoughts that are elaborate, extensive or bizarre on a daily basis

13. **SUICIDAL IDEATION**

- ☐ 1 Understands the word "suicide" but does not apply term to self
- ☐ 2 Sharp denial of suicidal thoughts
- ☐ 3 Has thoughts about suicide, usually when angry.
- ☐ 4
- ☐ 5 Has recurrent thoughts of suicide
- ☐ 6
- ☐ 7 Has made suicide attempt within the last month or is actively suicidal

14. **WEEPING**:

- ☐ 1 Normal for age.
- ☐ 2 Suggestive statements that child cries, or feels like crying, more frequently than peers.
- ☐ 3 Child cries slightly more than peers.
- ☐ 4
- ☐ 5 Cries or feels like crying frequently (several times a week). Admits to crying without knowing reason why.
- ☐ 6
- ☐ 7 Cries nearly every day.

15. **DEPRESSED AFFECT:**

- ☐ 1 Definitely not depressed. Facial expression and voice animated during interview.
- ☐ 2 Mild suppression of affect. Some loss of spontaneity.
- ☐ 3 Overall loss of spontaneity. Looks distinctly unhappy during parts of the interview. May still be able to smile when discussing non-threatening areas.
- ☐ 4
- ☐ 5 Moderate restriction of affect throughout most of interview. Has longer and frequent periods of looking distinctly unhappy.
- ☐ 6
- ☐ 7 Severe. Looks sad, withdrawn. Minimal verbal interaction throughout interview. Cries or may appear tearful.

16. **TEMPO OF SPEECH:**

- ☐ 1 Normal
- ☐ 2 Slow
- ☐ 3 Slow: delays interview.
- ☐ 4
- ☐ 5 Severe. Low; marked interference with interview.

17. **HYPOACTIVITY:**

- ☐ 1 None
- ☐ 2
- ☐ 3 Mild. Some body movements.
- ☐ 4
- ☐ 5 Moderate. Definite motor retardation.
- ☐ 6
- ☐ 7 Severe. Motionless throughout interview.

(DNDE)

Total of 1 - 17 _____

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CLINICAL GLOBAL IMPRESSION: EFFICACY INDEX

Using the worksheet below, enter the 2-digit efficacy index rating.

1. Efficacy index rating ___ ___

(DNDE)

EFFICACY INDEX WORKSHEET

Rate this item on the basis of DRUG EFFECT ONLY.

Select the terms that best describe the degrees of therapeutic effect and side effects and record the number from the box where the two items intersect in the blanks above.

THERAPEUTIC EFFECT	SIDE EFFECTS			
	None	Do not significantly interfere with patient's functioning	Significantly interferes with patient's functioning	Outweighs therapeutic effect
MARKED - Vast improvement. Complete or nearly complete remission of all symptoms.	**01**	**02**	**03**	**04**
MODERATE - Decided improvement. Partial remission of symptoms.	**05**	**06**	**07**	**08**
MINIMAL - Slight improvement which doesn't alter status of care of patient.	**09**	**10**	**11**	**12**
UNCHANGED OR WORSE	**13**	**14**	**15**	**16**
Not Assessed = **98**				

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B1Y-MC-HCJE

CLINICAL GLOBAL IMPRESSION: SEVERITY

INFORMATION NOT OBTAINED ☐

Considering your total clinical experience with this particular population, how mentally ill is the patient at this time?

- ☐ 1 Normal, not at all ill
- ☐ 2 Borderline ill
- ☐ 3 Mildly ill
- ☐ 4 Moderately ill
- ☐ 5 Markedly ill
- ☐ 6 Severely ill
- ☐ 7 Among the most extremely ill patients

Evaluator's initials _____ _____ _____
First Middle Last

CLINICAL GLOBAL IMPRESSION: IMPROVEMENT

INFORMATION NOT OBTAINED ☐

Rate total improvement, whether or not in your judgement it is due entirely to drug treatment. Compared to the patient's condition at Visit 1, how much has he/she changed?

- ☐ 1 Very much improved
- ☐ 2 Much improved
- ☐ 3 Minimally improved
- ☐ 4 No change
- ☐ 5 Minimally worse
- ☐ 6 Much worse
- ☐ 7 Very much worse

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MONTGOMERY - ASBERG DEPRESSION RATING SCALE (MADRS)

INFORMATION NOT OBTAINED ☐

The rating should be based on a clinical interview moving from broadly phrased questions about symptoms to more detailed ones which allow a precise rating of severity. The rater must decide whether the rating lies on the defined scale steps (0, 2, 4, 6) or between them (1, 3, 5).

Check the box (number) that best characterizes the patient at this time

1. **APPARENT SADNESS**
   Representing despondency, gloom, and despair (more than just ordinary transient low spirits), reflected in speech, facial expression, and posture. Rate by depth and inability to brighten up.

   ☐ 0 No sadness.
   ☐ 1
   ☐ 2 Looks dispirited but does brighten up without difficulty.
   ☐ 3
   ☐ 4 Appears sad and unhappy most of the time.
   ☐ 5
   ☐ 6 Looks miserable all the time. Extremely despondent.

2. **REPORTED SADNESS**
   Represented by reports of depressed mood, regardless of whether it is reflected in appearance or not. Includes low spirits, despondency, or the feeling of being beyond help and without hope. Rate according to intensity, duration, and the extent to which the mood is reported to be influenced by events.

   ☐ 0 Occasional sadness in keeping with the circumstances.
   ☐ 1
   ☐ 2 Sad or low but brightens up without difficulty.
   ☐ 3
   ☐ 4 Pervasive feelings of sadness or gloominess. The mood is still influenced by external circumstances.
   ☐ 5
   ☐ 6 Continuous unvarying sadness, misery or despondency.

3. **INNER TENSION**
   Representing feelings of ill-defined discomfort, edginess, inner turmoil, mental tension mounting to either panic, dread, or anguish. Rate according to intensity, frequency, duration, and the extent of reassurance called for.

   ☐ 0 Placid. Only fleeting inner tension.
   ☐ 1
   ☐ 2 Occasional feelings of edginess and ill-defined discomfort.
   ☐ 3
   ☐ 4 Continuous feelings of inner tension or intermittent panic which the patient can only master with some difficulty.
   ☐ 5
   ☐ 6 Unrelenting dread or anguish. Overwhelming panic.

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MONTGOMERY - ASBERG DEPRESSION RATING SCALE (MADRS)

4. **REDUCED SLEEP**
Representing the experience of reduced duration or depth of sleep compared to the subject's own pattern when well.

- ☐ 0 Sleeps as usual.
- ☐ 1
- ☐ 2 Slight difficulty dropping off to sleep or slightly reduced, light or fitful sleep.
- ☐ 3
- ☐ 4 Sleep reduced or broken by at least two hours.
- ☐ 5
- ☐ 6 Less than two or three hours sleep.

5. **REDUCED APPETITE**
Representing the feeling of a loss of appetite compared with when well. Rate by loss of desire for food or the need to force oneself to eat.

- ☐ 0 Normal or increased appetite
- ☐ 1
- ☐ 2 Slightly reduced appetite.
- ☐ 3
- ☐ 4 No appetite. Food is tasteless.
- ☐ 5
- ☐ 6 Needs persuasion to eat at all.

6. **CONCENTRATION DIFFICULTIES**
Representing difficulties in collecting one's thoughts mounting to incapacitating lack of concentration.

- ☐ 0 No difficulties in concentrating.
- ☐ 1
- ☐ 2 Occasional difficulties in collecting one's thoughts.
- ☐ 3
- ☐ 4 Difficulties in concentrating and sustaining thought which reduces ability to read or hold a conversation.
- ☐ 5
- ☐ 6 Unable to read or converse without great difficulty.

7. **LASSITUDE**
Representing a difficulty getting started or slowness initiating and performing everyday activities.

- ☐ 0 Hardly any difficulty in getting started. No sluggishness.
- ☐ 1
- ☐ 2 Difficulties in starting activities
- ☐ 3
- ☐ 4 Difficulties in starting simple routine activities which are carried out with effort.
- ☐ 5
- ☐ 6 Complete lassitude. Unable to do anything without help.

8. **INABILITY TO FEEL**
Representing the subjective experience of reduced interest in the surroundings, or activities that normally give pleasure. The ability to react with adequate emotion to circumstances or people is reduced.

- ☐ 0 Normal interest in the surroundings and other people.
- ☐ 1
- ☐ 2 Reduced ability to enjoy usual interests.
- ☐ 3
- ☐ 4 Loss of interest in the surroundings. Loss of feelings for friends and acquaintances.
- ☐ 5
- ☐ 6 The experience of being emotionally paralyzed, inability to feel anger, grief, or pleasure and a complete or even painful failure to feel for close relatives and friends.

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B1Y-MC-HCJE

MONTGOMERY - ASBERG DEPRESSION RATING SCALE (MADRS)

9. **PESSIMISTIC THOUGHTS**
Representing thoughts of guilt, inferiority, self-reproach, sinfulness, remorse, and ruin

- ☐ 0 No pessimistic thoughts.
- ☐ 1
- ☐ 2 Fluctuating ideas of failure, self-reproach, or self-depreciation.
- ☐ 3
- ☐ 4 Persistent self-accusations, or definite but still rational ideas of guilt, or sin. Increasingly pessimistic about the future.
- ☐ 5
- ☐ 6 Delusions of ruin, remorse, or unredeemable sin. Self-accusations which are absurd and unshakable.

10. **SUICIDAL THOUGHTS**
Representing the feeling that life is not worth living, that a natural death would be welcome, suicidal thoughts, and preparations for suicide. Suicidal attempts should not in themselves influence the rating.

- ☐ 0 Enjoys life or takes it as it comes.
- ☐ 1
- ☐ 2 Weary of life. Only fleeting suicidal thoughts.
- ☐ 3
- ☐ 4 Probably better off dead. Suicidal thoughts are common, and suicide is considered as a possible solution, but without specific plans or intention.
- ☐ 5
- ☐ 6 Explicit plans for suicide when there is an opportunity. Active preparations for suicide.

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B1Y-MC-HCJE

COMMENTS : VISIT

NO COMMENTS ☐

Comments should address any clinical report form items that require further explanation. Repeating information from the clinical report form is discouraged.

Comment on all clinically significant lab values that are outside a clinically accepted reference range or clinically significant values that differ importantly from previous values.

If the patient is ending participation in the study at this visit, enter only comments that apply to this visit; then complete the Patient Summary and Study Summary Comments pages.

Print legibly and do not use abbreviations or symbols.

The information reported for this visit is accurate and complete.

_____ _____/_____/_____
Signature MM DD YY

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Clinical Report Form
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B1Y-MC-HCJE

PATIENT AND VISIT IDENTIFICATION

Patient initials _____ _____ _____
First Middle Last

Visit date _____/_____/_____
MM DD YY

VITAL SIGNS : BLOOD PRESSURE AND HEART RATE

INFORMATION NOT OBTAINED ☐

Position
SI = Sitting

Position	Blood Pressure (mm Hg) Systolic/Diastolic	Heart Rate (bpm)
SI	/	

VITAL SIGNS: TEMPERATURE

INFORMATION NOT OBTAINED ☐

Temperature ___ ___ ___ . ___

Unit of measure (F) Fahrenheit

Method (E) Ear

REMINDER

On the Pre-existing Conditions and Study Adverse Events pages, record new events that occurred since the previous visit and re-evaluate any on-going conditions or events.

On the Concomitant Medication pages, record new medications the patient has taken since the previous visit, any changes to ongoing medications, and a stop date for any medication the patient is no longer taking.

Initials
Date Verified
Initials
Date Keyed
Date Received at Lilly
Reviewed
Inspected
Date

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B1Y-MC-HCJE

STUDY DRUG : DATES OF MISSED DOSES

NO MISSED DOSES ☐

Record the date for any day on which the patient missed a full or partial dose of study drug.

	Dates of Missed Doses MM	DD	YY
0.			
1.			
2.			
3.			
4.			
5.			
6.			
7.			
8.			
9.			

NOTE: If the patient has missed 3 or more consecutive days of medication, the patient must be discontinued from the study.

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Clinical Report Form
Fluoxetine Versus Placebo in Childhood/Adolescent Depression
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SIDE EFFECTS CHECKLIST

INFORMATION NOT OBTAINED ☐

Since your last visit, have you been bothered with or had any trouble with any of the items listed below? Check the box which best tells how much you were bothered.

	Not at all	Just a little	Pretty much	Very much	Don't know
1. Eating?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
2. Drinking?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
3. Dry mouth and lips?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
4. Wetness in mouth?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
5. Constipation?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
6. Diarrhea?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
7. Stomachaches?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
8. Muscle cramps?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
9. Being sick to your stomach?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
10. Wetting the bed?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
11. Urinating?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
12. Itchy or scratchy skin?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
13. Rashes?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
14. Cold or sniffles?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
15. Headache?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4

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Clinical Report Form
Fluoxetine Versus Placebo in Childhood/Adolescent Depression
B1Y-MC-HCJE

SIDE EFFECTS CHECKLIST

	Not at all	Just a little	Pretty much	Very much	Don't know
16. Dizziness?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
17. Playing sports?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
18. Shakiness?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
19. Pronouncing words?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
20. Doing things with your hands?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
21. Sitting still?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
22. Tiredness?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
23. Feeling sleepy?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
24. Trouble sleeping?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
25. Bad dreams?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
26. Getting along with parents?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
27. Getting along with kids?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
28. Crying?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
29. Getting mad?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
30. Not being happy?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
31. Being sad?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
32. Paying attention?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4

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CHILDRENS DEPRESSION RATING SCALE - REVISED

INFORMATION NOT OBTAINED ☐

CHECK THE NUMERIC CODE which best describes the patient.

1. **SCHOOLWORK**:

☐ 1 Performance consistent with ability
☐ 2
☐ 3 Decrease in school performance
☐ 4
☐ 5 Major interference in most subjects
☐ 6
☐ 7 No motivation to perform

2. **CAPACITY TO HAVE FUN**

☐ 1 Interest and activities realistically appropriate for age, personality, and social environment. Shows no appreciable change with present illness.
☐ 2
☐ 3 Describes some activities realistically available several times a week but not on a daily basis. Shows interest but not enthusiasm.
☐ 4
☐ 5 Is easily bored. Complains of "nothing to do." Participates in structured activities with a "going through the motions" attitude. May express interest primarily in activities that are (realistically) unavailable on a daily or weekly basis.
☐ 6
☐ 7 Has no initiative to become involved in any activities. Primarily passive. Watches others play or watches TV but shows little interest. Requires coaxing and/or pushing to get involved in activity. Shows no enthusiasm or real interest. Has difficulty naming activities.

3. **SOCIAL WITHDRAWAL**

☐ 1 Enjoys friendships with peers at school and home
☐ 2
☐ 3 May not actively seek out friendships but waits for others to initiate a relationship or may occasionally reject opportunities to play without a describable alternative
☐ 4
☐ 5 Frequently avoids or refuses opportunities for desirable interaction with others and/or sets up situations where rejection is inevitable.
☐ 6
☐ 7 Does not currently relate to other children. States he or she has "no friends" or actively rejects new or former friends.

4. **SLEEP**

☐ 1 No (or occasional) difficulty. (Goes to sleep within 1/2 hour or less.)
☐ 2
☐ 3 Frequently has mild difficulty with sleep
☐ 4
☐ 5 Moderate difficulty with sleep nearly every night.

5. **APPETITE OR EATING PATTERNS**

☐ 1 No problems or change in eating pattern
☐ 2
☐ 3 Mild change from usual eating habits within onset of current behavioral problem
☐ 4
☐ 5 Is not hungry most of the time or has excessive food intake since onset of current behavioral problems or marked increase in appetite

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B1Y-MC-HCJE

CHILDRENS DEPRESSION RATING SCALE - REVISED

CHECK THE NUMERIC CODE which best describes the patient.

6. **EXCESSIVE FATIGUE**

- ☐ 1 No unusual complaints of "feeling tired" during the day
- ☐ 2
- ☐ 3 Complaints of fatigue which seem somewhat excessive and not related to boredom
- ☐ 4
- ☐ 5 Daily complaints of feeling tired
- ☐ 6
- ☐ 7 Complains of feeling tired most of the day. May voluntarily take long naps without feeling refreshed. Interferes with play activities.

7. **PHYSICAL COMPLAINTS**:

- ☐ 1 Occasional complaints
- ☐ 2
- ☐ 3 Complaints appear mildly excessive
- ☐ 4
- ☐ 5 Complains daily. Some interference with the ability of the child to function
- ☐ 6
- ☐ 7 Preoccupied with aches and pains; interferes with play activities several times a week

8. **IRRITABILITY**

- ☐ 1 Rare
- ☐ 2 Occasional
- ☐ 3 Several times a week for short periods
- ☐ 4
- ☐ 5 Several times a week for longer periods
- ☐ 6
- ☐ 7 Constant

9. **GUILT**

- ☐ 1 Does not express any undue feeling of guilt. Appears appropriate to precipitating event.
- ☐ 2
- ☐ 3 Exaggerates guilt and/or shame out of proportion to the event described.
- ☐ 4
- ☐ 5 Feels guilty over things not under his or her control. Guilt is definitely pathological.
- ☐ 6
- ☐ 7 Severe delusions of guilt

10. **SELF-ESTEEM**

- ☐ 1 Describes self in primarily positive terms
- ☐ 2
- ☐ 3 Describes self with one important area where the child feels deficit
- ☐ 4
- ☐ 5 Describes self in preponderance of negative terms or gives bland answers to questions
- ☐ 6
- ☐ 7 Refers to self in derogatory terms. Reports that other children refer to him/her frequently by using derogatory nicknames and child puts self down

11. **DEPRESSED FEELINGS**

- ☐ 1 Occasional feelings of unhappiness which quickly disappear
- ☐ 2
- ☐ 3 Describes sustained periods of unhappiness which appear excessive for events described
- ☐ 4
- ☐ 5 Feels unhappy most of the time without a major precipitating cause
- ☐ 6
- ☐ 7 Feels unhappy all of the time. Accompanied by psychic pain (e.g., "I can't stand it").

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Fluoxetine Versus Placebo in Childhood/Adolescent Depression
B1Y-MC-HCJE

CHILDRENS DEPRESSION RATING SCALE - REVISED

CHECK THE NUMERIC CODE which best describes the patient.

12. **MORBID IDEATION**

- ☐ 1 None
- ☐ 2
- ☐ 3 Has some morbid thought, all of which relate to a reality event but seem excessive.
- ☐ 4
- ☐ 5 Preoccupied with morbid thoughts several times a week. Morbid thoughts extend beyond external reality
- ☐ 6
- ☐ 7 Preoccupied with death themes or morbid thoughts that are elaborate, extensive or bizarre on a daily basis

13. **SUICIDAL IDEATION**

- ☐ 1 Understands the word "suicide" but does not apply term to self
- ☐ 2 Sharp denial of suicidal thoughts
- ☐ 3 Has thoughts about suicide, usually when angry.
- ☐ 4
- ☐ 5 Has recurrent thoughts of suicide
- ☐ 6
- ☐ 7 Has made suicide attempt within the last month or is actively suicidal

14. **WEEPING**:

- ☐ 1 Normal for age.
- ☐ 2 Suggestive statements that child cries, or feels like crying, more frequently than peers.
- ☐ 3 Child cries slightly more than peers.
- ☐ 4
- ☐ 5 Cries or feels like crying frequently (several times a week). Admits to crying without knowing reason why.
- ☐ 6
- ☐ 7 Cries nearly every day.

15. **DEPRESSED AFFECT:**

- ☐ 1 Definitely not depressed. Facial expression and voice animated during interview.
- ☐ 2 Mild suppression of affect. Some loss of spontaneity.
- ☐ 3 Overall loss of spontaneity. Looks distinctly unhappy during parts of the interview. May still be able to smile when discussing non-threatening areas.
- ☐ 4
- ☐ 5 Moderate restriction of affect throughout most of interview. Has longer and frequent periods of looking distinctly unhappy.
- ☐ 6
- ☐ 7 Severe. Looks sad, withdrawn. Minimal verbal interaction throughout interview. Cries or may appear tearful.

16. **TEMPO OF SPEECH:**

- ☐ 1 Normal
- ☐ 2 Slow
- ☐ 3 Slow: delays interview.
- ☐ 4
- ☐ 5 Severe. Low; marked interference with interview.

17. **HYPOACTIVITY:**

- ☐ 1 None
- ☐ 2
- ☐ 3 Mild. Some body movements.
- ☐ 4
- ☐ 5 Moderate. Definite motor retardation.
- ☐ 6
- ☐ 7 Severe. Motionless throughout interview.

(DNDE)

Total of 1 - 17 _____

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Fluoxetine Versus Placebo in Childhood/Adolescent Depression
B1Y-MC-HCJE

CLINICAL GLOBAL IMPRESSION: EFFICACY INDEX

Using the worksheet below, enter the 2-digit efficacy index rating.

1. Efficacy index rating ___ ___

(DNDE)

EFFICACY INDEX WORKSHEET

Rate this item on the basis of DRUG EFFECT ONLY.

Select the terms that best describe the degrees of therapeutic effect and side effects and record the number from the box where the two items intersect in the blanks above.

THERAPEUTIC EFFECT	SIDE EFFECTS			
	None	Do not significantly interfere with patient's functioning	Significantly interferes with patient's functioning	Outweighs therapeutic effect
MARKED - Vast improvement. Complete or nearly complete remission of all symptoms.	**01**	**02**	**03**	**04**
MODERATE - Decided improvement. Partial remission of symptoms.	**05**	**06**	**07**	**08**
MINIMAL - Slight improvement which doesn't alter status of care of patient.	**09**	**10**	**11**	**12**
UNCHANGED OR WORSE	**13**	**14**	**15**	**16**
Not Assessed = **98**				

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CLINICAL GLOBAL IMPRESSION: SEVERITY

INFORMATION NOT OBTAINED ☐

Considering your total clinical experience with this particular population, how mentally ill is the patient at this time?

- ☐ 1 Normal, not at all ill
- ☐ 2 Borderline ill
- ☐ 3 Mildly ill
- ☐ 4 Moderately ill
- ☐ 5 Markedly ill
- ☐ 6 Severely ill
- ☐ 7 Among the most extremely ill patients

Evaluator's initials _____ _____ _____
First Middle Last

CLINICAL GLOBAL IMPRESSION: IMPROVEMENT

INFORMATION NOT OBTAINED ☐

Rate total improvement, whether or not in your judgement it is due entirely to drug treatment. Compared to the patient's condition at Visit 1, how much has he/she changed?

- ☐ 1 Very much improved
- ☐ 2 Much improved
- ☐ 3 Minimally improved
- ☐ 4 No change
- ☐ 5 Minimally worse
- ☐ 6 Much worse
- ☐ 7 Very much worse

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B1Y-MC-HCJE

MONTGOMERY - ASBERG DEPRESSION RATING SCALE (MADRS)

INFORMATION NOT OBTAINED ☐

The rating should be based on a clinical interview moving from broadly phrased questions about symptoms to more detailed ones which allow a precise rating of severity. The rater must decide whether the rating lies on the defined scale steps (0, 2, 4, 6) or between them (1, 3, 5).

Check the box (number) that best characterizes the patient at this time

1. **APPARENT SADNESS**
   Representing despondency, gloom, and despair (more than just ordinary transient low spirits), reflected in speech, facial expression, and posture. Rate by depth and inability to brighten up.

   ☐ 0 No sadness.
   ☐ 1
   ☐ 2 Looks dispirited but does brighten up without difficulty.
   ☐ 3
   ☐ 4 Appears sad and unhappy most of the time.
   ☐ 5
   ☐ 6 Looks miserable all the time. Extremely despondent.

2. **REPORTED SADNESS**
   Represented by reports of depressed mood, regardless of whether it is reflected in appearance or not. Includes low spirits, despondency, or the feeling of being beyond help and without hope. Rate according to intensity, duration, and the extent to which the mood is reported to be influenced by events.

   ☐ 0 Occasional sadness in keeping with the circumstances.
   ☐ 1
   ☐ 2 Sad or low but brightens up without difficulty.
   ☐ 3
   ☐ 4 Pervasive feelings of sadness or gloominess. The mood is still influenced by external circumstances.
   ☐ 5
   ☐ 6 Continuous unvarying sadness, misery or despondency.

3. **INNER TENSION**
   Representing feelings of ill-defined discomfort, edginess, inner turmoil, mental tension mounting to either panic, dread, or anguish. Rate according to intensity, frequency, duration, and the extent of reassurance called for.

   ☐ 0 Placid. Only fleeting inner tension.
   ☐ 1
   ☐ 2 Occasional feelings of edginess and ill-defined discomfort.
   ☐ 3
   ☐ 4 Continuous feelings of inner tension or intermittent panic which the patient can only master with some difficulty.
   ☐ 5
   ☐ 6 Unrelenting dread or anguish. Overwhelming panic.

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MONTGOMERY - ASBERG DEPRESSION RATING SCALE (MADRS)

4. **REDUCED SLEEP**
Representing the experience of reduced duration or depth of sleep compared to the subject's own pattern when well.

- ☐ 0 Sleeps as usual.
- ☐ 1
- ☐ 2 Slight difficulty dropping off to sleep or slightly reduced, light or fitful sleep.
- ☐ 3
- ☐ 4 Sleep reduced or broken by at least two hours.
- ☐ 5
- ☐ 6 Less than two or three hours sleep.

5. **REDUCED APPETITE**
Representing the feeling of a loss of appetite compared with when well. Rate by loss of desire for food or the need to force oneself to eat.

- ☐ 0 Normal or increased appetite
- ☐ 1
- ☐ 2 Slightly reduced appetite.
- ☐ 3
- ☐ 4 No appetite. Food is tasteless.
- ☐ 5
- ☐ 6 Needs persuasion to eat at all.

6. **CONCENTRATION DIFFICULTIES**
Representing difficulties in collecting one's thoughts mounting to incapacitating lack of concentration.

- ☐ 0 No difficulties in concentrating.
- ☐ 1
- ☐ 2 Occasional difficulties in collecting one's thoughts.
- ☐ 3
- ☐ 4 Difficulties in concentrating and sustaining thought which reduces ability to read or hold a conversation.
- ☐ 5
- ☐ 6 Unable to read or converse without great difficulty.

7. **LASSITUDE**
Representing a difficulty getting started or slowness initiating and performing everyday activities.

- ☐ 0 Hardly any difficulty in getting started. No sluggishness.
- ☐ 1
- ☐ 2 Difficulties in starting activities
- ☐ 3
- ☐ 4 Difficulties in starting simple routine activities which are carried out with effort.
- ☐ 5
- ☐ 6 Complete lassitude. Unable to do anything without help.

8. **INABILITY TO FEEL**
Representing the subjective experience of reduced interest in the surroundings, or activities that normally give pleasure. The ability to react with adequate emotion to circumstances or people is reduced.

- ☐ 0 Normal interest in the surroundings and other people.
- ☐ 1
- ☐ 2 Reduced ability to enjoy usual interests.
- ☐ 3
- ☐ 4 Loss of interest in the surroundings. Loss of feelings for friends and acquaintances.
- ☐ 5
- ☐ 6 The experience of being emotionally paralyzed, inability to feel anger, grief, or pleasure and a complete or even painful failure to feel for close relatives and friends.

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B1Y-MC-HCJE

MONTGOMERY - ASBERG DEPRESSION RATING SCALE (MADRS)

9. **PESSIMISTIC THOUGHTS**
Representing thoughts of guilt, inferiority, self-reproach, sinfulness, remorse, and ruin

- ☐ 0 No pessimistic thoughts.
- ☐ 1
- ☐ 2 Fluctuating ideas of failure, self-reproach, or self-depreciation.
- ☐ 3
- ☐ 4 Persistent self-accusations, or definite but still rational ideas of guilt, or sin. Increasingly pessimistic about the future.
- ☐ 5
- ☐ 6 Delusions of ruin, remorse, or unredeemable sin. Self-accusations which are absurd and unshakable.

10. **SUICIDAL THOUGHTS**
Representing the feeling that life is not worth living, that a natural death would be welcome, suicidal thoughts, and preparations for suicide. Suicidal attempts should not in themselves influence the rating.

- ☐ 0 Enjoys life or takes it as it comes.
- ☐ 1
- ☐ 2 Weary of life. Only fleeting suicidal thoughts.
- ☐ 3
- ☐ 4 Probably better off dead. Suicidal thoughts are common, and suicide is considered as a possible solution, but without specific plans or intention.
- ☐ 5
- ☐ 6 Explicit plans for suicide when there is an opportunity. Active preparations for suicide.

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Fluoxetine Versus Placebo in Childhood/Adolescent Depression
B1Y-MC-HCJE

CHILDREN'S DEPRESSION INDEX (CDI)

NOTE: Only complete if patient was 8 to 12 years old at Visit 1. If patient was not 8 to 12 years old, check the Information Not Obtained box.

INFORMATION NOT OBTAINED ☐

This lists the feelings and ideas in groups. From each group of three sentences, pick one sentence that describes you **best** for the past two weeks. After you pick a sentence from the first group, go on to the next group. There is no right answer or wrong answer. Just pick the sentence that best describes the way you have been recently. Put an "X" in the box next to your answer.
Remember: pick out the sentences that describe you best **in the past two weeks**.

Item 1

- ☐ 0 I am sad once in a while.
- ☐ 1 I am sad many times.
- ☐ 2 I am sad all the time.

Item 2

- ☐ 2 Nothing will ever work out for me.
- ☐ 1 I am not sure if things will work out for me.
- ☐ 0 Things will work out for me O.K.

Item 3

- ☐ 0 I do most things O.K.
- ☐ 1 I do many things wrong.
- ☐ 2 I do everything wrong.

Item 4

- ☐ 0 I have fun in many things.
- ☐ 1 I have fun in some things.
- ☐ 2 Nothing is fun at all.

Item 5

- ☐ 2 I am bad all the time.
- ☐ 1 I am bad many times.
- ☐ 0 I am bad once in a while.

Item 6

- ☐ 0 I think about bad things happening to me once in a while.
- ☐ 1 I worry that bad things will happen to me.
- ☐ 2 I am sure that terrible things will happen to me.

Item 7

- ☐ 2 I hate myself.
- ☐ 1 I do not like myself.
- ☐ 0 I like myself.

Item 8

- ☐ 2 All bad things are my fault.
- ☐ 1 Many bad things are my fault.
- ☐ 0 Bad things are not usually my fault.

Item 9

- ☐ 0 I do not think about killing myself.
- ☐ 1 I think about killing myself but I would not do it.
- ☐ 2 I want to kill myself.

Item 10

- ☐ 2 I feel like crying every day.
- ☐ 1 I feel like crying many days.
- ☐ 0 I feel like crying once in a while.

Item 11

- ☐ 2 Things bother me all the time.
- ☐ 1 Things bother me many times.
- ☐ 0 Things bother me once in a while.

Item 12

- ☐ 0 I like being with people.
- ☐ 1 I do not like being with people many times.
- ☐ 2 I do not want to be with people at all.

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CHILDREN'S DEPRESSION INDEX (CDI)

Item 13

- ☐ 2 I cannot make up my mind about things.
- ☐ 1 It is hard to make up my mind about things.
- ☐ 0 I make up my mind about things easily.

Item 14

- ☐ 0 I look O.K.
- ☐ 1 There are some bad things about my looks.
- ☐ 2 I look ugly.

Item 15

- ☐ 2 I have to push myself all the time to do my schoolwork.
- ☐ 1 I have to push myself many times to do my schoolwork.
- ☐ 0 Doing schoolwork is not a big problem.

Item 16

- ☐ 2 I have trouble sleeping every night.
- ☐ 1 I have trouble sleeping many nights.
- ☐ 0 I sleep pretty well.

Item 17

- ☐ 0 I am tired once in a while.
- ☐ 1 I am tired many days.
- ☐ 2 I am tired all the time.

Item 18

- ☐ 2 Most days I do not feel like eating.
- ☐ 1 Many days I do not feel like eating.
- ☐ 0 I eat pretty well.

Item 19

- ☐ 0 I do not worry about aches and pains.
- ☐ 1 I worry about aches and pains many times.
- ☐ 2 I worry about aches and pains all the time.

Item 20

- ☐ 0 I do not feel alone.
- ☐ 1 I feel alone many times.
- ☐ 2 I feel alone all the time.

Item 21

- ☐ 2 I never have fun at school.
- ☐ 1 I have fun at school only once in a while.
- ☐ 0 I have fun at school many times.

Item 22

- ☐ 0 I have plenty of friends.
- ☐ 1 I have some friends but I wish I had more.
- ☐ 2 I do not have any friends.

Item 23

- ☐ 0 My schoolwork is alright.
- ☐ 1 My schoolwork is not as good as before.
- ☐ 2 I do very badly in subjects I used to be good in.

Item 24

- ☐ 2 I can never be as good as other kids.
- ☐ 1 I can be as good as other kids if I want to.
- ☐ 0 I am just as good as other kids.

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CHILDREN'S DEPRESSION INDEX (CDI)

Item 25

- ☐ 2 Nobody really loves me.
- ☐ 1 I am not sure if anybody loves me.
- ☐ 0 I am sure that somebody loves me.

Item 26

- ☐ 0 I usually do what I am told.
- ☐ 1 I do not do what I am told most times.
- ☐ 2 I never do what I am told.

Item 27

- ☐ 0 I get along with people.
- ☐ 1 I get into fights many times.
- ☐ 2 I get into fights all the time.

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BECK DEPRESSION INVENTORY

NOTE: Only complete if patient was 13 to 17 years old at Visit 1. If patient was not 13 to 17 years old, check the Information Not Obtained box.

INFORMATION NOT OBTAINED ☐

This questionnaire consists of 21 groups of statements. After reading each group of statements carefully circle the number (0, 1, 2, 3) next to the one statement in each group which best describes the way you have been feeling **the past week, including today**. If several statements within a group seem to apply equally well, circle each one. Be sure to read all the statements in each group before making your choice.

1

0 I do not feel sad.
1 I feel sad.
2 I am sad all the time and I can't snap out of it.
3 I am so sad or unhappy that I can't stand it.

2

0 I am not particularly discouraged about the future.
1 I feel discouraged about the future.
2 I feel I have nothing to look forward to.
3 I feel that the future is hopeless and that things cannot improve.

3

0 I do not feel like a failure.
1 I feel I have failed more than the average person.
2 As I look back on my life, all I can see is a lot of failures.
3 I feel I am a complete failure as a person.

4

0 I get as much satisfaction out of things as I used to.
1 I don't enjoy things the way I used to.
2 I don't get real satisfaction out of anything anymore.
3 I am dissatisfied or bored with everything.

5

0 I don't feel particularly guilty.
1 I feel guilty a good part of the time.
2 I feel quite guilty most of the time.
3 I feel guilty all of the time.

6

0 I don't feel I am being punished.
1 I feel I may be punished.
2 I expect to be punished.
3 I feel I am being punished.

7

0 I don't feel disappointed in myself.
1 I am disappointed in myself.
2 I am disgusted with myself.
3 I hate myself.

8

0 I don't feel I am any worse than anybody else.
1 I am critical of myself for my weaknesses or mistakes.
2 I blame myself all the time for my faults.
3 I blame myself for everything bad that happens.

9

0 I don't have any thoughts of killing myself.
1 I have thoughts of killing myself, but I would not carry them out.
2 I would like to kill myself.
3 I would kill myself if I had the chance.

10

0 I don't cry any more than usual.
1 I cry more now than I used to.
2 I cry all the time now.
3 I used to be able to cry, but now I can't cry even though I want to.

11

0 I am no more irritated now than I ever am.
1 I get annoyed or irritated more easily than I used to.
2 I feel irritated all the time now.
3 I don't get irritated at all by the things that used to irritate me.

12

0 I have not lost interest in other people.
1 I am less interested in other people than I used to be.
2 I have lost most of my interest in other people.
3 I have lost all of my interest in other people.

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BECK DEPRESSION INVENTORY

13

0 I make decisions about as well as I ever could.
1 I put off making decisions more than I used to.
2 I have greater difficulty in making decisions than before.
3 I can't make decisions at all anymore.

14

0 I don't feel I look any worse than I used to.
1 I am worried that I am looking old or unattractive.
2 I feel that there are permanent changes in my appearance that make me look unattractive.
3 I believe that I look ugly.

15

0 I can work about as well as before.
1 It takes an extra effort to get started at doing something.
2 I have to push myself very hard to do anything.
3 I can't do any work at all.

16

0 I can sleep as well as usual.
1 I don't sleep as well as I used to.
2 I wake up 1-2 hours earlier than usual and find it hard to get back to sleep.
3 I wake up several hours earlier than I used to and cannot get back to sleep.

17

0 I don't get more tired than usual.
1 I get tired more easily than I used to.
2 I get tired from doing almost anything.
3 I am too tired to do anything.

18

0 My appetite is no worse than usual.
1 My appetite is not as good as it used to be.
2 My appetite is much worse now.
3 I have no appetite at all anymore.

19

0 I haven't lost much weight, if any, lately.
1 I have lost more than 5 pounds.
2 I have lost more than 10 pounds.
3 I have lost more than 15 pounds.

19a

I am purposely trying to lose weight by eating less.
1 Yes
2 No

20

0 I am no more worried about my health than usual.
1 I am worried about physical problems such as aches and pains; or upset stomach or constipation.
2 I am very worried about physical problems and it's hard to think of much else.
3 I am so worried about my physical problems that I cannot think about anything else.

21

0 I have not noticed any recent change in my interest in sex.
1 I am less interested in sex than I used to be.
2 I am much less interested in sex now.
3 I have lost interest in sex completely.

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HAMILTON ANXIETY SCALE

INFORMATION NOT OBTAINED ☐

For each of the items below, **CHECK ONE BOX** that best describes the patient.

1. **ANXIOUS MOOD:** Worries, anticipation of the worst, fearful anticipation, irritability

   ☐ 0 Not present
   ☐ 1 Mild
   ☐ 2 Moderate
   ☐ 3 Severe
   ☐ 4 Very severe

2. **TENSION**: Feelings of tension, fatigability, startle response, moved to tears easily, trembling, feeling of restlessness, inability to relax

   ☐ 0 Not present
   ☐ 1 Mild
   ☐ 2 Moderate
   ☐ 3 Severe
   ☐ 4 Very severe

3. **FEARS**: Of dark, of strangers, of being alone, of animals, of traffic, of crowds

   ☐ 0 Not present
   ☐ 1 Mild
   ☐ 2 Moderate
   ☐ 3 Severe
   ☐ 4 Very severe

4. **INSOMNIA**: Difficulty in falling asleep, broken sleep, unsatisfying sleep and fatigue on waking, dreams, nightmares, night terrors

   ☐ 0 Not present
   ☐ 1 Mild
   ☐ 2 Moderate
   ☐ 3 Severe
   ☐ 4 Very severe

5. **INTELLECTUAL (COGNITIVE)**: Difficulty in concentration, poor memory

   ☐ 0 Not present
   ☐ 1 Mild
   ☐ 2 Moderate
   ☐ 3 Severe
   ☐ 4 Very severe

6. **DEPRESSED MOOD**: Loss of interest, lack of pleasure in hobbies, depression, early waking, diurnal swing

   ☐ 0 Not present
   ☐ 1 Mild
   ☐ 2 Moderate
   ☐ 3 Severe
   ☐ 4 Very severe

7. **SOMATIC (MUSCULAR)**: Pains and aches, twitchings, stiffness, myoclonic jerks, grinding of teeth, unsteady voice, increased muscular tone

   ☐ 0 Not present
   ☐ 1 Mild
   ☐ 2 Moderate
   ☐ 3 Severe
   ☐ 4 Very severe

8. **SOMATIC (SENSORY)**: Tinnitus, blurring of vision, hot and cold flushes, feeling of weakness, pricking sensation

   ☐ 0 Not present
   ☐ 1 Mild
   ☐ 2 Moderate
   ☐ 3 Severe
   ☐ 4 Very severe

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B1Y-MC-HCJE

HAMILTON ANXIETY SCALE

9. **CARDIOVASCULAR SYMPTOMS:** Tachycardia, palpitations, pain in chest, throbbing of vessels, fainting feelings, missing beat

- ☐ 0 Not present
- ☐ 1 Mild
- ☐ 2 Moderate
- ☐ 3 Severe
- ☐ 4 Very severe

10. **RESPIRATORY SYMPTOMS:** Pressure or constriction in chest, choking feelings, sighing, dyspnea

- ☐ 0 Not present
- ☐ 1 Mild
- ☐ 2 Moderate
- ☐ 3 Severe
- ☐ 4 Very severe

11. **GASTROINTESTINAL SYMPTOMS:** Difficulty in swallowing, wind, abdominal pain, burning sensations, abdominal fullness, nausea, vomiting, borborygmi, looseness of bowels, loss of weight, constipation

- ☐ 0 Not present
- ☐ 1 Mild
- ☐ 2 Moderate
- ☐ 3 Severe
- ☐ 4 Very severe

12. **GENITOURINARY SYMPTOMS:** Frequency of micturition, urgency of micturition, amenorrhea, menorrhagia, development of frigidity, premature ejaculation, loss of libido, impotence

- ☐ 0 Not present
- ☐ 1 Mild
- ☐ 2 Moderate
- ☐ 3 Severe
- ☐ 4 Very severe

13. **AUTONOMIC SYMPTOMS:** Dry mouth, flushing, pallor, tendency to sweat, giddiness, tension headache, raising of hair

- ☐ 0 Not present
- ☐ 1 Mild
- ☐ 2 Moderate
- ☐ 3 Severe
- ☐ 4 Very severe

14. **BEHAVIOR AT INTERVIEW:** Fidgeting, restlessness or pacing, tremor of hands, furrowed brow, strained face, sighing or rapid respiration, facial pallor, swallowing, belching, brisk tendon jerks, dilated pupils, exophthalmos

- ☐ 0 Not present
- ☐ 1 Mild
- ☐ 2 Moderate
- ☐ 3 Severe
- ☐ 4 Very severe

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B1Y-MC-HCJE

COMMENTS : VISIT

NO COMMENTS ☐

Comments should address any clinical report form items that require further explanation. Repeating information from the clinical report form is discouraged.

Comment on all clinically significant lab values that are outside a clinically accepted reference range or clinically significant values that differ importantly from previous values.

If the patient is ending participation in the study at this visit, enter only comments that apply to this visit; then complete the Patient Summary and Study Summary Comments pages.

Print legibly and do not use abbreviations or symbols.

The information reported for this visit is accurate and complete.

_____ _____/_____/_____
Signature MM DD YY

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PATIENT AND VISIT IDENTIFICATION

Patient initials _____ _____ _____
First Middle Last

Visit date _____/_____/_____
MM DD YY

VITAL SIGNS : BLOOD PRESSURE AND HEART RATE

INFORMATION NOT OBTAINED ☐

Position
SI = Sitting

Position	Blood Pressure (mm Hg) Systolic/Diastolic	Heart Rate (bpm)
SI	/	

VITAL SIGNS: TEMPERATURE

INFORMATION NOT OBTAINED ☐

Temperature ___ ___ ___ . ___

Unit of measure (F) Fahrenheit

Method (E) Ear

REMINDER

On the Pre-existing Conditions and Study Adverse Events pages, record new events that occurred since the previous visit and re-evaluate any on-going conditions or events.

On the Concomitant Medication pages, record new medications the patient has taken since the previous visit, any changes to ongoing medications, and a stop date for any medication the patient is no longer taking.

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Date Verified
Initials
Date Keyed
Date Received at Lilly
Reviewed
Inspected
Date

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STUDY DRUG : DATES OF MISSED DOSES

NO MISSED DOSES ☐

Record the date for any day on which the patient missed a full or partial dose of study drug.

	Dates of Missed Doses MM	DD	YY
0.			
1.			
2.			
3.			
4.			
5.			
6.			
7.			
8.			
9.			

NOTE: If the patient has missed 3 or more consecutive days of medication, the patient must be discontinued from the study.

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B1Y-MC-HCJE

SIDE EFFECTS CHECKLIST

INFORMATION NOT OBTAINED ☐

Since your last visit, have you been bothered with or had any trouble with any of the items listed below? Check the box which best tells how much you were bothered.

	Not at all	Just a little	Pretty much	Very much	Don't know
1. Eating?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
2. Drinking?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
3. Dry mouth and lips?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
4. Wetness in mouth?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
5. Constipation?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
6. Diarrhea?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
7. Stomachaches?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
8. Muscle cramps?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
9. Being sick to your stomach?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
10. Wetting the bed?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
11. Urinating?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
12. Itchy or scratchy skin?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
13. Rashes?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
14. Cold or sniffles?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
15. Headache?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4

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SIDE EFFECTS CHECKLIST

	Not at all	Just a little	Pretty much	Very much	Don't know
16. Dizziness?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
17. Playing sports?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
18. Shakiness?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
19. Pronouncing words?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
20. Doing things with your hands?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
21. Sitting still?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
22. Tiredness?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
23. Feeling sleepy?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
24. Trouble sleeping?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
25. Bad dreams?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
26. Getting along with parents?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
27. Getting along with kids?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
28. Crying?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
29. Getting mad?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
30. Not being happy?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
31. Being sad?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
32. Paying attention?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4

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CHILDRENS DEPRESSION RATING SCALE - REVISED

INFORMATION NOT OBTAINED ☐

CHECK THE NUMERIC CODE which best describes the patient.

1. **SCHOOLWORK**:

☐ 1 Performance consistent with ability
☐ 2
☐ 3 Decrease in school performance
☐ 4
☐ 5 Major interference in most subjects
☐ 6
☐ 7 No motivation to perform

2. **CAPACITY TO HAVE FUN**

☐ 1 Interest and activities realistically appropriate for age, personality, and social environment. Shows no appreciable change with present illness.
☐ 2
☐ 3 Describes some activities realistically available several times a week but not on a daily basis. Shows interest but not enthusiasm.
☐ 4
☐ 5 Is easily bored. Complains of "nothing to do." Participates in structured activities with a "going through the motions" attitude. May express interest primarily in activities that are (realistically) unavailable on a daily or weekly basis.
☐ 6
☐ 7 Has no initiative to become involved in any activities. Primarily passive. Watches others play or watches TV but shows little interest. Requires coaxing and/or pushing to get involved in activity. Shows no enthusiasm or real interest. Has difficulty naming activities.

3. **SOCIAL WITHDRAWAL**

☐ 1 Enjoys friendships with peers at school and home
☐ 2
☐ 3 May not actively seek out friendships but waits for others to initiate a relationship or may occasionally reject opportunities to play without a describable alternative
☐ 4
☐ 5 Frequently avoids or refuses opportunities for desirable interaction with others and/or sets up situations where rejection is inevitable.
☐ 6
☐ 7 Does not currently relate to other children. States he or she has "no friends" or actively rejects new or former friends.

4. **SLEEP**

☐ 1 No (or occasional) difficulty. (Goes to sleep within 1/2 hour or less.)
☐ 2
☐ 3 Frequently has mild difficulty with sleep
☐ 4
☐ 5 Moderate difficulty with sleep nearly every night.

5. **APPETITE OR EATING PATTERNS**

☐ 1 No problems or change in eating pattern
☐ 2
☐ 3 Mild change from usual eating habits within onset of current behavioral problem
☐ 4
☐ 5 Is not hungry most of the time or has excessive food intake since onset of current behavioral problems or marked increase in appetite

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CHILDRENS DEPRESSION RATING SCALE - REVISED

CHECK THE NUMERIC CODE which best describes the patient.

6. **EXCESSIVE FATIGUE**

- ☐ 1 No unusual complaints of "feeling tired" during the day
- ☐ 2
- ☐ 3 Complaints of fatigue which seem somewhat excessive and not related to boredom
- ☐ 4
- ☐ 5 Daily complaints of feeling tired
- ☐ 6
- ☐ 7 Complains of feeling tired most of the day. May voluntarily take long naps without feeling refreshed. Interferes with play activities.

7. **PHYSICAL COMPLAINTS**:

- ☐ 1 Occasional complaints
- ☐ 2
- ☐ 3 Complaints appear mildly excessive
- ☐ 4
- ☐ 5 Complains daily. Some interference with the ability of the child to function
- ☐ 6
- ☐ 7 Preoccupied with aches and pains; interferes with play activities several times a week

8. **IRRITABILITY**

- ☐ 1 Rare
- ☐ 2 Occasional
- ☐ 3 Several times a week for short periods
- ☐ 4
- ☐ 5 Several times a week for longer periods
- ☐ 6
- ☐ 7 Constant

9. **GUILT**

- ☐ 1 Does not express any undue feeling of guilt. Appears appropriate to precipitating event.
- ☐ 2
- ☐ 3 Exaggerates guilt and/or shame out of proportion to the event described.
- ☐ 4
- ☐ 5 Feels guilty over things not under his or her control. Guilt is definitely pathological.
- ☐ 6
- ☐ 7 Severe delusions of guilt

10. **SELF-ESTEEM**

- ☐ 1 Describes self in primarily positive terms
- ☐ 2
- ☐ 3 Describes self with one important area where the child feels deficit
- ☐ 4
- ☐ 5 Describes self in preponderance of negative terms or gives bland answers to questions
- ☐ 6
- ☐ 7 Refers to self in derogatory terms. Reports that other children refer to him/her frequently by using derogatory nicknames and child puts self down

11. **DEPRESSED FEELINGS**

- ☐ 1 Occasional feelings of unhappiness which quickly disappear
- ☐ 2
- ☐ 3 Describes sustained periods of unhappiness which appear excessive for events described
- ☐ 4
- ☐ 5 Feels unhappy most of the time without a major precipitating cause
- ☐ 6
- ☐ 7 Feels unhappy all of the time. Accompanied by psychic pain (e.g., "I can't stand it").

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CHILDRENS DEPRESSION RATING SCALE - REVISED

CHECK THE NUMERIC CODE which best describes the patient.

12. **MORBID IDEATION**

- ☐ 1 None
- ☐ 2
- ☐ 3 Has some morbid thought, all of which relate to a reality event but seem excessive.
- ☐ 4
- ☐ 5 Preoccupied with morbid thoughts several times a week. Morbid thoughts extend beyond external reality
- ☐ 6
- ☐ 7 Preoccupied with death themes or morbid thoughts that are elaborate, extensive or bizarre on a daily basis

13. **SUICIDAL IDEATION**

- ☐ 1 Understands the word "suicide" but does not apply term to self
- ☐ 2 Sharp denial of suicidal thoughts
- ☐ 3 Has thoughts about suicide, usually when angry.
- ☐ 4
- ☐ 5 Has recurrent thoughts of suicide
- ☐ 6
- ☐ 7 Has made suicide attempt within the last month or is actively suicidal

14. **WEEPING**:

- ☐ 1 Normal for age.
- ☐ 2 Suggestive statements that child cries, or feels like crying, more frequently than peers.
- ☐ 3 Child cries slightly more than peers.
- ☐ 4
- ☐ 5 Cries or feels like crying frequently (several times a week). Admits to crying without knowing reason why.
- ☐ 6
- ☐ 7 Cries nearly every day.

15. **DEPRESSED AFFECT:**

- ☐ 1 Definitely not depressed. Facial expression and voice animated during interview.
- ☐ 2 Mild suppression of affect. Some loss of spontaneity.
- ☐ 3 Overall loss of spontaneity. Looks distinctly unhappy during parts of the interview. May still be able to smile when discussing non-threatening areas.
- ☐ 4
- ☐ 5 Moderate restriction of affect throughout most of interview. Has longer and frequent periods of looking distinctly unhappy.
- ☐ 6
- ☐ 7 Severe. Looks sad, withdrawn. Minimal verbal interaction throughout interview. Cries or may appear tearful.

16. **TEMPO OF SPEECH:**

- ☐ 1 Normal
- ☐ 2 Slow
- ☐ 3 Slow: delays interview.
- ☐ 4
- ☐ 5 Severe. Low; marked interference with interview.

17. **HYPOACTIVITY:**

- ☐ 1 None
- ☐ 2
- ☐ 3 Mild. Some body movements.
- ☐ 4
- ☐ 5 Moderate. Definite motor retardation.
- ☐ 6
- ☐ 7 Severe. Motionless throughout interview.

(DNDE)

Total of 1 - 17 _____

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CLINICAL GLOBAL IMPRESSION: EFFICACY INDEX

Using the worksheet below, enter the 2-digit efficacy index rating.

1. Efficacy index rating ___ ___

(DNDE)

EFFICACY INDEX WORKSHEET

Rate this item on the basis of DRUG EFFECT ONLY.

Select the terms that best describe the degrees of therapeutic effect and side effects and record the number from the box where the two items intersect in the blanks above.

THERAPEUTIC EFFECT	SIDE EFFECTS			
	None	Do not significantly interfere with patient's functioning	Significantly interferes with patient's functioning	Outweighs therapeutic effect
MARKED - Vast improvement. Complete or nearly complete remission of all symptoms.	**01**	**02**	**03**	**04**
MODERATE - Decided improvement. Partial remission of symptoms.	**05**	**06**	**07**	**08**
MINIMAL - Slight improvement which doesn't alter status of care of patient.	**09**	**10**	**11**	**12**
UNCHANGED OR WORSE	**13**	**14**	**15**	**16**
Not Assessed = **98**				

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B1Y-MC-HCJE

CLINICAL GLOBAL IMPRESSION: SEVERITY

INFORMATION NOT OBTAINED ☐

Considering your total clinical experience with this particular population, how mentally ill is the patient at this time?

- ☐ 1 Normal, not at all ill
- ☐ 2 Borderline ill
- ☐ 3 Mildly ill
- ☐ 4 Moderately ill
- ☐ 5 Markedly ill
- ☐ 6 Severely ill
- ☐ 7 Among the most extremely ill patients

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First Middle Last

CLINICAL GLOBAL IMPRESSION: IMPROVEMENT

INFORMATION NOT OBTAINED ☐

Rate total improvement, whether or not in your judgement it is due entirely to drug treatment. Compared to the patient's condition at Visit 1, how much has he/she changed?

- ☐ 1 Very much improved
- ☐ 2 Much improved
- ☐ 3 Minimally improved
- ☐ 4 No change
- ☐ 5 Minimally worse
- ☐ 6 Much worse
- ☐ 7 Very much worse

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MONTGOMERY - ASBERG DEPRESSION RATING SCALE (MADRS)

INFORMATION NOT OBTAINED ☐

The rating should be based on a clinical interview moving from broadly phrased questions about symptoms to more detailed ones which allow a precise rating of severity. The rater must decide whether the rating lies on the defined scale steps (0, 2, 4, 6) or between them (1, 3, 5).

Check the box (number) that best characterizes the patient at this time

1. **APPARENT SADNESS**
   Representing despondency, gloom, and despair (more than just ordinary transient low spirits), reflected in speech, facial expression, and posture. Rate by depth and inability to brighten up.

   ☐ 0 No sadness.
   ☐ 1
   ☐ 2 Looks dispirited but does brighten up without difficulty.
   ☐ 3
   ☐ 4 Appears sad and unhappy most of the time.
   ☐ 5
   ☐ 6 Looks miserable all the time. Extremely despondent.

2. **REPORTED SADNESS**
   Represented by reports of depressed mood, regardless of whether it is reflected in appearance or not. Includes low spirits, despondency, or the feeling of being beyond help and without hope. Rate according to intensity, duration, and the extent to which the mood is reported to be influenced by events.

   ☐ 0 Occasional sadness in keeping with the circumstances.
   ☐ 1
   ☐ 2 Sad or low but brightens up without difficulty.
   ☐ 3
   ☐ 4 Pervasive feelings of sadness or gloominess. The mood is still influenced by external circumstances.
   ☐ 5
   ☐ 6 Continuous unvarying sadness, misery or despondency.

3. **INNER TENSION**
   Representing feelings of ill-defined discomfort, edginess, inner turmoil, mental tension mounting to either panic, dread, or anguish. Rate according to intensity, frequency, duration, and the extent of reassurance called for.

   ☐ 0 Placid. Only fleeting inner tension.
   ☐ 1
   ☐ 2 Occasional feelings of edginess and ill-defined discomfort.
   ☐ 3
   ☐ 4 Continuous feelings of inner tension or intermittent panic which the patient can only master with some difficulty.
   ☐ 5
   ☐ 6 Unrelenting dread or anguish. Overwhelming panic.

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MONTGOMERY - ASBERG DEPRESSION RATING SCALE (MADRS)

4. **REDUCED SLEEP**
Representing the experience of reduced duration or depth of sleep compared to the subject's own pattern when well.

- ☐ 0 Sleeps as usual.
- ☐ 1
- ☐ 2 Slight difficulty dropping off to sleep or slightly reduced, light or fitful sleep.
- ☐ 3
- ☐ 4 Sleep reduced or broken by at least two hours.
- ☐ 5
- ☐ 6 Less than two or three hours sleep.

5. **REDUCED APPETITE**
Representing the feeling of a loss of appetite compared with when well. Rate by loss of desire for food or the need to force oneself to eat.

- ☐ 0 Normal or increased appetite
- ☐ 1
- ☐ 2 Slightly reduced appetite.
- ☐ 3
- ☐ 4 No appetite. Food is tasteless.
- ☐ 5
- ☐ 6 Needs persuasion to eat at all.

6. **CONCENTRATION DIFFICULTIES**
Representing difficulties in collecting one's thoughts mounting to incapacitating lack of concentration.

- ☐ 0 No difficulties in concentrating.
- ☐ 1
- ☐ 2 Occasional difficulties in collecting one's thoughts.
- ☐ 3
- ☐ 4 Difficulties in concentrating and sustaining thought which reduces ability to read or hold a conversation.
- ☐ 5
- ☐ 6 Unable to read or converse without great difficulty.

7. **LASSITUDE**
Representing a difficulty getting started or slowness initiating and performing everyday activities.

- ☐ 0 Hardly any difficulty in getting started. No sluggishness.
- ☐ 1
- ☐ 2 Difficulties in starting activities
- ☐ 3
- ☐ 4 Difficulties in starting simple routine activities which are carried out with effort.
- ☐ 5
- ☐ 6 Complete lassitude. Unable to do anything without help.

8. **INABILITY TO FEEL**
Representing the subjective experience of reduced interest in the surroundings, or activities that normally give pleasure. The ability to react with adequate emotion to circumstances or people is reduced.

- ☐ 0 Normal interest in the surroundings and other people.
- ☐ 1
- ☐ 2 Reduced ability to enjoy usual interests.
- ☐ 3
- ☐ 4 Loss of interest in the surroundings. Loss of feelings for friends and acquaintances.
- ☐ 5
- ☐ 6 The experience of being emotionally paralyzed, inability to feel anger, grief, or pleasure and a complete or even painful failure to feel for close relatives and friends.

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MONTGOMERY - ASBERG DEPRESSION RATING SCALE (MADRS)

9. **PESSIMISTIC THOUGHTS**
Representing thoughts of guilt, inferiority, self-reproach, sinfulness, remorse, and ruin

- ☐ 0 No pessimistic thoughts.
- ☐ 1
- ☐ 2 Fluctuating ideas of failure, self-reproach, or self-depreciation.
- ☐ 3
- ☐ 4 Persistent self-accusations, or definite but still rational ideas of guilt, or sin. Increasingly pessimistic about the future.
- ☐ 5
- ☐ 6 Delusions of ruin, remorse, or unredeemable sin. Self-accusations which are absurd and unshakable.

10. **SUICIDAL THOUGHTS**
Representing the feeling that life is not worth living, that a natural death would be welcome, suicidal thoughts, and preparations for suicide. Suicidal attempts should not in themselves influence the rating.

- ☐ 0 Enjoys life or takes it as it comes.
- ☐ 1
- ☐ 2 Weary of life. Only fleeting suicidal thoughts.
- ☐ 3
- ☐ 4 Probably better off dead. Suicidal thoughts are common, and suicide is considered as a possible solution, but without specific plans or intention.
- ☐ 5
- ☐ 6 Explicit plans for suicide when there is an opportunity. Active preparations for suicide.

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COMMENTS : VISIT

NO COMMENTS ☐

Comments should address any clinical report form items that require further explanation. Repeating information from the clinical report form is discouraged.

Comment on all clinically significant lab values that are outside a clinically accepted reference range or clinically significant values that differ importantly from previous values.

If the patient is ending participation in the study at this visit, enter only comments that apply to this visit; then complete the Patient Summary and Study Summary Comments pages.

Print legibly and do not use abbreviations or symbols.

The information reported for this visit is accurate and complete.

_____ _____/_____/_____
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PATIENT AND VISIT IDENTIFICATION

Patient initials _____ _____ _____
First Middle Last

Visit date _____/_____/_____
MM DD YY

K-SADS : AFFECTIVE DISORDERS

INFORMATION NOT OBTAINED ☐

Check the appropriate boxes.

Depressive Disorders - Current	☐ 1 Yes	☐ 2 No
Depressive Disorders - Past	☐ 1 Yes	☐ 2 No
Mania - Current	☐ 1 Yes	☐ 2 No
Mania -Past	☐ 1 Yes	☐ 2 No

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First Middle Last

Initials
Date Verified
Initials
Date Keyed
Date Received at Lilly
Reviewed
Inspected
Date

REMINDER

On the Pre-existing Conditions and Study Adverse Events pages, record new events that occurred since the previous visit and re-evaluate any on-going conditions or events.

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Fluoxetine Versus Placebo in Childhood/Adolescent Depression
B1Y-MC-HCJE

GLOBAL ASSESSMENT OF FUNCTIONING SCALE (GAF SCALE)

INFORMATION NOT OBTAINED ☐

Enter the number (between 1 and 90) that best represents the patient's:

1. **Current** level of functioning _____
2. **Highest** level of functioning in *past year* _____

Level of Functioning Definitions	
90 – 81	Absent or minimal symptoms, good functioning in all areas, interested and involved in a wide range of activities, socially effective, generally satisfied with life, no more than everyday problems or concerns.
80 – 71	If symptoms are present, they are transient and expectable reactions to psychosocial stressors; no more than slight impairment in social, occupational, or school functioning.
70 – 61	Some mild symptoms OR some difficulty in social, occupational, or school functioning, but generally functioning pretty well, has some meaningful interpersonal relationships.
60 – 51	Moderate symptoms OR any moderate difficulty in social, occupational, or school functioning.
50 – 41	Serious symptoms OR any serious impairment in social, occupational, or school functioning.
40 – 31	Some impairment in reality testing or communication OR major impairment in several areas, such as work or school, family relations, judgment, thinking, or mood.
30 – 21	Behavior is considered influenced by delusions or hallucinations OR serious impairment in communications or judgment OR inability to function in almost all areas.
20 – 11	Some danger of hurting self or other OR occasionally fails to maintain minimal personal hygiene OR gross impairment in communication.
10 – 1	Persistent danger of severely hurting self or others OR persistent inability to maintain minimum personal hygiene OR serious suicidal act with clear expectation of death.

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VITAL SIGNS : BLOOD PRESSURE AND HEART RATE

INFORMATION NOT OBTAINED ☐

Position
SI = Sitting

Position	Blood Pressure (mm Hg) Systolic/Diastolic	Heart Rate (bpm)
SI	/	

VITAL SIGNS: TEMPERATURE

INFORMATION NOT OBTAINED ☐

Temperature ___ ___ ___ . ___

Unit of measure (F) Fahrenheit

Method (E) Ear

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B1Y-MC-HCJE

STUDY DRUG : DATES OF MISSED DOSES

NO MISSED DOSES ☐

Record the date for any day on which the patient missed a full or partial dose of study drug.

	Dates of Missed Doses MM	DD	YY
0.			
1.			
2.			
3.			
4.			
5.			
6.			
7.			
8.			
9.			

NOTE: If the patient has missed 3 or more consecutive days of medication, the patient must be discontinued from the study.

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Clinical Report Form
Fluoxetine Versus Placebo in Childhood/Adolescent Depression
B1Y-MC-HCJE

SIDE EFFECTS CHECKLIST

INFORMATION NOT OBTAINED ☐

Since your last visit, have you been bothered with or had any trouble with any of the items listed below? Check the box which best tells how much you were bothered.

	Not at all	Just a little	Pretty much	Very much	Don't know
1. Eating?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
2. Drinking?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
3. Dry mouth and lips?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
4. Wetness in mouth?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
5. Constipation?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
6. Diarrhea?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
7. Stomachaches?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
8. Muscle cramps?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
9. Being sick to your stomach?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
10. Wetting the bed?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
11. Urinating?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
12. Itchy or scratchy skin?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
13. Rashes?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
14. Cold or sniffles?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
15. Headache?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4

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Clinical Report Form
Fluoxetine Versus Placebo in Childhood/Adolescent Depression
B1Y-MC-HCJE

SIDE EFFECTS CHECKLIST

	Not at all	Just a little	Pretty much	Very much	Don't know
16. Dizziness?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
17. Playing sports?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
18. Shakiness?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
19. Pronouncing words?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
20. Doing things with your hands?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
21. Sitting still?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
22. Tiredness?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
23. Feeling sleepy?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
24. Trouble sleeping?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
25. Bad dreams?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
26. Getting along with parents?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
27. Getting along with kids?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
28. Crying?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
29. Getting mad?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
30. Not being happy?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
31. Being sad?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
32. Paying attention?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4

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Clinical Report Form
Fluoxetine Versus Placebo in Childhood/Adolescent Depression
B1Y-MC-HCJE

CHILDRENS DEPRESSION RATING SCALE - REVISED

INFORMATION NOT OBTAINED ☐

CHECK THE NUMERIC CODE which best describes the patient.

1. **SCHOOLWORK**:

☐ 1 Performance consistent with ability
☐ 2
☐ 3 Decrease in school performance
☐ 4
☐ 5 Major interference in most subjects
☐ 6
☐ 7 No motivation to perform

2. **CAPACITY TO HAVE FUN**

☐ 1 Interest and activities realistically appropriate for age, personality, and social environment. Shows no appreciable change with present illness.
☐ 2
☐ 3 Describes some activities realistically available several times a week but not on a daily basis. Shows interest but not enthusiasm.
☐ 4
☐ 5 Is easily bored. Complains of "nothing to do." Participates in structured activities with a "going through the motions" attitude. May express interest primarily in activities that are (realistically) unavailable on a daily or weekly basis.
☐ 6
☐ 7 Has no initiative to become involved in any activities. Primarily passive. Watches others play or watches TV but shows little interest. Requires coaxing and/or pushing to get involved in activity. Shows no enthusiasm or real interest. Has difficulty naming activities.

3. **SOCIAL WITHDRAWAL**

☐ 1 Enjoys friendships with peers at school and home
☐ 2
☐ 3 May not actively seek out friendships but waits for others to initiate a relationship or may occasionally reject opportunities to play without a describable alternative
☐ 4
☐ 5 Frequently avoids or refuses opportunities for desirable interaction with others and/or sets up situations where rejection is inevitable.
☐ 6
☐ 7 Does not currently relate to other children. States he or she has "no friends" or actively rejects new or former friends.

4. **SLEEP**

☐ 1 No (or occasional) difficulty. (Goes to sleep within 1/2 hour or less.)
☐ 2
☐ 3 Frequently has mild difficulty with sleep
☐ 4
☐ 5 Moderate difficulty with sleep nearly every night.

5. **APPETITE OR EATING PATTERNS**

☐ 1 No problems or change in eating pattern
☐ 2
☐ 3 Mild change from usual eating habits within onset of current behavioral problem
☐ 4
☐ 5 Is not hungry most of the time or has excessive food intake since onset of current behavioral problems or marked increase in appetite

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CHILDRENS DEPRESSION RATING SCALE - REVISED

CHECK THE NUMERIC CODE which best describes the patient.

6. **EXCESSIVE FATIGUE**

- ☐ 1 No unusual complaints of "feeling tired" during the day
- ☐ 2
- ☐ 3 Complaints of fatigue which seem somewhat excessive and not related to boredom
- ☐ 4
- ☐ 5 Daily complaints of feeling tired
- ☐ 6
- ☐ 7 Complains of feeling tired most of the day. May voluntarily take long naps without feeling refreshed. Interferes with play activities.

7. **PHYSICAL COMPLAINTS**:

- ☐ 1 Occasional complaints
- ☐ 2
- ☐ 3 Complaints appear mildly excessive
- ☐ 4
- ☐ 5 Complains daily. Some interference with the ability of the child to function
- ☐ 6
- ☐ 7 Preoccupied with aches and pains; interferes with play activities several times a week

8. **IRRITABILITY**

- ☐ 1 Rare
- ☐ 2 Occasional
- ☐ 3 Several times a week for short periods
- ☐ 4
- ☐ 5 Several times a week for longer periods
- ☐ 6
- ☐ 7 Constant

9. **GUILT**

- ☐ 1 Does not express any undue feeling of guilt. Appears appropriate to precipitating event.
- ☐ 2
- ☐ 3 Exaggerates guilt and/or shame out of proportion to the event described.
- ☐ 4
- ☐ 5 Feels guilty over things not under his or her control. Guilt is definitely pathological.
- ☐ 6
- ☐ 7 Severe delusions of guilt

10. **SELF-ESTEEM**

- ☐ 1 Describes self in primarily positive terms
- ☐ 2
- ☐ 3 Describes self with one important area where the child feels deficit
- ☐ 4
- ☐ 5 Describes self in preponderance of negative terms or gives bland answers to questions
- ☐ 6
- ☐ 7 Refers to self in derogatory terms. Reports that other children refer to him/her frequently by using derogatory nicknames and child puts self down

11. **DEPRESSED FEELINGS**

- ☐ 1 Occasional feelings of unhappiness which quickly disappear
- ☐ 2
- ☐ 3 Describes sustained periods of unhappiness which appear excessive for events described
- ☐ 4
- ☐ 5 Feels unhappy most of the time without a major precipitating cause
- ☐ 6
- ☐ 7 Feels unhappy all of the time. Accompanied by psychic pain (e.g., "I can't stand it").

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Clinical Report Form
Fluoxetine Versus Placebo in Childhood/Adolescent Depression
B1Y-MC-HCJE

CHILDRENS DEPRESSION RATING SCALE - REVISED

CHECK THE NUMERIC CODE which best describes the patient.

12. **MORBID IDEATION**

- ☐ 1 None
- ☐ 2
- ☐ 3 Has some morbid thought, all of which relate to a reality event but seem excessive.
- ☐ 4
- ☐ 5 Preoccupied with morbid thoughts several times a week. Morbid thoughts extend beyond external reality
- ☐ 6
- ☐ 7 Preoccupied with death themes or morbid thoughts that are elaborate, extensive or bizarre on a daily basis

13. **SUICIDAL IDEATION**

- ☐ 1 Understands the word "suicide" but does not apply term to self
- ☐ 2 Sharp denial of suicidal thoughts
- ☐ 3 Has thoughts about suicide, usually when angry.
- ☐ 4
- ☐ 5 Has recurrent thoughts of suicide
- ☐ 6
- ☐ 7 Has made suicide attempt within the last month or is actively suicidal

14. **WEEPING**:

- ☐ 1 Normal for age.
- ☐ 2 Suggestive statements that child cries, or feels like crying, more frequently than peers.
- ☐ 3 Child cries slightly more than peers.
- ☐ 4
- ☐ 5 Cries or feels like crying frequently (several times a week). Admits to crying without knowing reason why.
- ☐ 6
- ☐ 7 Cries nearly every day.

15. **DEPRESSED AFFECT:**

- ☐ 1 Definitely not depressed. Facial expression and voice animated during interview.
- ☐ 2 Mild suppression of affect. Some loss of spontaneity.
- ☐ 3 Overall loss of spontaneity. Looks distinctly unhappy during parts of the interview. May still be able to smile when discussing non-threatening areas.
- ☐ 4
- ☐ 5 Moderate restriction of affect throughout most of interview. Has longer and frequent periods of looking distinctly unhappy.
- ☐ 6
- ☐ 7 Severe. Looks sad, withdrawn. Minimal verbal interaction throughout interview. Cries or may appear tearful.

16. **TEMPO OF SPEECH:**

- ☐ 1 Normal
- ☐ 2 Slow
- ☐ 3 Slow: delays interview.
- ☐ 4
- ☐ 5 Severe. Low; marked interference with interview.

17. **HYPOACTIVITY:**

- ☐ 1 None
- ☐ 2
- ☐ 3 Mild. Some body movements.
- ☐ 4
- ☐ 5 Moderate. Definite motor retardation.
- ☐ 6
- ☐ 7 Severe. Motionless throughout interview.

(DNDE)

Total of 1 - 17 _____

Evaluator's initials _____ _____ _____
First Middle Last

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Clinical Report Form
Fluoxetine Versus Placebo in Childhood/Adolescent Depression
B1Y-MC-HCJE

CLINICAL GLOBAL IMPRESSION: EFFICACY INDEX

Using the worksheet below, enter the 2-digit efficacy index rating.

1. Efficacy index rating ___ ___

(DNDE)

EFFICACY INDEX WORKSHEET

Rate this item on the basis of DRUG EFFECT ONLY.

Select the terms that best describe the degrees of therapeutic effect and side effects and record the number from the box where the two items intersect in the blanks above.

THERAPEUTIC EFFECT	SIDE EFFECTS			
	None	Do not significantly interfere with patient's functioning	Significantly interferes with patient's functioning	Outweighs therapeutic effect
MARKED - Vast improvement. Complete or nearly complete remission of all symptoms.	**01**	**02**	**03**	**04**
MODERATE - Decided improvement. Partial remission of symptoms.	**05**	**06**	**07**	**08**
MINIMAL - Slight improvement which doesn't alter status of care of patient.	**09**	**10**	**11**	**12**
UNCHANGED OR WORSE	**13**	**14**	**15**	**16**
Not Assessed = **98**				

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CLINICAL GLOBAL IMPRESSION: SEVERITY

INFORMATION NOT OBTAINED ☐

Considering your total clinical experience with this particular population, how mentally ill is the patient at this time?

- ☐ 1 Normal, not at all ill
- ☐ 2 Borderline ill
- ☐ 3 Mildly ill
- ☐ 4 Moderately ill
- ☐ 5 Markedly ill
- ☐ 6 Severely ill
- ☐ 7 Among the most extremely ill patients

Evaluator's initials _____ _____ _____
First Middle Last

CLINICAL GLOBAL IMPRESSION: IMPROVEMENT

INFORMATION NOT OBTAINED ☐

Rate total improvement, whether or not in your judgement it is due entirely to drug treatment. Compared to the patient's condition at Visit 1, how much has he/she changed?

- ☐ 1 Very much improved
- ☐ 2 Much improved
- ☐ 3 Minimally improved
- ☐ 4 No change
- ☐ 5 Minimally worse
- ☐ 6 Much worse
- ☐ 7 Very much worse

Evaluator's initials _____ _____ _____
First Middle Last

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MONTGOMERY - ASBERG DEPRESSION RATING SCALE (MADRS)

INFORMATION NOT OBTAINED ☐

The rating should be based on a clinical interview moving from broadly phrased questions about symptoms to more detailed ones which allow a precise rating of severity. The rater must decide whether the rating lies on the defined scale steps (0, 2, 4, 6) or between them (1, 3, 5).

Check the box (number) that best characterizes the patient at this time

1. **APPARENT SADNESS**
   Representing despondency, gloom, and despair (more than just ordinary transient low spirits), reflected in speech, facial expression, and posture. Rate by depth and inability to brighten up.

   ☐ 0 No sadness.
   ☐ 1
   ☐ 2 Looks dispirited but does brighten up without difficulty.
   ☐ 3
   ☐ 4 Appears sad and unhappy most of the time.
   ☐ 5
   ☐ 6 Looks miserable all the time. Extremely despondent.

2. **REPORTED SADNESS**
   Represented by reports of depressed mood, regardless of whether it is reflected in appearance or not. Includes low spirits, despondency, or the feeling of being beyond help and without hope. Rate according to intensity, duration, and the extent to which the mood is reported to be influenced by events.

   ☐ 0 Occasional sadness in keeping with the circumstances.
   ☐ 1
   ☐ 2 Sad or low but brightens up without difficulty.
   ☐ 3
   ☐ 4 Pervasive feelings of sadness or gloominess. The mood is still influenced by external circumstances.
   ☐ 5
   ☐ 6 Continuous unvarying sadness, misery or despondency.

3. **INNER TENSION**
   Representing feelings of ill-defined discomfort, edginess, inner turmoil, mental tension mounting to either panic, dread, or anguish. Rate according to intensity, frequency, duration, and the extent of reassurance called for.

   ☐ 0 Placid. Only fleeting inner tension.
   ☐ 1
   ☐ 2 Occasional feelings of edginess and ill-defined discomfort.
   ☐ 3
   ☐ 4 Continuous feelings of inner tension or intermittent panic which the patient can only master with some difficulty.
   ☐ 5
   ☐ 6 Unrelenting dread or anguish. Overwhelming panic.

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MONTGOMERY - ASBERG DEPRESSION RATING SCALE (MADRS)

4. **REDUCED SLEEP**
Representing the experience of reduced duration or depth of sleep compared to the subject's own pattern when well.

- ☐ 0 Sleeps as usual.
- ☐ 1
- ☐ 2 Slight difficulty dropping off to sleep or slightly reduced, light or fitful sleep.
- ☐ 3
- ☐ 4 Sleep reduced or broken by at least two hours.
- ☐ 5
- ☐ 6 Less than two or three hours sleep.

5. **REDUCED APPETITE**
Representing the feeling of a loss of appetite compared with when well. Rate by loss of desire for food or the need to force oneself to eat.

- ☐ 0 Normal or increased appetite
- ☐ 1
- ☐ 2 Slightly reduced appetite.
- ☐ 3
- ☐ 4 No appetite. Food is tasteless.
- ☐ 5
- ☐ 6 Needs persuasion to eat at all.

6. **CONCENTRATION DIFFICULTIES**
Representing difficulties in collecting one's thoughts mounting to incapacitating lack of concentration.

- ☐ 0 No difficulties in concentrating.
- ☐ 1
- ☐ 2 Occasional difficulties in collecting one's thoughts.
- ☐ 3
- ☐ 4 Difficulties in concentrating and sustaining thought which reduces ability to read or hold a conversation.
- ☐ 5
- ☐ 6 Unable to read or converse without great difficulty.

7. **LASSITUDE**
Representing a difficulty getting started or slowness initiating and performing everyday activities.

- ☐ 0 Hardly any difficulty in getting started. No sluggishness.
- ☐ 1
- ☐ 2 Difficulties in starting activities
- ☐ 3
- ☐ 4 Difficulties in starting simple routine activities which are carried out with effort.
- ☐ 5
- ☐ 6 Complete lassitude. Unable to do anything without help.

8. **INABILITY TO FEEL**
Representing the subjective experience of reduced interest in the surroundings, or activities that normally give pleasure. The ability to react with adequate emotion to circumstances or people is reduced.

- ☐ 0 Normal interest in the surroundings and other people.
- ☐ 1
- ☐ 2 Reduced ability to enjoy usual interests.
- ☐ 3
- ☐ 4 Loss of interest in the surroundings. Loss of feelings for friends and acquaintances.
- ☐ 5
- ☐ 6 The experience of being emotionally paralyzed, inability to feel anger, grief, or pleasure and a complete or even painful failure to feel for close relatives and friends.

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Fluoxetine Versus Placebo in Childhood/Adolescent Depression
B1Y-MC-HCJE

MONTGOMERY - ASBERG DEPRESSION RATING SCALE (MADRS)

9. **PESSIMISTIC THOUGHTS**
Representing thoughts of guilt, inferiority, self-reproach, sinfulness, remorse, and ruin

- ☐ 0 No pessimistic thoughts.
- ☐ 1
- ☐ 2 Fluctuating ideas of failure, self-reproach, or self-depreciation.
- ☐ 3
- ☐ 4 Persistent self-accusations, or definite but still rational ideas of guilt, or sin. Increasingly pessimistic about the future.
- ☐ 5
- ☐ 6 Delusions of ruin, remorse, or unredeemable sin. Self-accusations which are absurd and unshakable.

10. **SUICIDAL THOUGHTS**
Representing the feeling that life is not worth living, that a natural death would be welcome, suicidal thoughts, and preparations for suicide. Suicidal attempts should not in themselves influence the rating.

- ☐ 0 Enjoys life or takes it as it comes.
- ☐ 1
- ☐ 2 Weary of life. Only fleeting suicidal thoughts.
- ☐ 3
- ☐ 4 Probably better off dead. Suicidal thoughts are common, and suicide is considered as a possible solution, but without specific plans or intention.
- ☐ 5
- ☐ 6 Explicit plans for suicide when there is an opportunity. Active preparations for suicide.

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Clinical Report Form
Fluoxetine Versus Placebo in Childhood/Adolescent Depression
B1Y-MC-HCJE

CHILDREN'S DEPRESSION INDEX (CDI)

NOTE: Only complete if patient was 8 to 12 years old at Visit 1. If patient was not 8 to 12 years old, check the Information Not Obtained box.

INFORMATION NOT OBTAINED ☐

This lists the feelings and ideas in groups. From each group of three sentences, pick one sentence that describes you **best** for the past two weeks. After you pick a sentence from the first group, go on to the next group. There is no right answer or wrong answer. Just pick the sentence that best describes the way you have been recently. Put an "X" in the box next to your answer.
Remember: pick out the sentences that describe you best **in the past two weeks**.

Item 1

- ☐ 0 I am sad once in a while.
- ☐ 1 I am sad many times.
- ☐ 2 I am sad all the time.

Item 2

- ☐ 2 Nothing will ever work out for me.
- ☐ 1 I am not sure if things will work out for me.
- ☐ 0 Things will work out for me O.K.

Item 3

- ☐ 0 I do most things O.K.
- ☐ 1 I do many things wrong.
- ☐ 2 I do everything wrong.

Item 4

- ☐ 0 I have fun in many things.
- ☐ 1 I have fun in some things.
- ☐ 2 Nothing is fun at all.

Item 5

- ☐ 2 I am bad all the time.
- ☐ 1 I am bad many times.
- ☐ 0 I am bad once in a while.

Item 6

- ☐ 0 I think about bad things happening to me once in a while.
- ☐ 1 I worry that bad things will happen to me.
- ☐ 2 I am sure that terrible things will happen to me.

Item 7

- ☐ 2 I hate myself.
- ☐ 1 I do not like myself.
- ☐ 0 I like myself.

Item 8

- ☐ 2 All bad things are my fault.
- ☐ 1 Many bad things are my fault.
- ☐ 0 Bad things are not usually my fault.

Item 9

- ☐ 0 I do not think about killing myself.
- ☐ 1 I think about killing myself but I would not do it.
- ☐ 2 I want to kill myself.

Item 10

- ☐ 2 I feel like crying every day.
- ☐ 1 I feel like crying many days.
- ☐ 0 I feel like crying once in a while.

Item 11

- ☐ 2 Things bother me all the time.
- ☐ 1 Things bother me many times.
- ☐ 0 Things bother me once in a while.

Item 12

- ☐ 0 I like being with people.
- ☐ 1 I do not like being with people many times.
- ☐ 2 I do not want to be with people at all.

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CHILDREN'S DEPRESSION INDEX (CDI)

Item 13

- ☐ 2 I cannot make up my mind about things.
- ☐ 1 It is hard to make up my mind about things.
- ☐ 0 I make up my mind about things easily.

Item 14

- ☐ 0 I look O.K.
- ☐ 1 There are some bad things about my looks.
- ☐ 2 I look ugly.

Item 15

- ☐ 2 I have to push myself all the time to do my schoolwork.
- ☐ 1 I have to push myself many times to do my schoolwork.
- ☐ 0 Doing schoolwork is not a big problem.

Item 16

- ☐ 2 I have trouble sleeping every night.
- ☐ 1 I have trouble sleeping many nights.
- ☐ 0 I sleep pretty well.

Item 17

- ☐ 0 I am tired once in a while.
- ☐ 1 I am tired many days.
- ☐ 2 I am tired all the time.

Item 18

- ☐ 2 Most days I do not feel like eating.
- ☐ 1 Many days I do not feel like eating.
- ☐ 0 I eat pretty well.

Item 19

- ☐ 0 I do not worry about aches and pains.
- ☐ 1 I worry about aches and pains many times.
- ☐ 2 I worry about aches and pains all the time.

Item 20

- ☐ 0 I do not feel alone.
- ☐ 1 I feel alone many times.
- ☐ 2 I feel alone all the time.

Item 21

- ☐ 2 I never have fun at school.
- ☐ 1 I have fun at school only once in a while.
- ☐ 0 I have fun at school many times.

Item 22

- ☐ 0 I have plenty of friends.
- ☐ 1 I have some friends but I wish I had more.
- ☐ 2 I do not have any friends.

Item 23

- ☐ 0 My schoolwork is alright.
- ☐ 1 My schoolwork is not as good as before.
- ☐ 2 I do very badly in subjects I used to be good in.

Item 24

- ☐ 2 I can never be as good as other kids.
- ☐ 1 I can be as good as other kids if I want to.
- ☐ 0 I am just as good as other kids.

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CHILDREN'S DEPRESSION INDEX (CDI)

Item 25

- ☐ 2 Nobody really loves me.
- ☐ 1 I am not sure if anybody loves me.
- ☐ 0 I am sure that somebody loves me.

Item 26

- ☐ 0 I usually do what I am told.
- ☐ 1 I do not do what I am told most times.
- ☐ 2 I never do what I am told.

Item 27

- ☐ 0 I get along with people.
- ☐ 1 I get into fights many times.
- ☐ 2 I get into fights all the time.

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BECK DEPRESSION INVENTORY

NOTE: Only complete if patient was 13 to 17 years old at Visit 1. If patient was not 13 to 17 years old, check the Information Not Obtained box.

INFORMATION NOT OBTAINED ☐

This questionnaire consists of 21 groups of statements. After reading each group of statements carefully circle the number (0, 1, 2, 3) next to the one statement in each group which best describes the way you have been feeling **the past week, including today**. If several statements within a group seem to apply equally well, circle each one. Be sure to read all the statements in each group before making your choice.

1

0 I do not feel sad.
1 I feel sad.
2 I am sad all the time and I can't snap out of it.
3 I am so sad or unhappy that I can't stand it.

2

0 I am not particularly discouraged about the future.
1 I feel discouraged about the future.
2 I feel I have nothing to look forward to.
3 I feel that the future is hopeless and that things cannot improve.

3

0 I do not feel like a failure.
1 I feel I have failed more than the average person.
2 As I look back on my life, all I can see is a lot of failures.
3 I feel I am a complete failure as a person.

4

0 I get as much satisfaction out of things as I used to.
1 I don't enjoy things the way I used to.
2 I don't get real satisfaction out of anything anymore.
3 I am dissatisfied or bored with everything.

5

0 I don't feel particularly guilty.
1 I feel guilty a good part of the time.
2 I feel quite guilty most of the time.
3 I feel guilty all of the time.

6

0 I don't feel I am being punished.
1 I feel I may be punished.
2 I expect to be punished.
3 I feel I am being punished.

7

0 I don't feel disappointed in myself.
1 I am disappointed in myself.
2 I am disgusted with myself.
3 I hate myself.

8

0 I don't feel I am any worse than anybody else.
1 I am critical of myself for my weaknesses or mistakes.
2 I blame myself all the time for my faults.
3 I blame myself for everything bad that happens.

9

0 I don't have any thoughts of killing myself.
1 I have thoughts of killing myself, but I would not carry them out.
2 I would like to kill myself.
3 I would kill myself if I had the chance.

10

0 I don't cry any more than usual.
1 I cry more now than I used to.
2 I cry all the time now.
3 I used to be able to cry, but now I can't cry even though I want to.

11

0 I am no more irritated now than I ever am.
1 I get annoyed or irritated more easily than I used to.
2 I feel irritated all the time now.
3 I don't get irritated at all by the things that used to irritate me.

12

0 I have not lost interest in other people.
1 I am less interested in other people than I used to be.
2 I have lost most of my interest in other people.
3 I have lost all of my interest in other people.

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BECK DEPRESSION INVENTORY

13

0 I make decisions about as well as I ever could.
1 I put off making decisions more than I used to.
2 I have greater difficulty in making decisions than before.
3 I can't make decisions at all anymore.

14

0 I don't feel I look any worse than I used to.
1 I am worried that I am looking old or unattractive.
2 I feel that there are permanent changes in my appearance that make me look unattractive.
3 I believe that I look ugly.

15

0 I can work about as well as before.
1 It takes an extra effort to get started at doing something.
2 I have to push myself very hard to do anything.
3 I can't do any work at all.

16

0 I can sleep as well as usual.
1 I don't sleep as well as I used to.
2 I wake up 1-2 hours earlier than usual and find it hard to get back to sleep.
3 I wake up several hours earlier than I used to and cannot get back to sleep.

17

0 I don't get more tired than usual.
1 I get tired more easily than I used to.
2 I get tired from doing almost anything.
3 I am too tired to do anything.

18

0 My appetite is no worse than usual.
1 My appetite is not as good as it used to be.
2 My appetite is much worse now.
3 I have no appetite at all anymore.

19

0 I haven't lost much weight, if any, lately.
1 I have lost more than 5 pounds.
2 I have lost more than 10 pounds.
3 I have lost more than 15 pounds.

19a

I am purposely trying to lose weight by eating less.
1 Yes
2 No

20

0 I am no more worried about my health than usual.
1 I am worried about physical problems such as aches and pains; or upset stomach or constipation.
2 I am very worried about physical problems and it's hard to think of much else.
3 I am so worried about my physical problems that I cannot think about anything else.

21

0 I have not noticed any recent change in my interest in sex.
1 I am less interested in sex than I used to be.
2 I am much less interested in sex now.
3 I have lost interest in sex completely.

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HAMILTON ANXIETY SCALE

INFORMATION NOT OBTAINED ☐

For each of the items below, **CHECK ONE BOX** that best describes the patient.

1. **ANXIOUS MOOD:** Worries, anticipation of the worst, fearful anticipation, irritability

   ☐ 0 Not present
   ☐ 1 Mild
   ☐ 2 Moderate
   ☐ 3 Severe
   ☐ 4 Very severe

2. **TENSION**: Feelings of tension, fatigability, startle response, moved to tears easily, trembling, feeling of restlessness, inability to relax

   ☐ 0 Not present
   ☐ 1 Mild
   ☐ 2 Moderate
   ☐ 3 Severe
   ☐ 4 Very severe

3. **FEARS**: Of dark, of strangers, of being alone, of animals, of traffic, of crowds

   ☐ 0 Not present
   ☐ 1 Mild
   ☐ 2 Moderate
   ☐ 3 Severe
   ☐ 4 Very severe

4. **INSOMNIA**: Difficulty in falling asleep, broken sleep, unsatisfying sleep and fatigue on waking, dreams, nightmares, night terrors

   ☐ 0 Not present
   ☐ 1 Mild
   ☐ 2 Moderate
   ☐ 3 Severe
   ☐ 4 Very severe

5. **INTELLECTUAL (COGNITIVE)**: Difficulty in concentration, poor memory

   ☐ 0 Not present
   ☐ 1 Mild
   ☐ 2 Moderate
   ☐ 3 Severe
   ☐ 4 Very severe

6. **DEPRESSED MOOD**: Loss of interest, lack of pleasure in hobbies, depression, early waking, diurnal swing

   ☐ 0 Not present
   ☐ 1 Mild
   ☐ 2 Moderate
   ☐ 3 Severe
   ☐ 4 Very severe

7. **SOMATIC (MUSCULAR)**: Pains and aches, twitchings, stiffness, myoclonic jerks, grinding of teeth, unsteady voice, increased muscular tone

   ☐ 0 Not present
   ☐ 1 Mild
   ☐ 2 Moderate
   ☐ 3 Severe
   ☐ 4 Very severe

8. **SOMATIC (SENSORY)**: Tinnitus, blurring of vision, hot and cold flushes, feeling of weakness, pricking sensation

   ☐ 0 Not present
   ☐ 1 Mild
   ☐ 2 Moderate
   ☐ 3 Severe
   ☐ 4 Very severe

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HAMILTON ANXIETY SCALE

9. **CARDIOVASCULAR SYMPTOMS:** Tachycardia, palpitations, pain in chest, throbbing of vessels, fainting feelings, missing beat

- ☐ 0 Not present
- ☐ 1 Mild
- ☐ 2 Moderate
- ☐ 3 Severe
- ☐ 4 Very severe

10. **RESPIRATORY SYMPTOMS:** Pressure or constriction in chest, choking feelings, sighing, dyspnea

- ☐ 0 Not present
- ☐ 1 Mild
- ☐ 2 Moderate
- ☐ 3 Severe
- ☐ 4 Very severe

11. **GASTROINTESTINAL SYMPTOMS:** Difficulty in swallowing, wind, abdominal pain, burning sensations, abdominal fullness, nausea, vomiting, borborygmi, looseness of bowels, loss of weight, constipation

- ☐ 0 Not present
- ☐ 1 Mild
- ☐ 2 Moderate
- ☐ 3 Severe
- ☐ 4 Very severe

12. **GENITOURINARY SYMPTOMS:** Frequency of micturition, urgency of micturition, amenorrhea, menorrhagia, development of frigidity, premature ejaculation, loss of libido, impotence

- ☐ 0 Not present
- ☐ 1 Mild
- ☐ 2 Moderate
- ☐ 3 Severe
- ☐ 4 Very severe

13. **AUTONOMIC SYMPTOMS:** Dry mouth, flushing, pallor, tendency to sweat, giddiness, tension headache, raising of hair

- ☐ 0 Not present
- ☐ 1 Mild
- ☐ 2 Moderate
- ☐ 3 Severe
- ☐ 4 Very severe

14. **BEHAVIOR AT INTERVIEW:** Fidgeting, restlessness or pacing, tremor of hands, furrowed brow, strained face, sighing or rapid respiration, facial pallor, swallowing, belching, brisk tendon jerks, dilated pupils, exophthalmos

- ☐ 0 Not present
- ☐ 1 Mild
- ☐ 2 Moderate
- ☐ 3 Severe
- ☐ 4 Very severe

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COMMENTS : VISIT

NO COMMENTS ☐

Comments should address any clinical report form items that require further explanation. Repeating information from the clinical report form is discouraged.

Comment on all clinically significant lab values that are outside a clinically accepted reference range or clinically significant values that differ importantly from previous values.

If the patient is ending participation in the study at this visit, enter only comments that apply to this visit; then complete the Patient Summary and Study Summary Comments pages.

Print legibly and do not use abbreviations or symbols.

The information reported for this visit is accurate and complete.

_____ _____/_____/_____
Signature MM DD YY

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B1Y-MC-HCJE

PATIENT AND VISIT IDENTIFICATION

Patient initials _____ _____ _____
First Middle Last

Visit date _____/_____/_____
MM DD YY

VITAL SIGNS : BLOOD PRESSURE AND HEART RATE

INFORMATION NOT OBTAINED ☐

Position
SI = Sitting

Position	Blood Pressure (mm Hg) Systolic/Diastolic	Heart Rate (bpm)
SI	/	

VITAL SIGNS: TEMPERATURE

INFORMATION NOT OBTAINED ☐

Temperature ___ ___ ___ . ___

Unit of measure (F) Fahrenheit

Method (E) Ear

REMINDER

On the Pre-existing Conditions and Study Adverse Events pages, record new events that occurred since the previous visit and re-evaluate any on-going conditions or events.

On the Concomitant Medication pages, record new medications the patient has taken since the previous visit, any changes to ongoing medications, and a stop date for any medication the patient is no longer taking.

Initials
Date Verified
Initials
Date Keyed
Date Received at Lilly
Reviewed
Inspected
Date

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B1Y-MC-HCJE

STUDY DRUG : DATES OF MISSED DOSES

NO MISSED DOSES ☐

Record the date for any day on which the patient missed a full or partial dose of study drug.

	Dates of Missed Doses MM	DD	YY
0.			
1.			
2.			
3.			
4.			
5.			
6.			
7.			
8.			
9.			

NOTE: If the patient has missed 3 or more consecutive days of medication, the patient must be discontinued from the study.

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B1Y-MC-HCJE

SIDE EFFECTS CHECKLIST

INFORMATION NOT OBTAINED ☐

Since your last visit, have you been bothered with or had any trouble with any of the items listed below? Check the box which best tells how much you were bothered.

	Not at all	Just a little	Pretty much	Very much	Don't know
1. Eating?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
2. Drinking?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
3. Dry mouth and lips?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
4. Wetness in mouth?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
5. Constipation?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
6. Diarrhea?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
7. Stomachaches?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
8. Muscle cramps?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
9. Being sick to your stomach?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
10. Wetting the bed?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
11. Urinating?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
12. Itchy or scratchy skin?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
13. Rashes?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
14. Cold or sniffles?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
15. Headache?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4

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Fluoxetine Versus Placebo in Childhood/Adolescent Depression
B1Y-MC-HCJE

SIDE EFFECTS CHECKLIST

	Not at all	Just a little	Pretty much	Very much	Don't know
16. Dizziness?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
17. Playing sports?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
18. Shakiness?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
19. Pronouncing words?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
20. Doing things with your hands?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
21. Sitting still?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
22. Tiredness?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
23. Feeling sleepy?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
24. Trouble sleeping?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
25. Bad dreams?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
26. Getting along with parents?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
27. Getting along with kids?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
28. Crying?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
29. Getting mad?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
30. Not being happy?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
31. Being sad?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
32. Paying attention?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4

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Fluoxetine Versus Placebo in Childhood/Adolescent Depression
B1Y-MC-HCJE

CHILDRENS DEPRESSION RATING SCALE - REVISED

INFORMATION NOT OBTAINED ☐

CHECK THE NUMERIC CODE which best describes the patient.

1. **SCHOOLWORK**:

☐ 1 Performance consistent with ability
☐ 2
☐ 3 Decrease in school performance
☐ 4
☐ 5 Major interference in most subjects
☐ 6
☐ 7 No motivation to perform

2. **CAPACITY TO HAVE FUN**

☐ 1 Interest and activities realistically appropriate for age, personality, and social environment. Shows no appreciable change with present illness.
☐ 2
☐ 3 Describes some activities realistically available several times a week but not on a daily basis. Shows interest but not enthusiasm.
☐ 4
☐ 5 Is easily bored. Complains of "nothing to do." Participates in structured activities with a "going through the motions" attitude. May express interest primarily in activities that are (realistically) unavailable on a daily or weekly basis.
☐ 6
☐ 7 Has no initiative to become involved in any activities. Primarily passive. Watches others play or watches TV but shows little interest. Requires coaxing and/or pushing to get involved in activity. Shows no enthusiasm or real interest. Has difficulty naming activities.

3. **SOCIAL WITHDRAWAL**

☐ 1 Enjoys friendships with peers at school and home
☐ 2
☐ 3 May not actively seek out friendships but waits for others to initiate a relationship or may occasionally reject opportunities to play without a describable alternative
☐ 4
☐ 5 Frequently avoids or refuses opportunities for desirable interaction with others and/or sets up situations where rejection is inevitable.
☐ 6
☐ 7 Does not currently relate to other children. States he or she has "no friends" or actively rejects new or former friends.

4. **SLEEP**

☐ 1 No (or occasional) difficulty. (Goes to sleep within 1/2 hour or less.)
☐ 2
☐ 3 Frequently has mild difficulty with sleep
☐ 4
☐ 5 Moderate difficulty with sleep nearly every night.

5. **APPETITE OR EATING PATTERNS**

☐ 1 No problems or change in eating pattern
☐ 2
☐ 3 Mild change from usual eating habits within onset of current behavioral problem
☐ 4
☐ 5 Is not hungry most of the time or has excessive food intake since onset of current behavioral problems or marked increase in appetite

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CHILDRENS DEPRESSION RATING SCALE - REVISED

CHECK THE NUMERIC CODE which best describes the patient.

6. **EXCESSIVE FATIGUE**

- ☐ 1 No unusual complaints of "feeling tired" during the day
- ☐ 2
- ☐ 3 Complaints of fatigue which seem somewhat excessive and not related to boredom
- ☐ 4
- ☐ 5 Daily complaints of feeling tired
- ☐ 6
- ☐ 7 Complains of feeling tired most of the day. May voluntarily take long naps without feeling refreshed. Interferes with play activities.

7. **PHYSICAL COMPLAINTS**:

- ☐ 1 Occasional complaints
- ☐ 2
- ☐ 3 Complaints appear mildly excessive
- ☐ 4
- ☐ 5 Complains daily. Some interference with the ability of the child to function
- ☐ 6
- ☐ 7 Preoccupied with aches and pains; interferes with play activities several times a week

8. **IRRITABILITY**

- ☐ 1 Rare
- ☐ 2 Occasional
- ☐ 3 Several times a week for short periods
- ☐ 4
- ☐ 5 Several times a week for longer periods
- ☐ 6
- ☐ 7 Constant

9. **GUILT**

- ☐ 1 Does not express any undue feeling of guilt. Appears appropriate to precipitating event.
- ☐ 2
- ☐ 3 Exaggerates guilt and/or shame out of proportion to the event described.
- ☐ 4
- ☐ 5 Feels guilty over things not under his or her control. Guilt is definitely pathological.
- ☐ 6
- ☐ 7 Severe delusions of guilt

10. **SELF-ESTEEM**

- ☐ 1 Describes self in primarily positive terms
- ☐ 2
- ☐ 3 Describes self with one important area where the child feels deficit
- ☐ 4
- ☐ 5 Describes self in preponderance of negative terms or gives bland answers to questions
- ☐ 6
- ☐ 7 Refers to self in derogatory terms. Reports that other children refer to him/her frequently by using derogatory nicknames and child puts self down

11. **DEPRESSED FEELINGS**

- ☐ 1 Occasional feelings of unhappiness which quickly disappear
- ☐ 2
- ☐ 3 Describes sustained periods of unhappiness which appear excessive for events described
- ☐ 4
- ☐ 5 Feels unhappy most of the time without a major precipitating cause
- ☐ 6
- ☐ 7 Feels unhappy all of the time. Accompanied by psychic pain (e.g., "I can't stand it").

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Fluoxetine Versus Placebo in Childhood/Adolescent Depression
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CHILDRENS DEPRESSION RATING SCALE - REVISED

CHECK THE NUMERIC CODE which best describes the patient.

12. **MORBID IDEATION**

- ☐ 1 None
- ☐ 2
- ☐ 3 Has some morbid thought, all of which relate to a reality event but seem excessive.
- ☐ 4
- ☐ 5 Preoccupied with morbid thoughts several times a week. Morbid thoughts extend beyond external reality
- ☐ 6
- ☐ 7 Preoccupied with death themes or morbid thoughts that are elaborate, extensive or bizarre on a daily basis

13. **SUICIDAL IDEATION**

- ☐ 1 Understands the word "suicide" but does not apply term to self
- ☐ 2 Sharp denial of suicidal thoughts
- ☐ 3 Has thoughts about suicide, usually when angry.
- ☐ 4
- ☐ 5 Has recurrent thoughts of suicide
- ☐ 6
- ☐ 7 Has made suicide attempt within the last month or is actively suicidal

14. **WEEPING**:

- ☐ 1 Normal for age.
- ☐ 2 Suggestive statements that child cries, or feels like crying, more frequently than peers.
- ☐ 3 Child cries slightly more than peers.
- ☐ 4
- ☐ 5 Cries or feels like crying frequently (several times a week). Admits to crying without knowing reason why.
- ☐ 6
- ☐ 7 Cries nearly every day.

15. **DEPRESSED AFFECT:**

- ☐ 1 Definitely not depressed. Facial expression and voice animated during interview.
- ☐ 2 Mild suppression of affect. Some loss of spontaneity.
- ☐ 3 Overall loss of spontaneity. Looks distinctly unhappy during parts of the interview. May still be able to smile when discussing non-threatening areas.
- ☐ 4
- ☐ 5 Moderate restriction of affect throughout most of interview. Has longer and frequent periods of looking distinctly unhappy.
- ☐ 6
- ☐ 7 Severe. Looks sad, withdrawn. Minimal verbal interaction throughout interview. Cries or may appear tearful.

16. **TEMPO OF SPEECH:**

- ☐ 1 Normal
- ☐ 2 Slow
- ☐ 3 Slow: delays interview.
- ☐ 4
- ☐ 5 Severe. Low; marked interference with interview.

17. **HYPOACTIVITY:**

- ☐ 1 None
- ☐ 2
- ☐ 3 Mild. Some body movements.
- ☐ 4
- ☐ 5 Moderate. Definite motor retardation.
- ☐ 6
- ☐ 7 Severe. Motionless throughout interview.

(DNDE)

Total of 1 - 17 _____

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CLINICAL GLOBAL IMPRESSION: EFFICACY INDEX

Using the worksheet below, enter the 2-digit efficacy index rating.

1. Efficacy index rating ___ ___

(DNDE)

EFFICACY INDEX WORKSHEET

Rate this item on the basis of DRUG EFFECT ONLY.

Select the terms that best describe the degrees of therapeutic effect and side effects and record the number from the box where the two items intersect in the blanks above.

THERAPEUTIC EFFECT	SIDE EFFECTS			
	None	Do not significantly interfere with patient's functioning	Significantly interferes with patient's functioning	Outweighs therapeutic effect
MARKED - Vast improvement. Complete or nearly complete remission of all symptoms.	**01**	**02**	**03**	**04**
MODERATE - Decided improvement. Partial remission of symptoms.	**05**	**06**	**07**	**08**
MINIMAL - Slight improvement which doesn't alter status of care of patient.	**09**	**10**	**11**	**12**
UNCHANGED OR WORSE	**13**	**14**	**15**	**16**
Not Assessed = **98**				

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CLINICAL GLOBAL IMPRESSION: SEVERITY

INFORMATION NOT OBTAINED ☐

Considering your total clinical experience with this particular population, how mentally ill is the patient at this time?

- ☐ 1 Normal, not at all ill
- ☐ 2 Borderline ill
- ☐ 3 Mildly ill
- ☐ 4 Moderately ill
- ☐ 5 Markedly ill
- ☐ 6 Severely ill
- ☐ 7 Among the most extremely ill patients

Evaluator's initials _____ _____ _____
First Middle Last

CLINICAL GLOBAL IMPRESSION: IMPROVEMENT

INFORMATION NOT OBTAINED ☐

Rate total improvement, whether or not in your judgement it is due entirely to drug treatment. Compared to the patient's condition at Visit 1, how much has he/she changed?

- ☐ 1 Very much improved
- ☐ 2 Much improved
- ☐ 3 Minimally improved
- ☐ 4 No change
- ☐ 5 Minimally worse
- ☐ 6 Much worse
- ☐ 7 Very much worse

Evaluator's initials _____ _____ _____
First Middle Last

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MONTGOMERY - ASBERG DEPRESSION RATING SCALE (MADRS)

INFORMATION NOT OBTAINED ☐

The rating should be based on a clinical interview moving from broadly phrased questions about symptoms to more detailed ones which allow a precise rating of severity. The rater must decide whether the rating lies on the defined scale steps (0, 2, 4, 6) or between them (1, 3, 5).

Check the box (number) that best characterizes the patient at this time

1. **APPARENT SADNESS**
   Representing despondency, gloom, and despair (more than just ordinary transient low spirits), reflected in speech, facial expression, and posture. Rate by depth and inability to brighten up.

   ☐ 0 No sadness.
   ☐ 1
   ☐ 2 Looks dispirited but does brighten up without difficulty.
   ☐ 3
   ☐ 4 Appears sad and unhappy most of the time.
   ☐ 5
   ☐ 6 Looks miserable all the time. Extremely despondent.

2. **REPORTED SADNESS**
   Represented by reports of depressed mood, regardless of whether it is reflected in appearance or not. Includes low spirits, despondency, or the feeling of being beyond help and without hope. Rate according to intensity, duration, and the extent to which the mood is reported to be influenced by events.

   ☐ 0 Occasional sadness in keeping with the circumstances.
   ☐ 1
   ☐ 2 Sad or low but brightens up without difficulty.
   ☐ 3
   ☐ 4 Pervasive feelings of sadness or gloominess. The mood is still influenced by external circumstances.
   ☐ 5
   ☐ 6 Continuous unvarying sadness, misery or despondency.

3. **INNER TENSION**
   Representing feelings of ill-defined discomfort, edginess, inner turmoil, mental tension mounting to either panic, dread, or anguish. Rate according to intensity, frequency, duration, and the extent of reassurance called for.

   ☐ 0 Placid. Only fleeting inner tension.
   ☐ 1
   ☐ 2 Occasional feelings of edginess and ill-defined discomfort.
   ☐ 3
   ☐ 4 Continuous feelings of inner tension or intermittent panic which the patient can only master with some difficulty.
   ☐ 5
   ☐ 6 Unrelenting dread or anguish. Overwhelming panic.

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MONTGOMERY - ASBERG DEPRESSION RATING SCALE (MADRS)

4. **REDUCED SLEEP**
Representing the experience of reduced duration or depth of sleep compared to the subject's own pattern when well.

- ☐ 0 Sleeps as usual.
- ☐ 1
- ☐ 2 Slight difficulty dropping off to sleep or slightly reduced, light or fitful sleep.
- ☐ 3
- ☐ 4 Sleep reduced or broken by at least two hours.
- ☐ 5
- ☐ 6 Less than two or three hours sleep.

5. **REDUCED APPETITE**
Representing the feeling of a loss of appetite compared with when well. Rate by loss of desire for food or the need to force oneself to eat.

- ☐ 0 Normal or increased appetite
- ☐ 1
- ☐ 2 Slightly reduced appetite.
- ☐ 3
- ☐ 4 No appetite. Food is tasteless.
- ☐ 5
- ☐ 6 Needs persuasion to eat at all.

6. **CONCENTRATION DIFFICULTIES**
Representing difficulties in collecting one's thoughts mounting to incapacitating lack of concentration.

- ☐ 0 No difficulties in concentrating.
- ☐ 1
- ☐ 2 Occasional difficulties in collecting one's thoughts.
- ☐ 3
- ☐ 4 Difficulties in concentrating and sustaining thought which reduces ability to read or hold a conversation.
- ☐ 5
- ☐ 6 Unable to read or converse without great difficulty.

7. **LASSITUDE**
Representing a difficulty getting started or slowness initiating and performing everyday activities.

- ☐ 0 Hardly any difficulty in getting started. No sluggishness.
- ☐ 1
- ☐ 2 Difficulties in starting activities
- ☐ 3
- ☐ 4 Difficulties in starting simple routine activities which are carried out with effort.
- ☐ 5
- ☐ 6 Complete lassitude. Unable to do anything without help.

8. **INABILITY TO FEEL**
Representing the subjective experience of reduced interest in the surroundings, or activities that normally give pleasure. The ability to react with adequate emotion to circumstances or people is reduced.

- ☐ 0 Normal interest in the surroundings and other people.
- ☐ 1
- ☐ 2 Reduced ability to enjoy usual interests.
- ☐ 3
- ☐ 4 Loss of interest in the surroundings. Loss of feelings for friends and acquaintances.
- ☐ 5
- ☐ 6 The experience of being emotionally paralyzed, inability to feel anger, grief, or pleasure and a complete or even painful failure to feel for close relatives and friends.

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B1Y-MC-HCJE

MONTGOMERY - ASBERG DEPRESSION RATING SCALE (MADRS)

9. **PESSIMISTIC THOUGHTS**
Representing thoughts of guilt, inferiority, self-reproach, sinfulness, remorse, and ruin

- ☐ 0 No pessimistic thoughts.
- ☐ 1
- ☐ 2 Fluctuating ideas of failure, self-reproach, or self-depreciation.
- ☐ 3
- ☐ 4 Persistent self-accusations, or definite but still rational ideas of guilt, or sin. Increasingly pessimistic about the future.
- ☐ 5
- ☐ 6 Delusions of ruin, remorse, or unredeemable sin. Self-accusations which are absurd and unshakable.

10. **SUICIDAL THOUGHTS**
Representing the feeling that life is not worth living, that a natural death would be welcome, suicidal thoughts, and preparations for suicide. Suicidal attempts should not in themselves influence the rating.

- ☐ 0 Enjoys life or takes it as it comes.
- ☐ 1
- ☐ 2 Weary of life. Only fleeting suicidal thoughts.
- ☐ 3
- ☐ 4 Probably better off dead. Suicidal thoughts are common, and suicide is considered as a possible solution, but without specific plans or intention.
- ☐ 5
- ☐ 6 Explicit plans for suicide when there is an opportunity. Active preparations for suicide.

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Clinical Report Form
Fluoxetine Versus Placebo in Childhood/Adolescent Depression
B1Y-MC-HCJE

CHILDREN'S DEPRESSION INDEX (CDI)

NOTE: Only complete if patient was 8 to 12 years old at Visit 1. If patient was not 8 to 12 years old, check the Information Not Obtained box.

INFORMATION NOT OBTAINED ☐

This lists the feelings and ideas in groups. From each group of three sentences, pick one sentence that describes you **best** for the past two weeks. After you pick a sentence from the first group, go on to the next group. There is no right answer or wrong answer. Just pick the sentence that best describes the way you have been recently. Put an "X" in the box next to your answer.
Remember: pick out the sentences that describe you best **in the past two weeks**.

Item 1

- ☐ 0 I am sad once in a while.
- ☐ 1 I am sad many times.
- ☐ 2 I am sad all the time.

Item 2

- ☐ 2 Nothing will ever work out for me.
- ☐ 1 I am not sure if things will work out for me.
- ☐ 0 Things will work out for me O.K.

Item 3

- ☐ 0 I do most things O.K.
- ☐ 1 I do many things wrong.
- ☐ 2 I do everything wrong.

Item 4

- ☐ 0 I have fun in many things.
- ☐ 1 I have fun in some things.
- ☐ 2 Nothing is fun at all.

Item 5

- ☐ 2 I am bad all the time.
- ☐ 1 I am bad many times.
- ☐ 0 I am bad once in a while.

Item 6

- ☐ 0 I think about bad things happening to me once in a while.
- ☐ 1 I worry that bad things will happen to me.
- ☐ 2 I am sure that terrible things will happen to me.

Item 7

- ☐ 2 I hate myself.
- ☐ 1 I do not like myself.
- ☐ 0 I like myself.

Item 8

- ☐ 2 All bad things are my fault.
- ☐ 1 Many bad things are my fault.
- ☐ 0 Bad things are not usually my fault.

Item 9

- ☐ 0 I do not think about killing myself.
- ☐ 1 I think about killing myself but I would not do it.
- ☐ 2 I want to kill myself.

Item 10

- ☐ 2 I feel like crying every day.
- ☐ 1 I feel like crying many days.
- ☐ 0 I feel like crying once in a while.

Item 11

- ☐ 2 Things bother me all the time.
- ☐ 1 Things bother me many times.
- ☐ 0 Things bother me once in a while.

Item 12

- ☐ 0 I like being with people.
- ☐ 1 I do not like being with people many times.
- ☐ 2 I do not want to be with people at all.

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CHILDREN'S DEPRESSION INDEX (CDI)

Item 13

- ☐ 2 I cannot make up my mind about things.
- ☐ 1 It is hard to make up my mind about things.
- ☐ 0 I make up my mind about things easily.

Item 14

- ☐ 0 I look O.K.
- ☐ 1 There are some bad things about my looks.
- ☐ 2 I look ugly.

Item 15

- ☐ 2 I have to push myself all the time to do my schoolwork.
- ☐ 1 I have to push myself many times to do my schoolwork.
- ☐ 0 Doing schoolwork is not a big problem.

Item 16

- ☐ 2 I have trouble sleeping every night.
- ☐ 1 I have trouble sleeping many nights.
- ☐ 0 I sleep pretty well.

Item 17

- ☐ 0 I am tired once in a while.
- ☐ 1 I am tired many days.
- ☐ 2 I am tired all the time.

Item 18

- ☐ 2 Most days I do not feel like eating.
- ☐ 1 Many days I do not feel like eating.
- ☐ 0 I eat pretty well.

Item 19

- ☐ 0 I do not worry about aches and pains.
- ☐ 1 I worry about aches and pains many times.
- ☐ 2 I worry about aches and pains all the time.

Item 20

- ☐ 0 I do not feel alone.
- ☐ 1 I feel alone many times.
- ☐ 2 I feel alone all the time.

Item 21

- ☐ 2 I never have fun at school.
- ☐ 1 I have fun at school only once in a while.
- ☐ 0 I have fun at school many times.

Item 22

- ☐ 0 I have plenty of friends.
- ☐ 1 I have some friends but I wish I had more.
- ☐ 2 I do not have any friends.

Item 23

- ☐ 0 My schoolwork is alright.
- ☐ 1 My schoolwork is not as good as before.
- ☐ 2 I do very badly in subjects I used to be good in.

Item 24

- ☐ 2 I can never be as good as other kids.
- ☐ 1 I can be as good as other kids if I want to.
- ☐ 0 I am just as good as other kids.

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CHILDREN'S DEPRESSION INDEX (CDI)

Item 25

- ☐ 2 Nobody really loves me.
- ☐ 1 I am not sure if anybody loves me.
- ☐ 0 I am sure that somebody loves me.

Item 26

- ☐ 0 I usually do what I am told.
- ☐ 1 I do not do what I am told most times.
- ☐ 2 I never do what I am told.

Item 27

- ☐ 0 I get along with people.
- ☐ 1 I get into fights many times.
- ☐ 2 I get into fights all the time.

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BECK DEPRESSION INVENTORY

NOTE: Only complete if patient was 13 to 17 years old at Visit 1. If patient was not 13 to 17 years old, check the Information Not Obtained box.

INFORMATION NOT OBTAINED ☐

This questionnaire consists of 21 groups of statements. After reading each group of statements carefully circle the number (0, 1, 2, 3) next to the one statement in each group which best describes the way you have been feeling **the past week, including today**. If several statements within a group seem to apply equally well, circle each one. Be sure to read all the statements in each group before making your choice.

1

0 I do not feel sad.
1 I feel sad.
2 I am sad all the time and I can't snap out of it.
3 I am so sad or unhappy that I can't stand it.

2

0 I am not particularly discouraged about the future.
1 I feel discouraged about the future.
2 I feel I have nothing to look forward to.
3 I feel that the future is hopeless and that things cannot improve.

3

0 I do not feel like a failure.
1 I feel I have failed more than the average person.
2 As I look back on my life, all I can see is a lot of failures.
3 I feel I am a complete failure as a person.

4

0 I get as much satisfaction out of things as I used to.
1 I don't enjoy things the way I used to.
2 I don't get real satisfaction out of anything anymore.
3 I am dissatisfied or bored with everything.

5

0 I don't feel particularly guilty.
1 I feel guilty a good part of the time.
2 I feel quite guilty most of the time.
3 I feel guilty all of the time.

6

0 I don't feel I am being punished.
1 I feel I may be punished.
2 I expect to be punished.
3 I feel I am being punished.

7

0 I don't feel disappointed in myself.
1 I am disappointed in myself.
2 I am disgusted with myself.
3 I hate myself.

8

0 I don't feel I am any worse than anybody else.
1 I am critical of myself for my weaknesses or mistakes.
2 I blame myself all the time for my faults.
3 I blame myself for everything bad that happens.

9

0 I don't have any thoughts of killing myself.
1 I have thoughts of killing myself, but I would not carry them out.
2 I would like to kill myself.
3 I would kill myself if I had the chance.

10

0 I don't cry any more than usual.
1 I cry more now than I used to.
2 I cry all the time now.
3 I used to be able to cry, but now I can't cry even though I want to.

11

0 I am no more irritated now than I ever am.
1 I get annoyed or irritated more easily than I used to.
2 I feel irritated all the time now.
3 I don't get irritated at all by the things that used to irritate me.

12

0 I have not lost interest in other people.
1 I am less interested in other people than I used to be.
2 I have lost most of my interest in other people.
3 I have lost all of my interest in other people.

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BECK DEPRESSION INVENTORY

13

0 I make decisions about as well as I ever could.
1 I put off making decisions more than I used to.
2 I have greater difficulty in making decisions than before.
3 I can't make decisions at all anymore.

14

0 I don't feel I look any worse than I used to.
1 I am worried that I am looking old or unattractive.
2 I feel that there are permanent changes in my appearance that make me look unattractive.
3 I believe that I look ugly.

15

0 I can work about as well as before.
1 It takes an extra effort to get started at doing something.
2 I have to push myself very hard to do anything.
3 I can't do any work at all.

16

0 I can sleep as well as usual.
1 I don't sleep as well as I used to.
2 I wake up 1-2 hours earlier than usual and find it hard to get back to sleep.
3 I wake up several hours earlier than I used to and cannot get back to sleep.

17

0 I don't get more tired than usual.
1 I get tired more easily than I used to.
2 I get tired from doing almost anything.
3 I am too tired to do anything.

18

0 My appetite is no worse than usual.
1 My appetite is not as good as it used to be.
2 My appetite is much worse now.
3 I have no appetite at all anymore.

19

0 I haven't lost much weight, if any, lately.
1 I have lost more than 5 pounds.
2 I have lost more than 10 pounds.
3 I have lost more than 15 pounds.

19a

I am purposely trying to lose weight by eating less.
1 Yes
2 No

20

0 I am no more worried about my health than usual.
1 I am worried about physical problems such as aches and pains; or upset stomach or constipation.
2 I am very worried about physical problems and it's hard to think of much else.
3 I am so worried about my physical problems that I cannot think about anything else.

21

0 I have not noticed any recent change in my interest in sex.
1 I am less interested in sex than I used to be.
2 I am much less interested in sex now.
3 I have lost interest in sex completely.

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HAMILTON ANXIETY SCALE

INFORMATION NOT OBTAINED ☐

For each of the items below, **CHECK ONE BOX** that best describes the patient.

1. **ANXIOUS MOOD:** Worries, anticipation of the worst, fearful anticipation, irritability

   ☐ 0 Not present
   ☐ 1 Mild
   ☐ 2 Moderate
   ☐ 3 Severe
   ☐ 4 Very severe

2. **TENSION**: Feelings of tension, fatigability, startle response, moved to tears easily, trembling, feeling of restlessness, inability to relax

   ☐ 0 Not present
   ☐ 1 Mild
   ☐ 2 Moderate
   ☐ 3 Severe
   ☐ 4 Very severe

3. **FEARS**: Of dark, of strangers, of being alone, of animals, of traffic, of crowds

   ☐ 0 Not present
   ☐ 1 Mild
   ☐ 2 Moderate
   ☐ 3 Severe
   ☐ 4 Very severe

4. **INSOMNIA**: Difficulty in falling asleep, broken sleep, unsatisfying sleep and fatigue on waking, dreams, nightmares, night terrors

   ☐ 0 Not present
   ☐ 1 Mild
   ☐ 2 Moderate
   ☐ 3 Severe
   ☐ 4 Very severe

5. **INTELLECTUAL (COGNITIVE)**: Difficulty in concentration, poor memory

   ☐ 0 Not present
   ☐ 1 Mild
   ☐ 2 Moderate
   ☐ 3 Severe
   ☐ 4 Very severe

6. **DEPRESSED MOOD**: Loss of interest, lack of pleasure in hobbies, depression, early waking, diurnal swing

   ☐ 0 Not present
   ☐ 1 Mild
   ☐ 2 Moderate
   ☐ 3 Severe
   ☐ 4 Very severe

7. **SOMATIC (MUSCULAR)**: Pains and aches, twitchings, stiffness, myoclonic jerks, grinding of teeth, unsteady voice, increased muscular tone

   ☐ 0 Not present
   ☐ 1 Mild
   ☐ 2 Moderate
   ☐ 3 Severe
   ☐ 4 Very severe

8. **SOMATIC (SENSORY)**: Tinnitus, blurring of vision, hot and cold flushes, feeling of weakness, pricking sensation

   ☐ 0 Not present
   ☐ 1 Mild
   ☐ 2 Moderate
   ☐ 3 Severe
   ☐ 4 Very severe

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HAMILTON ANXIETY SCALE

9. **CARDIOVASCULAR SYMPTOMS:** Tachycardia, palpitations, pain in chest, throbbing of vessels, fainting feelings, missing beat

- ☐ 0 Not present
- ☐ 1 Mild
- ☐ 2 Moderate
- ☐ 3 Severe
- ☐ 4 Very severe

10. **RESPIRATORY SYMPTOMS:** Pressure or constriction in chest, choking feelings, sighing, dyspnea

- ☐ 0 Not present
- ☐ 1 Mild
- ☐ 2 Moderate
- ☐ 3 Severe
- ☐ 4 Very severe

11. **GASTROINTESTINAL SYMPTOMS:** Difficulty in swallowing, wind, abdominal pain, burning sensations, abdominal fullness, nausea, vomiting, borborygmi, looseness of bowels, loss of weight, constipation

- ☐ 0 Not present
- ☐ 1 Mild
- ☐ 2 Moderate
- ☐ 3 Severe
- ☐ 4 Very severe

12. **GENITOURINARY SYMPTOMS:** Frequency of micturition, urgency of micturition, amenorrhea, menorrhagia, development of frigidity, premature ejaculation, loss of libido, impotence

- ☐ 0 Not present
- ☐ 1 Mild
- ☐ 2 Moderate
- ☐ 3 Severe
- ☐ 4 Very severe

13. **AUTONOMIC SYMPTOMS:** Dry mouth, flushing, pallor, tendency to sweat, giddiness, tension headache, raising of hair

- ☐ 0 Not present
- ☐ 1 Mild
- ☐ 2 Moderate
- ☐ 3 Severe
- ☐ 4 Very severe

14. **BEHAVIOR AT INTERVIEW:** Fidgeting, restlessness or pacing, tremor of hands, furrowed brow, strained face, sighing or rapid respiration, facial pallor, swallowing, belching, brisk tendon jerks, dilated pupils, exophthalmos

- ☐ 0 Not present
- ☐ 1 Mild
- ☐ 2 Moderate
- ☐ 3 Severe
- ☐ 4 Very severe

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B1Y-MC-HCJE

COMMENTS : VISIT

NO COMMENTS ☐

Comments should address any clinical report form items that require further explanation. Repeating information from the clinical report form is discouraged.

Comment on all clinically significant lab values that are outside a clinically accepted reference range or clinically significant values that differ importantly from previous values.

If the patient is ending participation in the study at this visit, enter only comments that apply to this visit; then complete the Patient Summary and Study Summary Comments pages.

Print legibly and do not use abbreviations or symbols.

The information reported for this visit is accurate and complete.

_____ _____/_____/_____
Signature MM DD YY

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Clinical Report Form
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B1Y-MC-HCJE

PATIENT AND VISIT IDENTIFICATION

Patient initials _____ _____ _____
First Middle Last

Visit date _____/_____/_____
MM DD YY

VITAL SIGNS : BLOOD PRESSURE AND HEART RATE

INFORMATION NOT OBTAINED ☐

Position
SI = Sitting

Position	Blood Pressure (mm Hg) Systolic/Diastolic	Heart Rate (bpm)
SI	/	

VITAL SIGNS: TEMPERATURE

INFORMATION NOT OBTAINED ☐

Temperature ___ ___ ___ . ___

Unit of measure (F) Fahrenheit

Method (E) Ear

REMINDER

On the Pre-existing Conditions and Study Adverse Events pages, record new events that occurred since the previous visit and re-evaluate any on-going conditions or events.

On the Concomitant Medication pages, record new medications the patient has taken since the previous visit, any changes to ongoing medications, and a stop date for any medication the patient is no longer taking.

Initials
Date Verified
Initials
Date Keyed
Date Received at Lilly
Reviewed
Inspected
Date

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B1Y-MC-HCJE

STUDY DRUG : DATES OF MISSED DOSES

NO MISSED DOSES ☐

Record the date for any day on which the patient missed a full or partial dose of study drug.

	Dates of Missed Doses MM	DD	YY
0.			
1.			
2.			
3.			
4.			
5.			
6.			
7.			
8.			
9.			

NOTE: If the patient has missed 3 or more consecutive days of medication, the patient must be discontinued from the study.

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SIDE EFFECTS CHECKLIST

INFORMATION NOT OBTAINED ☐

Since your last visit, have you been bothered with or had any trouble with any of the items listed below? Check the box which best tells how much you were bothered.

	Not at all	Just a little	Pretty much	Very much	Don't know
1. Eating?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
2. Drinking?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
3. Dry mouth and lips?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
4. Wetness in mouth?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
5. Constipation?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
6. Diarrhea?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
7. Stomachaches?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
8. Muscle cramps?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
9. Being sick to your stomach?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
10. Wetting the bed?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
11. Urinating?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
12. Itchy or scratchy skin?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
13. Rashes?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
14. Cold or sniffles?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
15. Headache?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4

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Fluoxetine Versus Placebo in Childhood/Adolescent Depression
B1Y-MC-HCJE

SIDE EFFECTS CHECKLIST

	Not at all	Just a little	Pretty much	Very much	Don't know
16. Dizziness?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
17. Playing sports?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
18. Shakiness?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
19. Pronouncing words?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
20. Doing things with your hands?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
21. Sitting still?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
22. Tiredness?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
23. Feeling sleepy?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
24. Trouble sleeping?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
25. Bad dreams?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
26. Getting along with parents?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
27. Getting along with kids?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
28. Crying?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
29. Getting mad?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
30. Not being happy?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
31. Being sad?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
32. Paying attention?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4

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B1Y-MC-HCJE

CHILDRENS DEPRESSION RATING SCALE - REVISED

INFORMATION NOT OBTAINED ☐

CHECK THE NUMERIC CODE which best describes the patient.

1. **SCHOOLWORK**:

☐ 1 Performance consistent with ability
☐ 2
☐ 3 Decrease in school performance
☐ 4
☐ 5 Major interference in most subjects
☐ 6
☐ 7 No motivation to perform

2. **CAPACITY TO HAVE FUN**

☐ 1 Interest and activities realistically appropriate for age, personality, and social environment. Shows no appreciable change with present illness.
☐ 2
☐ 3 Describes some activities realistically available several times a week but not on a daily basis. Shows interest but not enthusiasm.
☐ 4
☐ 5 Is easily bored. Complains of "nothing to do." Participates in structured activities with a "going through the motions" attitude. May express interest primarily in activities that are (realistically) unavailable on a daily or weekly basis.
☐ 6
☐ 7 Has no initiative to become involved in any activities. Primarily passive. Watches others play or watches TV but shows little interest. Requires coaxing and/or pushing to get involved in activity. Shows no enthusiasm or real interest. Has difficulty naming activities.

3. **SOCIAL WITHDRAWAL**

☐ 1 Enjoys friendships with peers at school and home
☐ 2
☐ 3 May not actively seek out friendships but waits for others to initiate a relationship or may occasionally reject opportunities to play without a describable alternative
☐ 4
☐ 5 Frequently avoids or refuses opportunities for desirable interaction with others and/or sets up situations where rejection is inevitable.
☐ 6
☐ 7 Does not currently relate to other children. States he or she has "no friends" or actively rejects new or former friends.

4. **SLEEP**

☐ 1 No (or occasional) difficulty. (Goes to sleep within 1/2 hour or less.)
☐ 2
☐ 3 Frequently has mild difficulty with sleep
☐ 4
☐ 5 Moderate difficulty with sleep nearly every night.

5. **APPETITE OR EATING PATTERNS**

☐ 1 No problems or change in eating pattern
☐ 2
☐ 3 Mild change from usual eating habits within onset of current behavioral problem
☐ 4
☐ 5 Is not hungry most of the time or has excessive food intake since onset of current behavioral problems or marked increase in appetite

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CHILDRENS DEPRESSION RATING SCALE - REVISED

CHECK THE NUMERIC CODE which best describes the patient.

6. **EXCESSIVE FATIGUE**

- ☐ 1 No unusual complaints of "feeling tired" during the day
- ☐ 2
- ☐ 3 Complaints of fatigue which seem somewhat excessive and not related to boredom
- ☐ 4
- ☐ 5 Daily complaints of feeling tired
- ☐ 6
- ☐ 7 Complains of feeling tired most of the day. May voluntarily take long naps without feeling refreshed. Interferes with play activities.

7. **PHYSICAL COMPLAINTS**:

- ☐ 1 Occasional complaints
- ☐ 2
- ☐ 3 Complaints appear mildly excessive
- ☐ 4
- ☐ 5 Complains daily. Some interference with the ability of the child to function
- ☐ 6
- ☐ 7 Preoccupied with aches and pains; interferes with play activities several times a week

8. **IRRITABILITY**

- ☐ 1 Rare
- ☐ 2 Occasional
- ☐ 3 Several times a week for short periods
- ☐ 4
- ☐ 5 Several times a week for longer periods
- ☐ 6
- ☐ 7 Constant

9. **GUILT**

- ☐ 1 Does not express any undue feeling of guilt. Appears appropriate to precipitating event.
- ☐ 2
- ☐ 3 Exaggerates guilt and/or shame out of proportion to the event described.
- ☐ 4
- ☐ 5 Feels guilty over things not under his or her control. Guilt is definitely pathological.
- ☐ 6
- ☐ 7 Severe delusions of guilt

10. **SELF-ESTEEM**

- ☐ 1 Describes self in primarily positive terms
- ☐ 2
- ☐ 3 Describes self with one important area where the child feels deficit
- ☐ 4
- ☐ 5 Describes self in preponderance of negative terms or gives bland answers to questions
- ☐ 6
- ☐ 7 Refers to self in derogatory terms. Reports that other children refer to him/her frequently by using derogatory nicknames and child puts self down

11. **DEPRESSED FEELINGS**

- ☐ 1 Occasional feelings of unhappiness which quickly disappear
- ☐ 2
- ☐ 3 Describes sustained periods of unhappiness which appear excessive for events described
- ☐ 4
- ☐ 5 Feels unhappy most of the time without a major precipitating cause
- ☐ 6
- ☐ 7 Feels unhappy all of the time. Accompanied by psychic pain (e.g., "I can't stand it").

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Fluoxetine Versus Placebo in Childhood/Adolescent Depression
B1Y-MC-HCJE

CHILDRENS DEPRESSION RATING SCALE - REVISED

CHECK THE NUMERIC CODE which best describes the patient.

12. **MORBID IDEATION**

- ☐ 1 None
- ☐ 2
- ☐ 3 Has some morbid thought, all of which relate to a reality event but seem excessive.
- ☐ 4
- ☐ 5 Preoccupied with morbid thoughts several times a week. Morbid thoughts extend beyond external reality
- ☐ 6
- ☐ 7 Preoccupied with death themes or morbid thoughts that are elaborate, extensive or bizarre on a daily basis

13. **SUICIDAL IDEATION**

- ☐ 1 Understands the word "suicide" but does not apply term to self
- ☐ 2 Sharp denial of suicidal thoughts
- ☐ 3 Has thoughts about suicide, usually when angry.
- ☐ 4
- ☐ 5 Has recurrent thoughts of suicide
- ☐ 6
- ☐ 7 Has made suicide attempt within the last month or is actively suicidal

14. **WEEPING**:

- ☐ 1 Normal for age.
- ☐ 2 Suggestive statements that child cries, or feels like crying, more frequently than peers.
- ☐ 3 Child cries slightly more than peers.
- ☐ 4
- ☐ 5 Cries or feels like crying frequently (several times a week). Admits to crying without knowing reason why.
- ☐ 6
- ☐ 7 Cries nearly every day.

15. **DEPRESSED AFFECT:**

- ☐ 1 Definitely not depressed. Facial expression and voice animated during interview.
- ☐ 2 Mild suppression of affect. Some loss of spontaneity.
- ☐ 3 Overall loss of spontaneity. Looks distinctly unhappy during parts of the interview. May still be able to smile when discussing non-threatening areas.
- ☐ 4
- ☐ 5 Moderate restriction of affect throughout most of interview. Has longer and frequent periods of looking distinctly unhappy.
- ☐ 6
- ☐ 7 Severe. Looks sad, withdrawn. Minimal verbal interaction throughout interview. Cries or may appear tearful.

16. **TEMPO OF SPEECH:**

- ☐ 1 Normal
- ☐ 2 Slow
- ☐ 3 Slow: delays interview.
- ☐ 4
- ☐ 5 Severe. Low; marked interference with interview.

17. **HYPOACTIVITY:**

- ☐ 1 None
- ☐ 2
- ☐ 3 Mild. Some body movements.
- ☐ 4
- ☐ 5 Moderate. Definite motor retardation.
- ☐ 6
- ☐ 7 Severe. Motionless throughout interview.

(DNDE)

Total of 1 - 17 _____

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CLINICAL GLOBAL IMPRESSION: EFFICACY INDEX

Using the worksheet below, enter the 2-digit efficacy index rating.

1. Efficacy index rating ___ ___

(DNDE)

EFFICACY INDEX WORKSHEET

Rate this item on the basis of DRUG EFFECT ONLY.

Select the terms that best describe the degrees of therapeutic effect and side effects and record the number from the box where the two items intersect in the blanks above.

THERAPEUTIC EFFECT	SIDE EFFECTS			
	None	Do not significantly interfere with patient's functioning	Significantly interferes with patient's functioning	Outweighs therapeutic effect
MARKED - Vast improvement. Complete or nearly complete remission of all symptoms.	**01**	**02**	**03**	**04**
MODERATE - Decided improvement. Partial remission of symptoms.	**05**	**06**	**07**	**08**
MINIMAL - Slight improvement which doesn't alter status of care of patient.	**09**	**10**	**11**	**12**
UNCHANGED OR WORSE	**13**	**14**	**15**	**16**
Not Assessed = **98**				

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B1Y-MC-HCJE

CLINICAL GLOBAL IMPRESSION: SEVERITY

INFORMATION NOT OBTAINED ☐

Considering your total clinical experience with this particular population, how mentally ill is the patient at this time?

- ☐ 1 Normal, not at all ill
- ☐ 2 Borderline ill
- ☐ 3 Mildly ill
- ☐ 4 Moderately ill
- ☐ 5 Markedly ill
- ☐ 6 Severely ill
- ☐ 7 Among the most extremely ill patients

Evaluator's initials _____ _____ _____
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CLINICAL GLOBAL IMPRESSION: IMPROVEMENT

INFORMATION NOT OBTAINED ☐

Rate total improvement, whether or not in your judgement it is due entirely to drug treatment. Compared to the patient's condition at Visit 1, how much has he/she changed?

- ☐ 1 Very much improved
- ☐ 2 Much improved
- ☐ 3 Minimally improved
- ☐ 4 No change
- ☐ 5 Minimally worse
- ☐ 6 Much worse
- ☐ 7 Very much worse

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MONTGOMERY - ASBERG DEPRESSION RATING SCALE (MADRS)

INFORMATION NOT OBTAINED ☐

The rating should be based on a clinical interview moving from broadly phrased questions about symptoms to more detailed ones which allow a precise rating of severity. The rater must decide whether the rating lies on the defined scale steps (0, 2, 4, 6) or between them (1, 3, 5).

Check the box (number) that best characterizes the patient at this time

1. **APPARENT SADNESS**
   Representing despondency, gloom, and despair (more than just ordinary transient low spirits), reflected in speech, facial expression, and posture. Rate by depth and inability to brighten up.

   ☐ 0 No sadness.
   ☐ 1
   ☐ 2 Looks dispirited but does brighten up without difficulty.
   ☐ 3
   ☐ 4 Appears sad and unhappy most of the time.
   ☐ 5
   ☐ 6 Looks miserable all the time. Extremely despondent.

2. **REPORTED SADNESS**
   Represented by reports of depressed mood, regardless of whether it is reflected in appearance or not. Includes low spirits, despondency, or the feeling of being beyond help and without hope. Rate according to intensity, duration, and the extent to which the mood is reported to be influenced by events.

   ☐ 0 Occasional sadness in keeping with the circumstances.
   ☐ 1
   ☐ 2 Sad or low but brightens up without difficulty.
   ☐ 3
   ☐ 4 Pervasive feelings of sadness or gloominess. The mood is still influenced by external circumstances.
   ☐ 5
   ☐ 6 Continuous unvarying sadness, misery or despondency.

3. **INNER TENSION**
   Representing feelings of ill-defined discomfort, edginess, inner turmoil, mental tension mounting to either panic, dread, or anguish. Rate according to intensity, frequency, duration, and the extent of reassurance called for.

   ☐ 0 Placid. Only fleeting inner tension.
   ☐ 1
   ☐ 2 Occasional feelings of edginess and ill-defined discomfort.
   ☐ 3
   ☐ 4 Continuous feelings of inner tension or intermittent panic which the patient can only master with some difficulty.
   ☐ 5
   ☐ 6 Unrelenting dread or anguish. Overwhelming panic.

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MONTGOMERY - ASBERG DEPRESSION RATING SCALE (MADRS)

4. **REDUCED SLEEP**
Representing the experience of reduced duration or depth of sleep compared to the subject's own pattern when well.

- ☐ 0 Sleeps as usual.
- ☐ 1
- ☐ 2 Slight difficulty dropping off to sleep or slightly reduced, light or fitful sleep.
- ☐ 3
- ☐ 4 Sleep reduced or broken by at least two hours.
- ☐ 5
- ☐ 6 Less than two or three hours sleep.

5. **REDUCED APPETITE**
Representing the feeling of a loss of appetite compared with when well. Rate by loss of desire for food or the need to force oneself to eat.

- ☐ 0 Normal or increased appetite
- ☐ 1
- ☐ 2 Slightly reduced appetite.
- ☐ 3
- ☐ 4 No appetite. Food is tasteless.
- ☐ 5
- ☐ 6 Needs persuasion to eat at all.

6. **CONCENTRATION DIFFICULTIES**
Representing difficulties in collecting one's thoughts mounting to incapacitating lack of concentration.

- ☐ 0 No difficulties in concentrating.
- ☐ 1
- ☐ 2 Occasional difficulties in collecting one's thoughts.
- ☐ 3
- ☐ 4 Difficulties in concentrating and sustaining thought which reduces ability to read or hold a conversation.
- ☐ 5
- ☐ 6 Unable to read or converse without great difficulty.

7. **LASSITUDE**
Representing a difficulty getting started or slowness initiating and performing everyday activities.

- ☐ 0 Hardly any difficulty in getting started. No sluggishness.
- ☐ 1
- ☐ 2 Difficulties in starting activities
- ☐ 3
- ☐ 4 Difficulties in starting simple routine activities which are carried out with effort.
- ☐ 5
- ☐ 6 Complete lassitude. Unable to do anything without help.

8. **INABILITY TO FEEL**
Representing the subjective experience of reduced interest in the surroundings, or activities that normally give pleasure. The ability to react with adequate emotion to circumstances or people is reduced.

- ☐ 0 Normal interest in the surroundings and other people.
- ☐ 1
- ☐ 2 Reduced ability to enjoy usual interests.
- ☐ 3
- ☐ 4 Loss of interest in the surroundings. Loss of feelings for friends and acquaintances.
- ☐ 5
- ☐ 6 The experience of being emotionally paralyzed, inability to feel anger, grief, or pleasure and a complete or even painful failure to feel for close relatives and friends.

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MONTGOMERY - ASBERG DEPRESSION RATING SCALE (MADRS)

9. **PESSIMISTIC THOUGHTS**
Representing thoughts of guilt, inferiority, self-reproach, sinfulness, remorse, and ruin

- ☐ 0 No pessimistic thoughts.
- ☐ 1
- ☐ 2 Fluctuating ideas of failure, self-reproach, or self-depreciation.
- ☐ 3
- ☐ 4 Persistent self-accusations, or definite but still rational ideas of guilt, or sin. Increasingly pessimistic about the future.
- ☐ 5
- ☐ 6 Delusions of ruin, remorse, or unredeemable sin. Self-accusations which are absurd and unshakable.

10. **SUICIDAL THOUGHTS**
Representing the feeling that life is not worth living, that a natural death would be welcome, suicidal thoughts, and preparations for suicide. Suicidal attempts should not in themselves influence the rating.

- ☐ 0 Enjoys life or takes it as it comes.
- ☐ 1
- ☐ 2 Weary of life. Only fleeting suicidal thoughts.
- ☐ 3
- ☐ 4 Probably better off dead. Suicidal thoughts are common, and suicide is considered as a possible solution, but without specific plans or intention.
- ☐ 5
- ☐ 6 Explicit plans for suicide when there is an opportunity. Active preparations for suicide.

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B1Y-MC-HCJE

COMMENTS : VISIT

NO COMMENTS ☐

Comments should address any clinical report form items that require further explanation. Repeating information from the clinical report form is discouraged.

Comment on all clinically significant lab values that are outside a clinically accepted reference range or clinically significant values that differ importantly from previous values.

If the patient is ending participation in the study at this visit, enter only comments that apply to this visit; then complete the Patient Summary and Study Summary Comments pages.

Print legibly and do not use abbreviations or symbols.

The information reported for this visit is accurate and complete.

_____ _____/_____/_____
Signature MM DD YY

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Clinical Report Form
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B1Y-MC-HCJE

PATIENT AND VISIT IDENTIFICATION

Patient initials _____ _____ _____
First Middle Last

Visit date _____/_____/_____
MM DD YY

VITAL SIGNS : BLOOD PRESSURE AND HEART RATE

INFORMATION NOT OBTAINED ☐

Position
SI = Sitting

Position	Blood Pressure (mm Hg) Systolic/Diastolic	Heart Rate (bpm)
SI	/	

VITAL SIGNS: TEMPERATURE

INFORMATION NOT OBTAINED ☐

Temperature ___ ___ ___ . ___

Unit of measure (F) Fahrenheit

Method (E) Ear

REMINDER

On the Pre-existing Conditions and Study Adverse Events pages, record new events that occurred since the previous visit and re-evaluate any on-going conditions or events.

On the Concomitant Medication pages, record new medications the patient has taken since the previous visit, any changes to ongoing medications, and a stop date for any medication the patient is no longer taking.

Initials
Date Verified
Initials
Date Keyed
Date Received at Lilly
Reviewed
Inspected
Date

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B1Y-MC-HCJE

STUDY DRUG : DATES OF MISSED DOSES

NO MISSED DOSES ☐

Record the date for any day on which the patient missed a full or partial dose of study drug.

	Dates of Missed Doses MM	DD	YY
0.			
1.			
2.			
3.			
4.			
5.			
6.			
7.			
8.			
9.			

NOTE: If the patient has missed 3 or more consecutive days of medication, the patient must be discontinued from the study.

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Fluoxetine Versus Placebo in Childhood/Adolescent Depression
B1Y-MC-HCJE

SIDE EFFECTS CHECKLIST

INFORMATION NOT OBTAINED ☐

Since your last visit, have you been bothered with or had any trouble with any of the items listed below? Check the box which best tells how much you were bothered.

	Not at all	Just a little	Pretty much	Very much	Don't know
1. Eating?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
2. Drinking?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
3. Dry mouth and lips?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
4. Wetness in mouth?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
5. Constipation?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
6. Diarrhea?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
7. Stomachaches?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
8. Muscle cramps?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
9. Being sick to your stomach?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
10. Wetting the bed?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
11. Urinating?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
12. Itchy or scratchy skin?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
13. Rashes?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
14. Cold or sniffles?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
15. Headache?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4

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Fluoxetine Versus Placebo in Childhood/Adolescent Depression
B1Y-MC-HCJE

SIDE EFFECTS CHECKLIST

	Not at all	Just a little	Pretty much	Very much	Don't know
16. Dizziness?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
17. Playing sports?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
18. Shakiness?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
19. Pronouncing words?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
20. Doing things with your hands?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
21. Sitting still?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
22. Tiredness?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
23. Feeling sleepy?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
24. Trouble sleeping?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
25. Bad dreams?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
26. Getting along with parents?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
27. Getting along with kids?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
28. Crying?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
29. Getting mad?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
30. Not being happy?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
31. Being sad?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
32. Paying attention?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4

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Fluoxetine Versus Placebo in Childhood/Adolescent Depression
B1Y-MC-HCJE

CHILDRENS DEPRESSION RATING SCALE - REVISED

INFORMATION NOT OBTAINED ☐

CHECK THE NUMERIC CODE which best describes the patient.

1. **SCHOOLWORK**:

☐ 1 Performance consistent with ability
☐ 2
☐ 3 Decrease in school performance
☐ 4
☐ 5 Major interference in most subjects
☐ 6
☐ 7 No motivation to perform

2. **CAPACITY TO HAVE FUN**

☐ 1 Interest and activities realistically appropriate for age, personality, and social environment. Shows no appreciable change with present illness.
☐ 2
☐ 3 Describes some activities realistically available several times a week but not on a daily basis. Shows interest but not enthusiasm.
☐ 4
☐ 5 Is easily bored. Complains of "nothing to do." Participates in structured activities with a "going through the motions" attitude. May express interest primarily in activities that are (realistically) unavailable on a daily or weekly basis.
☐ 6
☐ 7 Has no initiative to become involved in any activities. Primarily passive. Watches others play or watches TV but shows little interest. Requires coaxing and/or pushing to get involved in activity. Shows no enthusiasm or real interest. Has difficulty naming activities.

3. **SOCIAL WITHDRAWAL**

☐ 1 Enjoys friendships with peers at school and home
☐ 2
☐ 3 May not actively seek out friendships but waits for others to initiate a relationship or may occasionally reject opportunities to play without a describable alternative
☐ 4
☐ 5 Frequently avoids or refuses opportunities for desirable interaction with others and/or sets up situations where rejection is inevitable.
☐ 6
☐ 7 Does not currently relate to other children. States he or she has "no friends" or actively rejects new or former friends.

4. **SLEEP**

☐ 1 No (or occasional) difficulty. (Goes to sleep within 1/2 hour or less.)
☐ 2
☐ 3 Frequently has mild difficulty with sleep
☐ 4
☐ 5 Moderate difficulty with sleep nearly every night.

5. **APPETITE OR EATING PATTERNS**

☐ 1 No problems or change in eating pattern
☐ 2
☐ 3 Mild change from usual eating habits within onset of current behavioral problem
☐ 4
☐ 5 Is not hungry most of the time or has excessive food intake since onset of current behavioral problems or marked increase in appetite

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CHILDRENS DEPRESSION RATING SCALE - REVISED

CHECK THE NUMERIC CODE which best describes the patient.

6. **EXCESSIVE FATIGUE**

- ☐ 1 No unusual complaints of "feeling tired" during the day
- ☐ 2
- ☐ 3 Complaints of fatigue which seem somewhat excessive and not related to boredom
- ☐ 4
- ☐ 5 Daily complaints of feeling tired
- ☐ 6
- ☐ 7 Complains of feeling tired most of the day. May voluntarily take long naps without feeling refreshed. Interferes with play activities.

7. **PHYSICAL COMPLAINTS**:

- ☐ 1 Occasional complaints
- ☐ 2
- ☐ 3 Complaints appear mildly excessive
- ☐ 4
- ☐ 5 Complains daily. Some interference with the ability of the child to function
- ☐ 6
- ☐ 7 Preoccupied with aches and pains; interferes with play activities several times a week

8. **IRRITABILITY**

- ☐ 1 Rare
- ☐ 2 Occasional
- ☐ 3 Several times a week for short periods
- ☐ 4
- ☐ 5 Several times a week for longer periods
- ☐ 6
- ☐ 7 Constant

9. **GUILT**

- ☐ 1 Does not express any undue feeling of guilt. Appears appropriate to precipitating event.
- ☐ 2
- ☐ 3 Exaggerates guilt and/or shame out of proportion to the event described.
- ☐ 4
- ☐ 5 Feels guilty over things not under his or her control. Guilt is definitely pathological.
- ☐ 6
- ☐ 7 Severe delusions of guilt

10. **SELF-ESTEEM**

- ☐ 1 Describes self in primarily positive terms
- ☐ 2
- ☐ 3 Describes self with one important area where the child feels deficit
- ☐ 4
- ☐ 5 Describes self in preponderance of negative terms or gives bland answers to questions
- ☐ 6
- ☐ 7 Refers to self in derogatory terms. Reports that other children refer to him/her frequently by using derogatory nicknames and child puts self down

11. **DEPRESSED FEELINGS**

- ☐ 1 Occasional feelings of unhappiness which quickly disappear
- ☐ 2
- ☐ 3 Describes sustained periods of unhappiness which appear excessive for events described
- ☐ 4
- ☐ 5 Feels unhappy most of the time without a major precipitating cause
- ☐ 6
- ☐ 7 Feels unhappy all of the time. Accompanied by psychic pain (e.g., "I can't stand it").

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B1Y-MC-HCJE

CHILDRENS DEPRESSION RATING SCALE - REVISED

CHECK THE NUMERIC CODE which best describes the patient.

12. **MORBID IDEATION**

- ☐ 1 None
- ☐ 2
- ☐ 3 Has some morbid thought, all of which relate to a reality event but seem excessive.
- ☐ 4
- ☐ 5 Preoccupied with morbid thoughts several times a week. Morbid thoughts extend beyond external reality
- ☐ 6
- ☐ 7 Preoccupied with death themes or morbid thoughts that are elaborate, extensive or bizarre on a daily basis

13. **SUICIDAL IDEATION**

- ☐ 1 Understands the word "suicide" but does not apply term to self
- ☐ 2 Sharp denial of suicidal thoughts
- ☐ 3 Has thoughts about suicide, usually when angry.
- ☐ 4
- ☐ 5 Has recurrent thoughts of suicide
- ☐ 6
- ☐ 7 Has made suicide attempt within the last month or is actively suicidal

14. **WEEPING**:

- ☐ 1 Normal for age.
- ☐ 2 Suggestive statements that child cries, or feels like crying, more frequently than peers.
- ☐ 3 Child cries slightly more than peers.
- ☐ 4
- ☐ 5 Cries or feels like crying frequently (several times a week). Admits to crying without knowing reason why.
- ☐ 6
- ☐ 7 Cries nearly every day.

15. **DEPRESSED AFFECT:**

- ☐ 1 Definitely not depressed. Facial expression and voice animated during interview.
- ☐ 2 Mild suppression of affect. Some loss of spontaneity.
- ☐ 3 Overall loss of spontaneity. Looks distinctly unhappy during parts of the interview. May still be able to smile when discussing non-threatening areas.
- ☐ 4
- ☐ 5 Moderate restriction of affect throughout most of interview. Has longer and frequent periods of looking distinctly unhappy.
- ☐ 6
- ☐ 7 Severe. Looks sad, withdrawn. Minimal verbal interaction throughout interview. Cries or may appear tearful.

16. **TEMPO OF SPEECH:**

- ☐ 1 Normal
- ☐ 2 Slow
- ☐ 3 Slow: delays interview.
- ☐ 4
- ☐ 5 Severe. Low; marked interference with interview.

17. **HYPOACTIVITY:**

- ☐ 1 None
- ☐ 2
- ☐ 3 Mild. Some body movements.
- ☐ 4
- ☐ 5 Moderate. Definite motor retardation.
- ☐ 6
- ☐ 7 Severe. Motionless throughout interview.

(DNDE)

Total of 1 - 17 _____

Evaluator's initials _____ _____ _____
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Clinical Report Form
Fluoxetine Versus Placebo in Childhood/Adolescent Depression
B1Y-MC-HCJE

CLINICAL GLOBAL IMPRESSION: EFFICACY INDEX

Using the worksheet below, enter the 2-digit efficacy index rating.

1. Efficacy index rating ___ ___

(DNDE)

EFFICACY INDEX WORKSHEET

Rate this item on the basis of DRUG EFFECT ONLY.

Select the terms that best describe the degrees of therapeutic effect and side effects and record the number from the box where the two items intersect in the blanks above.

THERAPEUTIC EFFECT	SIDE EFFECTS			
	None	Do not significantly interfere with patient's functioning	Significantly interferes with patient's functioning	Outweighs therapeutic effect
MARKED - Vast improvement. Complete or nearly complete remission of all symptoms.	**01**	**02**	**03**	**04**
MODERATE - Decided improvement. Partial remission of symptoms.	**05**	**06**	**07**	**08**
MINIMAL - Slight improvement which doesn't alter status of care of patient.	**09**	**10**	**11**	**12**
UNCHANGED OR WORSE	**13**	**14**	**15**	**16**
Not Assessed = **98**				

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B1Y-MC-HCJE

CLINICAL GLOBAL IMPRESSION: SEVERITY

INFORMATION NOT OBTAINED ☐

Considering your total clinical experience with this particular population, how mentally ill is the patient at this time?

- ☐ 1 Normal, not at all ill
- ☐ 2 Borderline ill
- ☐ 3 Mildly ill
- ☐ 4 Moderately ill
- ☐ 5 Markedly ill
- ☐ 6 Severely ill
- ☐ 7 Among the most extremely ill patients

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CLINICAL GLOBAL IMPRESSION: IMPROVEMENT

INFORMATION NOT OBTAINED ☐

Rate total improvement, whether or not in your judgement it is due entirely to drug treatment. Compared to the patient's condition at Visit 1, how much has he/she changed?

- ☐ 1 Very much improved
- ☐ 2 Much improved
- ☐ 3 Minimally improved
- ☐ 4 No change
- ☐ 5 Minimally worse
- ☐ 6 Much worse
- ☐ 7 Very much worse

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MONTGOMERY - ASBERG DEPRESSION RATING SCALE (MADRS)

INFORMATION NOT OBTAINED ☐

The rating should be based on a clinical interview moving from broadly phrased questions about symptoms to more detailed ones which allow a precise rating of severity. The rater must decide whether the rating lies on the defined scale steps (0, 2, 4, 6) or between them (1, 3, 5).

Check the box (number) that best characterizes the patient at this time

1. **APPARENT SADNESS**
   Representing despondency, gloom, and despair (more than just ordinary transient low spirits), reflected in speech, facial expression, and posture. Rate by depth and inability to brighten up.

   ☐ 0 No sadness.
   ☐ 1
   ☐ 2 Looks dispirited but does brighten up without difficulty.
   ☐ 3
   ☐ 4 Appears sad and unhappy most of the time.
   ☐ 5
   ☐ 6 Looks miserable all the time. Extremely despondent.

2. **REPORTED SADNESS**
   Represented by reports of depressed mood, regardless of whether it is reflected in appearance or not. Includes low spirits, despondency, or the feeling of being beyond help and without hope. Rate according to intensity, duration, and the extent to which the mood is reported to be influenced by events.

   ☐ 0 Occasional sadness in keeping with the circumstances.
   ☐ 1
   ☐ 2 Sad or low but brightens up without difficulty.
   ☐ 3
   ☐ 4 Pervasive feelings of sadness or gloominess. The mood is still influenced by external circumstances.
   ☐ 5
   ☐ 6 Continuous unvarying sadness, misery or despondency.

3. **INNER TENSION**
   Representing feelings of ill-defined discomfort, edginess, inner turmoil, mental tension mounting to either panic, dread, or anguish. Rate according to intensity, frequency, duration, and the extent of reassurance called for.

   ☐ 0 Placid. Only fleeting inner tension.
   ☐ 1
   ☐ 2 Occasional feelings of edginess and ill-defined discomfort.
   ☐ 3
   ☐ 4 Continuous feelings of inner tension or intermittent panic which the patient can only master with some difficulty.
   ☐ 5
   ☐ 6 Unrelenting dread or anguish. Overwhelming panic.

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MONTGOMERY - ASBERG DEPRESSION RATING SCALE (MADRS)

4. **REDUCED SLEEP**
Representing the experience of reduced duration or depth of sleep compared to the subject's own pattern when well.

- ☐ 0 Sleeps as usual.
- ☐ 1
- ☐ 2 Slight difficulty dropping off to sleep or slightly reduced, light or fitful sleep.
- ☐ 3
- ☐ 4 Sleep reduced or broken by at least two hours.
- ☐ 5
- ☐ 6 Less than two or three hours sleep.

5. **REDUCED APPETITE**
Representing the feeling of a loss of appetite compared with when well. Rate by loss of desire for food or the need to force oneself to eat.

- ☐ 0 Normal or increased appetite
- ☐ 1
- ☐ 2 Slightly reduced appetite.
- ☐ 3
- ☐ 4 No appetite. Food is tasteless.
- ☐ 5
- ☐ 6 Needs persuasion to eat at all.

6. **CONCENTRATION DIFFICULTIES**
Representing difficulties in collecting one's thoughts mounting to incapacitating lack of concentration.

- ☐ 0 No difficulties in concentrating.
- ☐ 1
- ☐ 2 Occasional difficulties in collecting one's thoughts.
- ☐ 3
- ☐ 4 Difficulties in concentrating and sustaining thought which reduces ability to read or hold a conversation.
- ☐ 5
- ☐ 6 Unable to read or converse without great difficulty.

7. **LASSITUDE**
Representing a difficulty getting started or slowness initiating and performing everyday activities.

- ☐ 0 Hardly any difficulty in getting started. No sluggishness.
- ☐ 1
- ☐ 2 Difficulties in starting activities
- ☐ 3
- ☐ 4 Difficulties in starting simple routine activities which are carried out with effort.
- ☐ 5
- ☐ 6 Complete lassitude. Unable to do anything without help.

8. **INABILITY TO FEEL**
Representing the subjective experience of reduced interest in the surroundings, or activities that normally give pleasure. The ability to react with adequate emotion to circumstances or people is reduced.

- ☐ 0 Normal interest in the surroundings and other people.
- ☐ 1
- ☐ 2 Reduced ability to enjoy usual interests.
- ☐ 3
- ☐ 4 Loss of interest in the surroundings. Loss of feelings for friends and acquaintances.
- ☐ 5
- ☐ 6 The experience of being emotionally paralyzed, inability to feel anger, grief, or pleasure and a complete or even painful failure to feel for close relatives and friends.

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B1Y-MC-HCJE

MONTGOMERY - ASBERG DEPRESSION RATING SCALE (MADRS)

9. **PESSIMISTIC THOUGHTS**
Representing thoughts of guilt, inferiority, self-reproach, sinfulness, remorse, and ruin

- ☐ 0 No pessimistic thoughts.
- ☐ 1
- ☐ 2 Fluctuating ideas of failure, self-reproach, or self-depreciation.
- ☐ 3
- ☐ 4 Persistent self-accusations, or definite but still rational ideas of guilt, or sin. Increasingly pessimistic about the future.
- ☐ 5
- ☐ 6 Delusions of ruin, remorse, or unredeemable sin. Self-accusations which are absurd and unshakable.

10. **SUICIDAL THOUGHTS**
Representing the feeling that life is not worth living, that a natural death would be welcome, suicidal thoughts, and preparations for suicide. Suicidal attempts should not in themselves influence the rating.

- ☐ 0 Enjoys life or takes it as it comes.
- ☐ 1
- ☐ 2 Weary of life. Only fleeting suicidal thoughts.
- ☐ 3
- ☐ 4 Probably better off dead. Suicidal thoughts are common, and suicide is considered as a possible solution, but without specific plans or intention.
- ☐ 5
- ☐ 6 Explicit plans for suicide when there is an opportunity. Active preparations for suicide.

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Clinical Report Form
Fluoxetine Versus Placebo in Childhood/Adolescent Depression
B1Y-MC-HCJE

CHILDREN'S DEPRESSION INDEX (CDI)

NOTE: Only complete if patient was 8 to 12 years old at Visit 1. If patient was not 8 to 12 years old, check the Information Not Obtained box.

INFORMATION NOT OBTAINED ☐

This lists the feelings and ideas in groups. From each group of three sentences, pick one sentence that describes you **best** for the past two weeks. After you pick a sentence from the first group, go on to the next group. There is no right answer or wrong answer. Just pick the sentence that best describes the way you have been recently. Put an "X" in the box next to your answer.
Remember: pick out the sentences that describe you best **in the past two weeks**.

Item 1

- ☐ 0 I am sad once in a while.
- ☐ 1 I am sad many times.
- ☐ 2 I am sad all the time.

Item 2

- ☐ 2 Nothing will ever work out for me.
- ☐ 1 I am not sure if things will work out for me.
- ☐ 0 Things will work out for me O.K.

Item 3

- ☐ 0 I do most things O.K.
- ☐ 1 I do many things wrong.
- ☐ 2 I do everything wrong.

Item 4

- ☐ 0 I have fun in many things.
- ☐ 1 I have fun in some things.
- ☐ 2 Nothing is fun at all.

Item 5

- ☐ 2 I am bad all the time.
- ☐ 1 I am bad many times.
- ☐ 0 I am bad once in a while.

Item 6

- ☐ 0 I think about bad things happening to me once in a while.
- ☐ 1 I worry that bad things will happen to me.
- ☐ 2 I am sure that terrible things will happen to me.

Item 7

- ☐ 2 I hate myself.
- ☐ 1 I do not like myself.
- ☐ 0 I like myself.

Item 8

- ☐ 2 All bad things are my fault.
- ☐ 1 Many bad things are my fault.
- ☐ 0 Bad things are not usually my fault.

Item 9

- ☐ 0 I do not think about killing myself.
- ☐ 1 I think about killing myself but I would not do it.
- ☐ 2 I want to kill myself.

Item 10

- ☐ 2 I feel like crying every day.
- ☐ 1 I feel like crying many days.
- ☐ 0 I feel like crying once in a while.

Item 11

- ☐ 2 Things bother me all the time.
- ☐ 1 Things bother me many times.
- ☐ 0 Things bother me once in a while.

Item 12

- ☐ 0 I like being with people.
- ☐ 1 I do not like being with people many times.
- ☐ 2 I do not want to be with people at all.

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CHILDREN'S DEPRESSION INDEX (CDI)

Item 13

- ☐ 2 I cannot make up my mind about things.
- ☐ 1 It is hard to make up my mind about things.
- ☐ 0 I make up my mind about things easily.

Item 14

- ☐ 0 I look O.K.
- ☐ 1 There are some bad things about my looks.
- ☐ 2 I look ugly.

Item 15

- ☐ 2 I have to push myself all the time to do my schoolwork.
- ☐ 1 I have to push myself many times to do my schoolwork.
- ☐ 0 Doing schoolwork is not a big problem.

Item 16

- ☐ 2 I have trouble sleeping every night.
- ☐ 1 I have trouble sleeping many nights.
- ☐ 0 I sleep pretty well.

Item 17

- ☐ 0 I am tired once in a while.
- ☐ 1 I am tired many days.
- ☐ 2 I am tired all the time.

Item 18

- ☐ 2 Most days I do not feel like eating.
- ☐ 1 Many days I do not feel like eating.
- ☐ 0 I eat pretty well.

Item 19

- ☐ 0 I do not worry about aches and pains.
- ☐ 1 I worry about aches and pains many times.
- ☐ 2 I worry about aches and pains all the time.

Item 20

- ☐ 0 I do not feel alone.
- ☐ 1 I feel alone many times.
- ☐ 2 I feel alone all the time.

Item 21

- ☐ 2 I never have fun at school.
- ☐ 1 I have fun at school only once in a while.
- ☐ 0 I have fun at school many times.

Item 22

- ☐ 0 I have plenty of friends.
- ☐ 1 I have some friends but I wish I had more.
- ☐ 2 I do not have any friends.

Item 23

- ☐ 0 My schoolwork is alright.
- ☐ 1 My schoolwork is not as good as before.
- ☐ 2 I do very badly in subjects I used to be good in.

Item 24

- ☐ 2 I can never be as good as other kids.
- ☐ 1 I can be as good as other kids if I want to.
- ☐ 0 I am just as good as other kids.

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CHILDREN'S DEPRESSION INDEX (CDI)

Item 25

- ☐ 2 Nobody really loves me.
- ☐ 1 I am not sure if anybody loves me.
- ☐ 0 I am sure that somebody loves me.

Item 26

- ☐ 0 I usually do what I am told.
- ☐ 1 I do not do what I am told most times.
- ☐ 2 I never do what I am told.

Item 27

- ☐ 0 I get along with people.
- ☐ 1 I get into fights many times.
- ☐ 2 I get into fights all the time.

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BECK DEPRESSION INVENTORY

NOTE: Only complete if patient was 13 to 17 years old at Visit 1. If patient was not 13 to 17 years old, check the Information Not Obtained box.

INFORMATION NOT OBTAINED ☐

This questionnaire consists of 21 groups of statements. After reading each group of statements carefully circle the number (0, 1, 2, 3) next to the one statement in each group which best describes the way you have been feeling **the past week, including today**. If several statements within a group seem to apply equally well, circle each one. Be sure to read all the statements in each group before making your choice.

1

0 I do not feel sad.
1 I feel sad.
2 I am sad all the time and I can't snap out of it.
3 I am so sad or unhappy that I can't stand it.

2

0 I am not particularly discouraged about the future.
1 I feel discouraged about the future.
2 I feel I have nothing to look forward to.
3 I feel that the future is hopeless and that things cannot improve.

3

0 I do not feel like a failure.
1 I feel I have failed more than the average person.
2 As I look back on my life, all I can see is a lot of failures.
3 I feel I am a complete failure as a person.

4

0 I get as much satisfaction out of things as I used to.
1 I don't enjoy things the way I used to.
2 I don't get real satisfaction out of anything anymore.
3 I am dissatisfied or bored with everything.

5

0 I don't feel particularly guilty.
1 I feel guilty a good part of the time.
2 I feel quite guilty most of the time.
3 I feel guilty all of the time.

6

0 I don't feel I am being punished.
1 I feel I may be punished.
2 I expect to be punished.
3 I feel I am being punished.

7

0 I don't feel disappointed in myself.
1 I am disappointed in myself.
2 I am disgusted with myself.
3 I hate myself.

8

0 I don't feel I am any worse than anybody else.
1 I am critical of myself for my weaknesses or mistakes.
2 I blame myself all the time for my faults.
3 I blame myself for everything bad that happens.

9

0 I don't have any thoughts of killing myself.
1 I have thoughts of killing myself, but I would not carry them out.
2 I would like to kill myself.
3 I would kill myself if I had the chance.

10

0 I don't cry any more than usual.
1 I cry more now than I used to.
2 I cry all the time now.
3 I used to be able to cry, but now I can't cry even though I want to.

11

0 I am no more irritated now than I ever am.
1 I get annoyed or irritated more easily than I used to.
2 I feel irritated all the time now.
3 I don't get irritated at all by the things that used to irritate me.

12

0 I have not lost interest in other people.
1 I am less interested in other people than I used to be.
2 I have lost most of my interest in other people.
3 I have lost all of my interest in other people.

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BECK DEPRESSION INVENTORY

13

0 I make decisions about as well as I ever could.
1 I put off making decisions more than I used to.
2 I have greater difficulty in making decisions than before.
3 I can't make decisions at all anymore.

14

0 I don't feel I look any worse than I used to.
1 I am worried that I am looking old or unattractive.
2 I feel that there are permanent changes in my appearance that make me look unattractive.
3 I believe that I look ugly.

15

0 I can work about as well as before.
1 It takes an extra effort to get started at doing something.
2 I have to push myself very hard to do anything.
3 I can't do any work at all.

16

0 I can sleep as well as usual.
1 I don't sleep as well as I used to.
2 I wake up 1-2 hours earlier than usual and find it hard to get back to sleep.
3 I wake up several hours earlier than I used to and cannot get back to sleep.

17

0 I don't get more tired than usual.
1 I get tired more easily than I used to.
2 I get tired from doing almost anything.
3 I am too tired to do anything.

18

0 My appetite is no worse than usual.
1 My appetite is not as good as it used to be.
2 My appetite is much worse now.
3 I have no appetite at all anymore.

19

0 I haven't lost much weight, if any, lately.
1 I have lost more than 5 pounds.
2 I have lost more than 10 pounds.
3 I have lost more than 15 pounds.

19a

I am purposely trying to lose weight by eating less.
1 Yes
2 No

20

0 I am no more worried about my health than usual.
1 I am worried about physical problems such as aches and pains; or upset stomach or constipation.
2 I am very worried about physical problems and it's hard to think of much else.
3 I am so worried about my physical problems that I cannot think about anything else.

21

0 I have not noticed any recent change in my interest in sex.
1 I am less interested in sex than I used to be.
2 I am much less interested in sex now.
3 I have lost interest in sex completely.

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HAMILTON ANXIETY SCALE

INFORMATION NOT OBTAINED ☐

For each of the items below, **CHECK ONE BOX** that best describes the patient.

1. **ANXIOUS MOOD:** Worries, anticipation of the worst, fearful anticipation, irritability

   ☐ 0 Not present
   ☐ 1 Mild
   ☐ 2 Moderate
   ☐ 3 Severe
   ☐ 4 Very severe

2. **TENSION**: Feelings of tension, fatigability, startle response, moved to tears easily, trembling, feeling of restlessness, inability to relax

   ☐ 0 Not present
   ☐ 1 Mild
   ☐ 2 Moderate
   ☐ 3 Severe
   ☐ 4 Very severe

3. **FEARS**: Of dark, of strangers, of being alone, of animals, of traffic, of crowds

   ☐ 0 Not present
   ☐ 1 Mild
   ☐ 2 Moderate
   ☐ 3 Severe
   ☐ 4 Very severe

4. **INSOMNIA**: Difficulty in falling asleep, broken sleep, unsatisfying sleep and fatigue on waking, dreams, nightmares, night terrors

   ☐ 0 Not present
   ☐ 1 Mild
   ☐ 2 Moderate
   ☐ 3 Severe
   ☐ 4 Very severe

5. **INTELLECTUAL (COGNITIVE)**: Difficulty in concentration, poor memory

   ☐ 0 Not present
   ☐ 1 Mild
   ☐ 2 Moderate
   ☐ 3 Severe
   ☐ 4 Very severe

6. **DEPRESSED MOOD**: Loss of interest, lack of pleasure in hobbies, depression, early waking, diurnal swing

   ☐ 0 Not present
   ☐ 1 Mild
   ☐ 2 Moderate
   ☐ 3 Severe
   ☐ 4 Very severe

7. **SOMATIC (MUSCULAR)**: Pains and aches, twitchings, stiffness, myoclonic jerks, grinding of teeth, unsteady voice, increased muscular tone

   ☐ 0 Not present
   ☐ 1 Mild
   ☐ 2 Moderate
   ☐ 3 Severe
   ☐ 4 Very severe

8. **SOMATIC (SENSORY)**: Tinnitus, blurring of vision, hot and cold flushes, feeling of weakness, pricking sensation

   ☐ 0 Not present
   ☐ 1 Mild
   ☐ 2 Moderate
   ☐ 3 Severe
   ☐ 4 Very severe

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HAMILTON ANXIETY SCALE

9. **CARDIOVASCULAR SYMPTOMS:** Tachycardia, palpitations, pain in chest, throbbing of vessels, fainting feelings, missing beat

- ☐ 0 Not present
- ☐ 1 Mild
- ☐ 2 Moderate
- ☐ 3 Severe
- ☐ 4 Very severe

10. **RESPIRATORY SYMPTOMS:** Pressure or constriction in chest, choking feelings, sighing, dyspnea

- ☐ 0 Not present
- ☐ 1 Mild
- ☐ 2 Moderate
- ☐ 3 Severe
- ☐ 4 Very severe

11. **GASTROINTESTINAL SYMPTOMS:** Difficulty in swallowing, wind, abdominal pain, burning sensations, abdominal fullness, nausea, vomiting, borborygmi, looseness of bowels, loss of weight, constipation

- ☐ 0 Not present
- ☐ 1 Mild
- ☐ 2 Moderate
- ☐ 3 Severe
- ☐ 4 Very severe

12. **GENITOURINARY SYMPTOMS:** Frequency of micturition, urgency of micturition, amenorrhea, menorrhagia, development of frigidity, premature ejaculation, loss of libido, impotence

- ☐ 0 Not present
- ☐ 1 Mild
- ☐ 2 Moderate
- ☐ 3 Severe
- ☐ 4 Very severe

13. **AUTONOMIC SYMPTOMS:** Dry mouth, flushing, pallor, tendency to sweat, giddiness, tension headache, raising of hair

- ☐ 0 Not present
- ☐ 1 Mild
- ☐ 2 Moderate
- ☐ 3 Severe
- ☐ 4 Very severe

14. **BEHAVIOR AT INTERVIEW:** Fidgeting, restlessness or pacing, tremor of hands, furrowed brow, strained face, sighing or rapid respiration, facial pallor, swallowing, belching, brisk tendon jerks, dilated pupils, exophthalmos

- ☐ 0 Not present
- ☐ 1 Mild
- ☐ 2 Moderate
- ☐ 3 Severe
- ☐ 4 Very severe

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PATIENT AND VISIT IDENTIFICATION

Patient initials _____ _____ _____
First Middle Last

Visit date _____/_____/_____
MM DD YY

VITAL SIGNS : BLOOD PRESSURE AND HEART RATE

INFORMATION NOT OBTAINED ☐

Position
SI = Sitting

Position	Blood Pressure (mm Hg) Systolic/Diastolic	Heart Rate (bpm)
SI	/	

VITAL SIGNS: TEMPERATURE

INFORMATION NOT OBTAINED ☐

Temperature ___ ___ ___ . ___

Unit of measure (F) Fahrenheit

Method (E) Ear

REMINDER

On the Pre-existing Conditions and Study Adverse Events pages, record new events that occurred since the previous visit and re-evaluate any on-going conditions or events.

On the Concomitant Medication pages, record new medications the patient has taken since the previous visit, any changes to ongoing medications, and a stop date for any medication the patient is no longer taking.

Initials
Date Verified
Initials
Date Keyed
Date Received at Lilly
Reviewed
Inspected
Date

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STUDY DRUG : DATES OF MISSED DOSES

NO MISSED DOSES ☐

Record the date for any day on which the patient missed a full or partial dose of study drug.

	Dates of Missed Doses MM	DD	YY
0.			
1.			
2.			
3.			
4.			
5.			
6.			
7.			
8.			
9.			

NOTE: If the patient has missed 3 or more consecutive days of medication, the patient must be discontinued from the study.

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B1Y-MC-HCJE

SIDE EFFECTS CHECKLIST

INFORMATION NOT OBTAINED ☐

Since your last visit, have you been bothered with or had any trouble with any of the items listed below? Check the box which best tells how much you were bothered.

	Not at all	Just a little	Pretty much	Very much	Don't know
1. Eating?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
2. Drinking?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
3. Dry mouth and lips?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
4. Wetness in mouth?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
5. Constipation?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
6. Diarrhea?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
7. Stomachaches?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
8. Muscle cramps?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
9. Being sick to your stomach?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
10. Wetting the bed?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
11. Urinating?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
12. Itchy or scratchy skin?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
13. Rashes?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
14. Cold or sniffles?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
15. Headache?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4

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SIDE EFFECTS CHECKLIST

	Not at all	Just a little	Pretty much	Very much	Don't know
16. Dizziness?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
17. Playing sports?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
18. Shakiness?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
19. Pronouncing words?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
20. Doing things with your hands?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
21. Sitting still?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
22. Tiredness?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
23. Feeling sleepy?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
24. Trouble sleeping?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
25. Bad dreams?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
26. Getting along with parents?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
27. Getting along with kids?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
28. Crying?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
29. Getting mad?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
30. Not being happy?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
31. Being sad?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
32. Paying attention?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4

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Clinical Report Form
Fluoxetine Versus Placebo in Childhood/Adolescent Depression
B1Y-MC-HCJE

CHILDRENS DEPRESSION RATING SCALE - REVISED

INFORMATION NOT OBTAINED ☐

CHECK THE NUMERIC CODE which best describes the patient.

1. **SCHOOLWORK**:

☐ 1 Performance consistent with ability
☐ 2
☐ 3 Decrease in school performance
☐ 4
☐ 5 Major interference in most subjects
☐ 6
☐ 7 No motivation to perform

2. **CAPACITY TO HAVE FUN**

☐ 1 Interest and activities realistically appropriate for age, personality, and social environment. Shows no appreciable change with present illness.
☐ 2
☐ 3 Describes some activities realistically available several times a week but not on a daily basis. Shows interest but not enthusiasm.
☐ 4
☐ 5 Is easily bored. Complains of "nothing to do." Participates in structured activities with a "going through the motions" attitude. May express interest primarily in activities that are (realistically) unavailable on a daily or weekly basis.
☐ 6
☐ 7 Has no initiative to become involved in any activities. Primarily passive. Watches others play or watches TV but shows little interest. Requires coaxing and/or pushing to get involved in activity. Shows no enthusiasm or real interest. Has difficulty naming activities.

3. **SOCIAL WITHDRAWAL**

☐ 1 Enjoys friendships with peers at school and home
☐ 2
☐ 3 May not actively seek out friendships but waits for others to initiate a relationship or may occasionally reject opportunities to play without a describable alternative
☐ 4
☐ 5 Frequently avoids or refuses opportunities for desirable interaction with others and/or sets up situations where rejection is inevitable.
☐ 6
☐ 7 Does not currently relate to other children. States he or she has "no friends" or actively rejects new or former friends.

4. **SLEEP**

☐ 1 No (or occasional) difficulty. (Goes to sleep within 1/2 hour or less.)
☐ 2
☐ 3 Frequently has mild difficulty with sleep
☐ 4
☐ 5 Moderate difficulty with sleep nearly every night.

5. **APPETITE OR EATING PATTERNS**

☐ 1 No problems or change in eating pattern
☐ 2
☐ 3 Mild change from usual eating habits within onset of current behavioral problem
☐ 4
☐ 5 Is not hungry most of the time or has excessive food intake since onset of current behavioral problems or marked increase in appetite

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CHILDRENS DEPRESSION RATING SCALE - REVISED

CHECK THE NUMERIC CODE which best describes the patient.

6. **EXCESSIVE FATIGUE**

- ☐ 1 No unusual complaints of "feeling tired" during the day
- ☐ 2
- ☐ 3 Complaints of fatigue which seem somewhat excessive and not related to boredom
- ☐ 4
- ☐ 5 Daily complaints of feeling tired
- ☐ 6
- ☐ 7 Complains of feeling tired most of the day. May voluntarily take long naps without feeling refreshed. Interferes with play activities.

7. **PHYSICAL COMPLAINTS**:

- ☐ 1 Occasional complaints
- ☐ 2
- ☐ 3 Complaints appear mildly excessive
- ☐ 4
- ☐ 5 Complains daily. Some interference with the ability of the child to function
- ☐ 6
- ☐ 7 Preoccupied with aches and pains; interferes with play activities several times a week

8. **IRRITABILITY**

- ☐ 1 Rare
- ☐ 2 Occasional
- ☐ 3 Several times a week for short periods
- ☐ 4
- ☐ 5 Several times a week for longer periods
- ☐ 6
- ☐ 7 Constant

9. **GUILT**

- ☐ 1 Does not express any undue feeling of guilt. Appears appropriate to precipitating event.
- ☐ 2
- ☐ 3 Exaggerates guilt and/or shame out of proportion to the event described.
- ☐ 4
- ☐ 5 Feels guilty over things not under his or her control. Guilt is definitely pathological.
- ☐ 6
- ☐ 7 Severe delusions of guilt

10. **SELF-ESTEEM**

- ☐ 1 Describes self in primarily positive terms
- ☐ 2
- ☐ 3 Describes self with one important area where the child feels deficit
- ☐ 4
- ☐ 5 Describes self in preponderance of negative terms or gives bland answers to questions
- ☐ 6
- ☐ 7 Refers to self in derogatory terms. Reports that other children refer to him/her frequently by using derogatory nicknames and child puts self down

11. **DEPRESSED FEELINGS**

- ☐ 1 Occasional feelings of unhappiness which quickly disappear
- ☐ 2
- ☐ 3 Describes sustained periods of unhappiness which appear excessive for events described
- ☐ 4
- ☐ 5 Feels unhappy most of the time without a major precipitating cause
- ☐ 6
- ☐ 7 Feels unhappy all of the time. Accompanied by psychic pain (e.g., "I can't stand it").

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Fluoxetine Versus Placebo in Childhood/Adolescent Depression
B1Y-MC-HCJE

CHILDRENS DEPRESSION RATING SCALE - REVISED

CHECK THE NUMERIC CODE which best describes the patient.

12. **MORBID IDEATION**

- ☐ 1 None
- ☐ 2
- ☐ 3 Has some morbid thought, all of which relate to a reality event but seem excessive.
- ☐ 4
- ☐ 5 Preoccupied with morbid thoughts several times a week. Morbid thoughts extend beyond external reality
- ☐ 6
- ☐ 7 Preoccupied with death themes or morbid thoughts that are elaborate, extensive or bizarre on a daily basis

13. **SUICIDAL IDEATION**

- ☐ 1 Understands the word "suicide" but does not apply term to self
- ☐ 2 Sharp denial of suicidal thoughts
- ☐ 3 Has thoughts about suicide, usually when angry.
- ☐ 4
- ☐ 5 Has recurrent thoughts of suicide
- ☐ 6
- ☐ 7 Has made suicide attempt within the last month or is actively suicidal

14. **WEEPING**:

- ☐ 1 Normal for age.
- ☐ 2 Suggestive statements that child cries, or feels like crying, more frequently than peers.
- ☐ 3 Child cries slightly more than peers.
- ☐ 4
- ☐ 5 Cries or feels like crying frequently (several times a week). Admits to crying without knowing reason why.
- ☐ 6
- ☐ 7 Cries nearly every day.

15. **DEPRESSED AFFECT:**

- ☐ 1 Definitely not depressed. Facial expression and voice animated during interview.
- ☐ 2 Mild suppression of affect. Some loss of spontaneity.
- ☐ 3 Overall loss of spontaneity. Looks distinctly unhappy during parts of the interview. May still be able to smile when discussing non-threatening areas.
- ☐ 4
- ☐ 5 Moderate restriction of affect throughout most of interview. Has longer and frequent periods of looking distinctly unhappy.
- ☐ 6
- ☐ 7 Severe. Looks sad, withdrawn. Minimal verbal interaction throughout interview. Cries or may appear tearful.

16. **TEMPO OF SPEECH:**

- ☐ 1 Normal
- ☐ 2 Slow
- ☐ 3 Slow: delays interview.
- ☐ 4
- ☐ 5 Severe. Low; marked interference with interview.

17. **HYPOACTIVITY:**

- ☐ 1 None
- ☐ 2
- ☐ 3 Mild. Some body movements.
- ☐ 4
- ☐ 5 Moderate. Definite motor retardation.
- ☐ 6
- ☐ 7 Severe. Motionless throughout interview.

(DNDE)

Total of 1 - 17 _____

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B1Y-MC-HCJE

CLINICAL GLOBAL IMPRESSION: EFFICACY INDEX

Using the worksheet below, enter the 2-digit efficacy index rating.

1. Efficacy index rating ___ ___

(DNDE)

EFFICACY INDEX WORKSHEET

Rate this item on the basis of DRUG EFFECT ONLY.

Select the terms that best describe the degrees of therapeutic effect and side effects and record the number from the box where the two items intersect in the blanks above.

THERAPEUTIC EFFECT	SIDE EFFECTS			
	None	Do not significantly interfere with patient's functioning	Significantly interferes with patient's functioning	Outweighs therapeutic effect
MARKED - Vast improvement. Complete or nearly complete remission of all symptoms.	**01**	**02**	**03**	**04**
MODERATE - Decided improvement. Partial remission of symptoms.	**05**	**06**	**07**	**08**
MINIMAL - Slight improvement which doesn't alter status of care of patient.	**09**	**10**	**11**	**12**
UNCHANGED OR WORSE	**13**	**14**	**15**	**16**
Not Assessed = **98**				

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B1Y-MC-HCJE

CLINICAL GLOBAL IMPRESSION: SEVERITY

INFORMATION NOT OBTAINED ☐

Considering your total clinical experience with this particular population, how mentally ill is the patient at this time?

- ☐ 1 Normal, not at all ill
- ☐ 2 Borderline ill
- ☐ 3 Mildly ill
- ☐ 4 Moderately ill
- ☐ 5 Markedly ill
- ☐ 6 Severely ill
- ☐ 7 Among the most extremely ill patients

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CLINICAL GLOBAL IMPRESSION: IMPROVEMENT

INFORMATION NOT OBTAINED ☐

Rate total improvement, whether or not in your judgement it is due entirely to drug treatment. Compared to the patient's condition at Visit 1, how much has he/she changed?

- ☐ 1 Very much improved
- ☐ 2 Much improved
- ☐ 3 Minimally improved
- ☐ 4 No change
- ☐ 5 Minimally worse
- ☐ 6 Much worse
- ☐ 7 Very much worse

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B1Y-MC-HCJE

MONTGOMERY - ASBERG DEPRESSION RATING SCALE (MADRS)

INFORMATION NOT OBTAINED ☐

The rating should be based on a clinical interview moving from broadly phrased questions about symptoms to more detailed ones which allow a precise rating of severity. The rater must decide whether the rating lies on the defined scale steps (0, 2, 4, 6) or between them (1, 3, 5).

Check the box (number) that best characterizes the patient at this time

1. **APPARENT SADNESS**
   Representing despondency, gloom, and despair (more than just ordinary transient low spirits), reflected in speech, facial expression, and posture. Rate by depth and inability to brighten up.

   ☐ 0 No sadness.
   ☐ 1
   ☐ 2 Looks dispirited but does brighten up without difficulty.
   ☐ 3
   ☐ 4 Appears sad and unhappy most of the time.
   ☐ 5
   ☐ 6 Looks miserable all the time. Extremely despondent.

2. **REPORTED SADNESS**
   Represented by reports of depressed mood, regardless of whether it is reflected in appearance or not. Includes low spirits, despondency, or the feeling of being beyond help and without hope. Rate according to intensity, duration, and the extent to which the mood is reported to be influenced by events.

   ☐ 0 Occasional sadness in keeping with the circumstances.
   ☐ 1
   ☐ 2 Sad or low but brightens up without difficulty.
   ☐ 3
   ☐ 4 Pervasive feelings of sadness or gloominess. The mood is still influenced by external circumstances.
   ☐ 5
   ☐ 6 Continuous unvarying sadness, misery or despondency.

3. **INNER TENSION**
   Representing feelings of ill-defined discomfort, edginess, inner turmoil, mental tension mounting to either panic, dread, or anguish. Rate according to intensity, frequency, duration, and the extent of reassurance called for.

   ☐ 0 Placid. Only fleeting inner tension.
   ☐ 1
   ☐ 2 Occasional feelings of edginess and ill-defined discomfort.
   ☐ 3
   ☐ 4 Continuous feelings of inner tension or intermittent panic which the patient can only master with some difficulty.
   ☐ 5
   ☐ 6 Unrelenting dread or anguish. Overwhelming panic.

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MONTGOMERY - ASBERG DEPRESSION RATING SCALE (MADRS)

4. **REDUCED SLEEP**
Representing the experience of reduced duration or depth of sleep compared to the subject's own pattern when well.

- ☐ 0 Sleeps as usual.
- ☐ 1
- ☐ 2 Slight difficulty dropping off to sleep or slightly reduced, light or fitful sleep.
- ☐ 3
- ☐ 4 Sleep reduced or broken by at least two hours.
- ☐ 5
- ☐ 6 Less than two or three hours sleep.

5. **REDUCED APPETITE**
Representing the feeling of a loss of appetite compared with when well. Rate by loss of desire for food or the need to force oneself to eat.

- ☐ 0 Normal or increased appetite
- ☐ 1
- ☐ 2 Slightly reduced appetite.
- ☐ 3
- ☐ 4 No appetite. Food is tasteless.
- ☐ 5
- ☐ 6 Needs persuasion to eat at all.

6. **CONCENTRATION DIFFICULTIES**
Representing difficulties in collecting one's thoughts mounting to incapacitating lack of concentration.

- ☐ 0 No difficulties in concentrating.
- ☐ 1
- ☐ 2 Occasional difficulties in collecting one's thoughts.
- ☐ 3
- ☐ 4 Difficulties in concentrating and sustaining thought which reduces ability to read or hold a conversation.
- ☐ 5
- ☐ 6 Unable to read or converse without great difficulty.

7. **LASSITUDE**
Representing a difficulty getting started or slowness initiating and performing everyday activities.

- ☐ 0 Hardly any difficulty in getting started. No sluggishness.
- ☐ 1
- ☐ 2 Difficulties in starting activities
- ☐ 3
- ☐ 4 Difficulties in starting simple routine activities which are carried out with effort.
- ☐ 5
- ☐ 6 Complete lassitude. Unable to do anything without help.

8. **INABILITY TO FEEL**
Representing the subjective experience of reduced interest in the surroundings, or activities that normally give pleasure. The ability to react with adequate emotion to circumstances or people is reduced.

- ☐ 0 Normal interest in the surroundings and other people.
- ☐ 1
- ☐ 2 Reduced ability to enjoy usual interests.
- ☐ 3
- ☐ 4 Loss of interest in the surroundings. Loss of feelings for friends and acquaintances.
- ☐ 5
- ☐ 6 The experience of being emotionally paralyzed, inability to feel anger, grief, or pleasure and a complete or even painful failure to feel for close relatives and friends.

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B1Y-MC-HCJE

MONTGOMERY - ASBERG DEPRESSION RATING SCALE (MADRS)

9. **PESSIMISTIC THOUGHTS**
Representing thoughts of guilt, inferiority, self-reproach, sinfulness, remorse, and ruin

- ☐ 0 No pessimistic thoughts.
- ☐ 1
- ☐ 2 Fluctuating ideas of failure, self-reproach, or self-depreciation.
- ☐ 3
- ☐ 4 Persistent self-accusations, or definite but still rational ideas of guilt, or sin. Increasingly pessimistic about the future.
- ☐ 5
- ☐ 6 Delusions of ruin, remorse, or unredeemable sin. Self-accusations which are absurd and unshakable.

10. **SUICIDAL THOUGHTS**
Representing the feeling that life is not worth living, that a natural death would be welcome, suicidal thoughts, and preparations for suicide. Suicidal attempts should not in themselves influence the rating.

- ☐ 0 Enjoys life or takes it as it comes.
- ☐ 1
- ☐ 2 Weary of life. Only fleeting suicidal thoughts.
- ☐ 3
- ☐ 4 Probably better off dead. Suicidal thoughts are common, and suicide is considered as a possible solution, but without specific plans or intention.
- ☐ 5
- ☐ 6 Explicit plans for suicide when there is an opportunity. Active preparations for suicide.

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Fluoxetine Versus Placebo in Childhood/Adolescent Depression
B1Y-MC-HCJE

COMMENTS : VISIT

NO COMMENTS ☐

Comments should address any clinical report form items that require further explanation. Repeating information from the clinical report form is discouraged.

Comment on all clinically significant lab values that are outside a clinically accepted reference range or clinically significant values that differ importantly from previous values.

If the patient is ending participation in the study at this visit, enter only comments that apply to this visit; then complete the Patient Summary and Study Summary Comments pages.

Print legibly and do not use abbreviations or symbols.

The information reported for this visit is accurate and complete.

_____ _____/_____/_____
Signature MM DD YY

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B1Y-MC-HCJE

PATIENT AND VISIT IDENTIFICATION

Patient initials _____ _____ _____
First Middle Last

Visit date _____/_____/_____
MM DD YY

K-SADS : AFFECTIVE DISORDERS

INFORMATION NOT OBTAINED ☐

Check the appropriate boxes.

Depressive Disorders - Current	☐ 1 Yes	☐ 2 No
Depressive Disorders - Past	☐ 1 Yes	☐ 2 No
Mania - Current	☐ 1 Yes	☐ 2 No
Mania -Past	☐ 1 Yes	☐ 2 No

Evaluator's initials _____ _____ _____
First Middle Last

Initials
Date Verified
Initials
Date Keyed
Date Received at Lilly
Reviewed
Inspected
Date

REMINDER

On the Pre-existing Conditions and Study Adverse Events pages, record new events that occurred since the previous visit and re-evaluate any on-going conditions or events.

On the Concomitant Medication pages, record new medications the patient has taken since the previous visit, any changes to ongoing medications, and a stop date for any medication the patient is no longer taking.

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B1Y-MC-HCJE

GLOBAL ASSESSMENT OF FUNCTIONING SCALE (GAF SCALE)

INFORMATION NOT OBTAINED ☐

Enter the number (between 1 and 90) that best represents the patient's:

1. **Current** level of functioning _____
2. **Highest** level of functioning in *past year* _____

Level of Functioning Definitions	
90 – 81	Absent or minimal symptoms, good functioning in all areas, interested and involved in a wide range of activities, socially effective, generally satisfied with life, no more than everyday problems or concerns.
80 – 71	If symptoms are present, they are transient and expectable reactions to psychosocial stressors; no more than slight impairment in social, occupational, or school functioning.
70 – 61	Some mild symptoms OR some difficulty in social, occupational, or school functioning, but generally functioning pretty well, has some meaningful interpersonal relationships.
60 – 51	Moderate symptoms OR any moderate difficulty in social, occupational, or school functioning.
50 – 41	Serious symptoms OR any serious impairment in social, occupational, or school functioning.
40 – 31	Some impairment in reality testing or communication OR major impairment in several areas, such as work or school, family relations, judgment, thinking, or mood.
30 – 21	Behavior is considered influenced by delusions or hallucinations OR serious impairment in communications or judgment OR inability to function in almost all areas.
20 – 11	Some danger of hurting self or other OR occasionally fails to maintain minimal personal hygiene OR gross impairment in communication.
10 – 1	Persistent danger of severely hurting self or others OR persistent inability to maintain minimum personal hygiene OR serious suicidal act with clear expectation of death.

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PROCEDURE : PHYSICAL EXAM

Was a physical exam performed? ☐1 Yes ☐2 No

WEIGHT

INFORMATION NOT OBTAINED ☐

Measure with shoes off. Round up or down to the nearest whole pound.

Weight ___ ___ ___ (lb)

HEIGHT

INFORMATION NOT OBTAINED ☐

Measure with shoes off. Round up or down to the nearest whole inch.

Height ___ ___ ___ (in)

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VITAL SIGNS : BLOOD PRESSURE AND HEART RATE

INFORMATION NOT OBTAINED ☐

Position
SI = Sitting

Position	Blood Pressure (mm Hg) Systolic/Diastolic	Heart Rate (bpm)
SI	/	

VITAL SIGNS: TEMPERATURE

INFORMATION NOT OBTAINED ☐

Temperature ___ ___ ___ . ___

Unit of measure (F) Fahrenheit

Method (E) Ear

MENSTRUAL CYCLE

INFORMATION NOT OBTAINED ☐

1. Does the patient menstruate? ☐ 1 Yes ☐ 2 No ☐ 96 Not Applicable (males)

2. First day of last menstrual cycle _____/_____/_____ (MM DD YY)

3. Are cycles regular? ☐ 1 Yes ☐ 2 No

4. Number of days in cycle _____ (days)

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CONTRACEPTION

INFORMATION NOT OBTAINED ☐

Contraception is ensured through:

- ☐13 Prepubertal status
- ☐9 Strict abstinence
- ☐7 Use of condom and spermicidal foam
- ☐4 Use of oral contraceptives
- ☐6 Use of contraceptive implant
- ☐5 Use of intra-uterine device (IUD)
- ☐11 Depo-Provera©
- ☐10 Solitary partner who is vasectomized
- ☐8 Homosexual lifestyle
- ☐1 Surgical sterilization
- ☐2 Radiation-induced sterilization
- ☐96 Not applicable (applies to male patients)

Note: If a female patient is not using one of the above methods of contraception, she cannot be entered into this phase of the study.

ELECTROCARDIOGRAM

INFORMATION NOT OBTAINED ☐

Electrocardiogram date _____/_____/_____
MM DD YY

Electrocardiogram result ☐12 Acceptable ☐13 Not Acceptable

Insert the ECG (original) in the envelope provided.

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B1Y-MC-HCJE

STUDY DRUG : DATES OF MISSED DOSES

NO MISSED DOSES ☐

Record the date for any day on which the patient missed a full or partial dose of study drug.

	Dates of Missed Doses MM	DD	YY
0.			
1.			
2.			
3.			
4.			
5.			
6.			
7.			
8.			
9.			

NOTE: If the patient has missed 3 or more consecutive days of medication, the patient must be discontinued from the study.

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Fluoxetine Versus Placebo in Childhood/Adolescent Depression
B1Y-MC-HCJE

SIDE EFFECTS CHECKLIST

INFORMATION NOT OBTAINED ☐

Since your last visit, have you been bothered with or had any trouble with any of the items listed below? Check the box which best tells how much you were bothered.

	Not at all	Just a little	Pretty much	Very much	Don't know
1. Eating?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
2. Drinking?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
3. Dry mouth and lips?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
4. Wetness in mouth?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
5. Constipation?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
6. Diarrhea?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
7. Stomachaches?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
8. Muscle cramps?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
9. Being sick to your stomach?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
10. Wetting the bed?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
11. Urinating?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
12. Itchy or scratchy skin?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
13. Rashes?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
14. Cold or sniffles?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
15. Headache?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4

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Fluoxetine Versus Placebo in Childhood/Adolescent Depression
B1Y-MC-HCJE

SIDE EFFECTS CHECKLIST

	Not at all	Just a little	Pretty much	Very much	Don't know
16. Dizziness?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
17. Playing sports?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
18. Shakiness?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
19. Pronouncing words?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
20. Doing things with your hands?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
21. Sitting still?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
22. Tiredness?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
23. Feeling sleepy?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
24. Trouble sleeping?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
25. Bad dreams?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
26. Getting along with parents?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
27. Getting along with kids?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
28. Crying?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
29. Getting mad?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
30. Not being happy?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
31. Being sad?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
32. Paying attention?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4

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Clinical Report Form
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B1Y-MC-HCJE

CHILDRENS DEPRESSION RATING SCALE - REVISED

INFORMATION NOT OBTAINED ☐

CHECK THE NUMERIC CODE which best describes the patient.

1. **SCHOOLWORK**:

☐ 1 Performance consistent with ability
☐ 2
☐ 3 Decrease in school performance
☐ 4
☐ 5 Major interference in most subjects
☐ 6
☐ 7 No motivation to perform

2. **CAPACITY TO HAVE FUN**

☐ 1 Interest and activities realistically appropriate for age, personality, and social environment. Shows no appreciable change with present illness.
☐ 2
☐ 3 Describes some activities realistically available several times a week but not on a daily basis. Shows interest but not enthusiasm.
☐ 4
☐ 5 Is easily bored. Complains of "nothing to do." Participates in structured activities with a "going through the motions" attitude. May express interest primarily in activities that are (realistically) unavailable on a daily or weekly basis.
☐ 6
☐ 7 Has no initiative to become involved in any activities. Primarily passive. Watches others play or watches TV but shows little interest. Requires coaxing and/or pushing to get involved in activity. Shows no enthusiasm or real interest. Has difficulty naming activities.

3. **SOCIAL WITHDRAWAL**

☐ 1 Enjoys friendships with peers at school and home
☐ 2
☐ 3 May not actively seek out friendships but waits for others to initiate a relationship or may occasionally reject opportunities to play without a describable alternative
☐ 4
☐ 5 Frequently avoids or refuses opportunities for desirable interaction with others and/or sets up situations where rejection is inevitable.
☐ 6
☐ 7 Does not currently relate to other children. States he or she has "no friends" or actively rejects new or former friends.

4. **SLEEP**

☐ 1 No (or occasional) difficulty. (Goes to sleep within 1/2 hour or less.)
☐ 2
☐ 3 Frequently has mild difficulty with sleep
☐ 4
☐ 5 Moderate difficulty with sleep nearly every night.

5. **APPETITE OR EATING PATTERNS**

☐ 1 No problems or change in eating pattern
☐ 2
☐ 3 Mild change from usual eating habits within onset of current behavioral problem
☐ 4
☐ 5 Is not hungry most of the time or has excessive food intake since onset of current behavioral problems or marked increase in appetite

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CHILDRENS DEPRESSION RATING SCALE - REVISED

CHECK THE NUMERIC CODE which best describes the patient.

6. **EXCESSIVE FATIGUE**

- ☐ 1 No unusual complaints of "feeling tired" during the day
- ☐ 2
- ☐ 3 Complaints of fatigue which seem somewhat excessive and not related to boredom
- ☐ 4
- ☐ 5 Daily complaints of feeling tired
- ☐ 6
- ☐ 7 Complains of feeling tired most of the day. May voluntarily take long naps without feeling refreshed. Interferes with play activities.

7. **PHYSICAL COMPLAINTS**:

- ☐ 1 Occasional complaints
- ☐ 2
- ☐ 3 Complaints appear mildly excessive
- ☐ 4
- ☐ 5 Complains daily. Some interference with the ability of the child to function
- ☐ 6
- ☐ 7 Preoccupied with aches and pains; interferes with play activities several times a week

8. **IRRITABILITY**

- ☐ 1 Rare
- ☐ 2 Occasional
- ☐ 3 Several times a week for short periods
- ☐ 4
- ☐ 5 Several times a week for longer periods
- ☐ 6
- ☐ 7 Constant

9. **GUILT**

- ☐ 1 Does not express any undue feeling of guilt. Appears appropriate to precipitating event.
- ☐ 2
- ☐ 3 Exaggerates guilt and/or shame out of proportion to the event described.
- ☐ 4
- ☐ 5 Feels guilty over things not under his or her control. Guilt is definitely pathological.
- ☐ 6
- ☐ 7 Severe delusions of guilt

10. **SELF-ESTEEM**

- ☐ 1 Describes self in primarily positive terms
- ☐ 2
- ☐ 3 Describes self with one important area where the child feels deficit
- ☐ 4
- ☐ 5 Describes self in preponderance of negative terms or gives bland answers to questions
- ☐ 6
- ☐ 7 Refers to self in derogatory terms. Reports that other children refer to him/her frequently by using derogatory nicknames and child puts self down

11. **DEPRESSED FEELINGS**

- ☐ 1 Occasional feelings of unhappiness which quickly disappear
- ☐ 2
- ☐ 3 Describes sustained periods of unhappiness which appear excessive for events described
- ☐ 4
- ☐ 5 Feels unhappy most of the time without a major precipitating cause
- ☐ 6
- ☐ 7 Feels unhappy all of the time. Accompanied by psychic pain (e.g., "I can't stand it").

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B1Y-MC-HCJE

CHILDRENS DEPRESSION RATING SCALE - REVISED

CHECK THE NUMERIC CODE which best describes the patient.

12. **MORBID IDEATION**

- ☐ 1 None
- ☐ 2
- ☐ 3 Has some morbid thought, all of which relate to a reality event but seem excessive.
- ☐ 4
- ☐ 5 Preoccupied with morbid thoughts several times a week. Morbid thoughts extend beyond external reality
- ☐ 6
- ☐ 7 Preoccupied with death themes or morbid thoughts that are elaborate, extensive or bizarre on a daily basis

13. **SUICIDAL IDEATION**

- ☐ 1 Understands the word "suicide" but does not apply term to self
- ☐ 2 Sharp denial of suicidal thoughts
- ☐ 3 Has thoughts about suicide, usually when angry.
- ☐ 4
- ☐ 5 Has recurrent thoughts of suicide
- ☐ 6
- ☐ 7 Has made suicide attempt within the last month or is actively suicidal

14. **WEEPING**:

- ☐ 1 Normal for age.
- ☐ 2 Suggestive statements that child cries, or feels like crying, more frequently than peers.
- ☐ 3 Child cries slightly more than peers.
- ☐ 4
- ☐ 5 Cries or feels like crying frequently (several times a week). Admits to crying without knowing reason why.
- ☐ 6
- ☐ 7 Cries nearly every day.

15. **DEPRESSED AFFECT:**

- ☐ 1 Definitely not depressed. Facial expression and voice animated during interview.
- ☐ 2 Mild suppression of affect. Some loss of spontaneity.
- ☐ 3 Overall loss of spontaneity. Looks distinctly unhappy during parts of the interview. May still be able to smile when discussing non-threatening areas.
- ☐ 4
- ☐ 5 Moderate restriction of affect throughout most of interview. Has longer and frequent periods of looking distinctly unhappy.
- ☐ 6
- ☐ 7 Severe. Looks sad, withdrawn. Minimal verbal interaction throughout interview. Cries or may appear tearful.

16. **TEMPO OF SPEECH:**

- ☐ 1 Normal
- ☐ 2 Slow
- ☐ 3 Slow: delays interview.
- ☐ 4
- ☐ 5 Severe. Low; marked interference with interview.

17. **HYPOACTIVITY:**

- ☐ 1 None
- ☐ 2
- ☐ 3 Mild. Some body movements.
- ☐ 4
- ☐ 5 Moderate. Definite motor retardation.
- ☐ 6
- ☐ 7 Severe. Motionless throughout interview.

(DNDE)

Total of 1 - 17 _____

Evaluator's initials _____ _____ _____
First Middle Last

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CLINICAL GLOBAL IMPRESSION: EFFICACY INDEX

Using the worksheet below, enter the 2-digit efficacy index rating.

1. Efficacy index rating ___ ___

(DNDE)

EFFICACY INDEX WORKSHEET

Rate this item on the basis of DRUG EFFECT ONLY.

Select the terms that best describe the degrees of therapeutic effect and side effects and record the number from the box where the two items intersect in the blanks above.

THERAPEUTIC EFFECT	SIDE EFFECTS			
	None	Do not significantly interfere with patient's functioning	Significantly interferes with patient's functioning	Outweighs therapeutic effect
MARKED - Vast improvement. Complete or nearly complete remission of all symptoms.	**01**	**02**	**03**	**04**
MODERATE - Decided improvement. Partial remission of symptoms.	**05**	**06**	**07**	**08**
MINIMAL - Slight improvement which doesn't alter status of care of patient.	**09**	**10**	**11**	**12**
UNCHANGED OR WORSE	**13**	**14**	**15**	**16**
Not Assessed = **98**				

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CLINICAL GLOBAL IMPRESSION: SEVERITY

INFORMATION NOT OBTAINED ☐

Considering your total clinical experience with this particular population, how mentally ill is the patient at this time?

- ☐ 1 Normal, not at all ill
- ☐ 2 Borderline ill
- ☐ 3 Mildly ill
- ☐ 4 Moderately ill
- ☐ 5 Markedly ill
- ☐ 6 Severely ill
- ☐ 7 Among the most extremely ill patients

Evaluator's initials _____ _____ _____
First Middle Last

CLINICAL GLOBAL IMPRESSION: IMPROVEMENT

INFORMATION NOT OBTAINED ☐

Rate total improvement, whether or not in your judgement it is due entirely to drug treatment. Compared to the patient's condition at Visit 1, how much has he/she changed?

- ☐ 1 Very much improved
- ☐ 2 Much improved
- ☐ 3 Minimally improved
- ☐ 4 No change
- ☐ 5 Minimally worse
- ☐ 6 Much worse
- ☐ 7 Very much worse

Evaluator's initials _____ _____ _____
First Middle Last

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MONTGOMERY - ASBERG DEPRESSION RATING SCALE (MADRS)

INFORMATION NOT OBTAINED ☐

The rating should be based on a clinical interview moving from broadly phrased questions about symptoms to more detailed ones which allow a precise rating of severity. The rater must decide whether the rating lies on the defined scale steps (0, 2, 4, 6) or between them (1, 3, 5).

Check the box (number) that best characterizes the patient at this time

1. **APPARENT SADNESS**
   Representing despondency, gloom, and despair (more than just ordinary transient low spirits), reflected in speech, facial expression, and posture. Rate by depth and inability to brighten up.

   ☐ 0 No sadness.
   ☐ 1
   ☐ 2 Looks dispirited but does brighten up without difficulty.
   ☐ 3
   ☐ 4 Appears sad and unhappy most of the time.
   ☐ 5
   ☐ 6 Looks miserable all the time. Extremely despondent.

2. **REPORTED SADNESS**
   Represented by reports of depressed mood, regardless of whether it is reflected in appearance or not. Includes low spirits, despondency, or the feeling of being beyond help and without hope. Rate according to intensity, duration, and the extent to which the mood is reported to be influenced by events.

   ☐ 0 Occasional sadness in keeping with the circumstances.
   ☐ 1
   ☐ 2 Sad or low but brightens up without difficulty.
   ☐ 3
   ☐ 4 Pervasive feelings of sadness or gloominess. The mood is still influenced by external circumstances.
   ☐ 5
   ☐ 6 Continuous unvarying sadness, misery or despondency.

3. **INNER TENSION**
   Representing feelings of ill-defined discomfort, edginess, inner turmoil, mental tension mounting to either panic, dread, or anguish. Rate according to intensity, frequency, duration, and the extent of reassurance called for.

   ☐ 0 Placid. Only fleeting inner tension.
   ☐ 1
   ☐ 2 Occasional feelings of edginess and ill-defined discomfort.
   ☐ 3
   ☐ 4 Continuous feelings of inner tension or intermittent panic which the patient can only master with some difficulty.
   ☐ 5
   ☐ 6 Unrelenting dread or anguish. Overwhelming panic.

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MONTGOMERY - ASBERG DEPRESSION RATING SCALE (MADRS)

4. **REDUCED SLEEP**
Representing the experience of reduced duration or depth of sleep compared to the subject's own pattern when well.

- ☐ 0 Sleeps as usual.
- ☐ 1
- ☐ 2 Slight difficulty dropping off to sleep or slightly reduced, light or fitful sleep.
- ☐ 3
- ☐ 4 Sleep reduced or broken by at least two hours.
- ☐ 5
- ☐ 6 Less than two or three hours sleep.

5. **REDUCED APPETITE**
Representing the feeling of a loss of appetite compared with when well. Rate by loss of desire for food or the need to force oneself to eat.

- ☐ 0 Normal or increased appetite
- ☐ 1
- ☐ 2 Slightly reduced appetite.
- ☐ 3
- ☐ 4 No appetite. Food is tasteless.
- ☐ 5
- ☐ 6 Needs persuasion to eat at all.

6. **CONCENTRATION DIFFICULTIES**
Representing difficulties in collecting one's thoughts mounting to incapacitating lack of concentration.

- ☐ 0 No difficulties in concentrating.
- ☐ 1
- ☐ 2 Occasional difficulties in collecting one's thoughts.
- ☐ 3
- ☐ 4 Difficulties in concentrating and sustaining thought which reduces ability to read or hold a conversation.
- ☐ 5
- ☐ 6 Unable to read or converse without great difficulty.

7. **LASSITUDE**
Representing a difficulty getting started or slowness initiating and performing everyday activities.

- ☐ 0 Hardly any difficulty in getting started. No sluggishness.
- ☐ 1
- ☐ 2 Difficulties in starting activities
- ☐ 3
- ☐ 4 Difficulties in starting simple routine activities which are carried out with effort.
- ☐ 5
- ☐ 6 Complete lassitude. Unable to do anything without help.

8. **INABILITY TO FEEL**
Representing the subjective experience of reduced interest in the surroundings, or activities that normally give pleasure. The ability to react with adequate emotion to circumstances or people is reduced.

- ☐ 0 Normal interest in the surroundings and other people.
- ☐ 1
- ☐ 2 Reduced ability to enjoy usual interests.
- ☐ 3
- ☐ 4 Loss of interest in the surroundings. Loss of feelings for friends and acquaintances.
- ☐ 5
- ☐ 6 The experience of being emotionally paralyzed, inability to feel anger, grief, or pleasure and a complete or even painful failure to feel for close relatives and friends.

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MONTGOMERY - ASBERG DEPRESSION RATING SCALE (MADRS)

9. **PESSIMISTIC THOUGHTS**
Representing thoughts of guilt, inferiority, self-reproach, sinfulness, remorse, and ruin

- ☐ 0 No pessimistic thoughts.
- ☐ 1
- ☐ 2 Fluctuating ideas of failure, self-reproach, or self-depreciation.
- ☐ 3
- ☐ 4 Persistent self-accusations, or definite but still rational ideas of guilt, or sin. Increasingly pessimistic about the future.
- ☐ 5
- ☐ 6 Delusions of ruin, remorse, or unredeemable sin. Self-accusations which are absurd and unshakable.

10. **SUICIDAL THOUGHTS**
Representing the feeling that life is not worth living, that a natural death would be welcome, suicidal thoughts, and preparations for suicide. Suicidal attempts should not in themselves influence the rating.

- ☐ 0 Enjoys life or takes it as it comes.
- ☐ 1
- ☐ 2 Weary of life. Only fleeting suicidal thoughts.
- ☐ 3
- ☐ 4 Probably better off dead. Suicidal thoughts are common, and suicide is considered as a possible solution, but without specific plans or intention.
- ☐ 5
- ☐ 6 Explicit plans for suicide when there is an opportunity. Active preparations for suicide.

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CHILDREN'S DEPRESSION INDEX (CDI)

NOTE: Only complete if patient was 8 to 12 years old at Visit 1. If patient was not 8 to 12 years old, check the Information Not Obtained box.

INFORMATION NOT OBTAINED ☐

This lists the feelings and ideas in groups. From each group of three sentences, pick one sentence that describes you **best** for the past two weeks. After you pick a sentence from the first group, go on to the next group. There is no right answer or wrong answer. Just pick the sentence that best describes the way you have been recently. Put an "X" in the box next to your answer.
Remember: pick out the sentences that describe you best **in the past two weeks**.

Item 1

- ☐ 0 I am sad once in a while.
- ☐ 1 I am sad many times.
- ☐ 2 I am sad all the time.

Item 2

- ☐ 2 Nothing will ever work out for me.
- ☐ 1 I am not sure if things will work out for me.
- ☐ 0 Things will work out for me O.K.

Item 3

- ☐ 0 I do most things O.K.
- ☐ 1 I do many things wrong.
- ☐ 2 I do everything wrong.

Item 4

- ☐ 0 I have fun in many things.
- ☐ 1 I have fun in some things.
- ☐ 2 Nothing is fun at all.

Item 5

- ☐ 2 I am bad all the time.
- ☐ 1 I am bad many times.
- ☐ 0 I am bad once in a while.

Item 6

- ☐ 0 I think about bad things happening to me once in a while.
- ☐ 1 I worry that bad things will happen to me.
- ☐ 2 I am sure that terrible things will happen to me.

Item 7

- ☐ 2 I hate myself.
- ☐ 1 I do not like myself.
- ☐ 0 I like myself.

Item 8

- ☐ 2 All bad things are my fault.
- ☐ 1 Many bad things are my fault.
- ☐ 0 Bad things are not usually my fault.

Item 9

- ☐ 0 I do not think about killing myself.
- ☐ 1 I think about killing myself but I would not do it.
- ☐ 2 I want to kill myself.

Item 10

- ☐ 2 I feel like crying every day.
- ☐ 1 I feel like crying many days.
- ☐ 0 I feel like crying once in a while.

Item 11

- ☐ 2 Things bother me all the time.
- ☐ 1 Things bother me many times.
- ☐ 0 Things bother me once in a while.

Item 12

- ☐ 0 I like being with people.
- ☐ 1 I do not like being with people many times.
- ☐ 2 I do not want to be with people at all.

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CHILDREN'S DEPRESSION INDEX (CDI)

Item 13

- ☐ 2 I cannot make up my mind about things.
- ☐ 1 It is hard to make up my mind about things.
- ☐ 0 I make up my mind about things easily.

Item 14

- ☐ 0 I look O.K.
- ☐ 1 There are some bad things about my looks.
- ☐ 2 I look ugly.

Item 15

- ☐ 2 I have to push myself all the time to do my schoolwork.
- ☐ 1 I have to push myself many times to do my schoolwork.
- ☐ 0 Doing schoolwork is not a big problem.

Item 16

- ☐ 2 I have trouble sleeping every night.
- ☐ 1 I have trouble sleeping many nights.
- ☐ 0 I sleep pretty well.

Item 17

- ☐ 0 I am tired once in a while.
- ☐ 1 I am tired many days.
- ☐ 2 I am tired all the time.

Item 18

- ☐ 2 Most days I do not feel like eating.
- ☐ 1 Many days I do not feel like eating.
- ☐ 0 I eat pretty well.

Item 19

- ☐ 0 I do not worry about aches and pains.
- ☐ 1 I worry about aches and pains many times.
- ☐ 2 I worry about aches and pains all the time.

Item 20

- ☐ 0 I do not feel alone.
- ☐ 1 I feel alone many times.
- ☐ 2 I feel alone all the time.

Item 21

- ☐ 2 I never have fun at school.
- ☐ 1 I have fun at school only once in a while.
- ☐ 0 I have fun at school many times.

Item 22

- ☐ 0 I have plenty of friends.
- ☐ 1 I have some friends but I wish I had more.
- ☐ 2 I do not have any friends.

Item 23

- ☐ 0 My schoolwork is alright.
- ☐ 1 My schoolwork is not as good as before.
- ☐ 2 I do very badly in subjects I used to be good in.

Item 24

- ☐ 2 I can never be as good as other kids.
- ☐ 1 I can be as good as other kids if I want to.
- ☐ 0 I am just as good as other kids.

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CHILDREN'S DEPRESSION INDEX (CDI)

Item 25

- ☐ 2 Nobody really loves me.
- ☐ 1 I am not sure if anybody loves me.
- ☐ 0 I am sure that somebody loves me.

Item 26

- ☐ 0 I usually do what I am told.
- ☐ 1 I do not do what I am told most times.
- ☐ 2 I never do what I am told.

Item 27

- ☐ 0 I get along with people.
- ☐ 1 I get into fights many times.
- ☐ 2 I get into fights all the time.

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BECK DEPRESSION INVENTORY

NOTE: Only complete if patient was 13 to 17 years old at Visit 1. If patient was not 13 to 17 years old, check the Information Not Obtained box.

INFORMATION NOT OBTAINED ☐

This questionnaire consists of 21 groups of statements. After reading each group of statements carefully circle the number (0, 1, 2, 3) next to the one statement in each group which best describes the way you have been feeling **the past week, including today**. If several statements within a group seem to apply equally well, circle each one. Be sure to read all the statements in each group before making your choice.

1

0 I do not feel sad.
1 I feel sad.
2 I am sad all the time and I can't snap out of it.
3 I am so sad or unhappy that I can't stand it.

2

0 I am not particularly discouraged about the future.
1 I feel discouraged about the future.
2 I feel I have nothing to look forward to.
3 I feel that the future is hopeless and that things cannot improve.

3

0 I do not feel like a failure.
1 I feel I have failed more than the average person.
2 As I look back on my life, all I can see is a lot of failures.
3 I feel I am a complete failure as a person.

4

0 I get as much satisfaction out of things as I used to.
1 I don't enjoy things the way I used to.
2 I don't get real satisfaction out of anything anymore.
3 I am dissatisfied or bored with everything.

5

0 I don't feel particularly guilty.
1 I feel guilty a good part of the time.
2 I feel quite guilty most of the time.
3 I feel guilty all of the time.

6

0 I don't feel I am being punished.
1 I feel I may be punished.
2 I expect to be punished.
3 I feel I am being punished.

7

0 I don't feel disappointed in myself.
1 I am disappointed in myself.
2 I am disgusted with myself.
3 I hate myself.

8

0 I don't feel I am any worse than anybody else.
1 I am critical of myself for my weaknesses or mistakes.
2 I blame myself all the time for my faults.
3 I blame myself for everything bad that happens.

9

0 I don't have any thoughts of killing myself.
1 I have thoughts of killing myself, but I would not carry them out.
2 I would like to kill myself.
3 I would kill myself if I had the chance.

10

0 I don't cry any more than usual.
1 I cry more now than I used to.
2 I cry all the time now.
3 I used to be able to cry, but now I can't cry even though I want to.

11

0 I am no more irritated now than I ever am.
1 I get annoyed or irritated more easily than I used to.
2 I feel irritated all the time now.
3 I don't get irritated at all by the things that used to irritate me.

12

0 I have not lost interest in other people.
1 I am less interested in other people than I used to be.
2 I have lost most of my interest in other people.
3 I have lost all of my interest in other people.

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BECK DEPRESSION INVENTORY

13

0 I make decisions about as well as I ever could.
1 I put off making decisions more than I used to.
2 I have greater difficulty in making decisions than before.
3 I can't make decisions at all anymore.

14

0 I don't feel I look any worse than I used to.
1 I am worried that I am looking old or unattractive.
2 I feel that there are permanent changes in my appearance that make me look unattractive.
3 I believe that I look ugly.

15

0 I can work about as well as before.
1 It takes an extra effort to get started at doing something.
2 I have to push myself very hard to do anything.
3 I can't do any work at all.

16

0 I can sleep as well as usual.
1 I don't sleep as well as I used to.
2 I wake up 1-2 hours earlier than usual and find it hard to get back to sleep.
3 I wake up several hours earlier than I used to and cannot get back to sleep.

17

0 I don't get more tired than usual.
1 I get tired more easily than I used to.
2 I get tired from doing almost anything.
3 I am too tired to do anything.

18

0 My appetite is no worse than usual.
1 My appetite is not as good as it used to be.
2 My appetite is much worse now.
3 I have no appetite at all anymore.

19

0 I haven't lost much weight, if any, lately.
1 I have lost more than 5 pounds.
2 I have lost more than 10 pounds.
3 I have lost more than 15 pounds.

19a

I am purposely trying to lose weight by eating less.
1 Yes
2 No

20

0 I am no more worried about my health than usual.
1 I am worried about physical problems such as aches and pains; or upset stomach or constipation.
2 I am very worried about physical problems and it's hard to think of much else.
3 I am so worried about my physical problems that I cannot think about anything else.

21

0 I have not noticed any recent change in my interest in sex.
1 I am less interested in sex than I used to be.
2 I am much less interested in sex now.
3 I have lost interest in sex completely.

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HAMILTON ANXIETY SCALE

INFORMATION NOT OBTAINED ☐

For each of the items below, **CHECK ONE BOX** that best describes the patient.

1. **ANXIOUS MOOD:** Worries, anticipation of the worst, fearful anticipation, irritability

   ☐ 0 Not present
   ☐ 1 Mild
   ☐ 2 Moderate
   ☐ 3 Severe
   ☐ 4 Very severe

2. **TENSION**: Feelings of tension, fatigability, startle response, moved to tears easily, trembling, feeling of restlessness, inability to relax

   ☐ 0 Not present
   ☐ 1 Mild
   ☐ 2 Moderate
   ☐ 3 Severe
   ☐ 4 Very severe

3. **FEARS**: Of dark, of strangers, of being alone, of animals, of traffic, of crowds

   ☐ 0 Not present
   ☐ 1 Mild
   ☐ 2 Moderate
   ☐ 3 Severe
   ☐ 4 Very severe

4. **INSOMNIA**: Difficulty in falling asleep, broken sleep, unsatisfying sleep and fatigue on waking, dreams, nightmares, night terrors

   ☐ 0 Not present
   ☐ 1 Mild
   ☐ 2 Moderate
   ☐ 3 Severe
   ☐ 4 Very severe

5. **INTELLECTUAL (COGNITIVE)**: Difficulty in concentration, poor memory

   ☐ 0 Not present
   ☐ 1 Mild
   ☐ 2 Moderate
   ☐ 3 Severe
   ☐ 4 Very severe

6. **DEPRESSED MOOD**: Loss of interest, lack of pleasure in hobbies, depression, early waking, diurnal swing

   ☐ 0 Not present
   ☐ 1 Mild
   ☐ 2 Moderate
   ☐ 3 Severe
   ☐ 4 Very severe

7. **SOMATIC (MUSCULAR)**: Pains and aches, twitchings, stiffness, myoclonic jerks, grinding of teeth, unsteady voice, increased muscular tone

   ☐ 0 Not present
   ☐ 1 Mild
   ☐ 2 Moderate
   ☐ 3 Severe
   ☐ 4 Very severe

8. **SOMATIC (SENSORY)**: Tinnitus, blurring of vision, hot and cold flushes, feeling of weakness, pricking sensation

   ☐ 0 Not present
   ☐ 1 Mild
   ☐ 2 Moderate
   ☐ 3 Severe
   ☐ 4 Very severe

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HAMILTON ANXIETY SCALE

9. **CARDIOVASCULAR SYMPTOMS:** Tachycardia, palpitations, pain in chest, throbbing of vessels, fainting feelings, missing beat

- ☐ 0 Not present
- ☐ 1 Mild
- ☐ 2 Moderate
- ☐ 3 Severe
- ☐ 4 Very severe

10. **RESPIRATORY SYMPTOMS:** Pressure or constriction in chest, choking feelings, sighing, dyspnea

- ☐ 0 Not present
- ☐ 1 Mild
- ☐ 2 Moderate
- ☐ 3 Severe
- ☐ 4 Very severe

11. **GASTROINTESTINAL SYMPTOMS:** Difficulty in swallowing, wind, abdominal pain, burning sensations, abdominal fullness, nausea, vomiting, borborygmi, looseness of bowels, loss of weight, constipation

- ☐ 0 Not present
- ☐ 1 Mild
- ☐ 2 Moderate
- ☐ 3 Severe
- ☐ 4 Very severe

12. **GENITOURINARY SYMPTOMS:** Frequency of micturition, urgency of micturition, amenorrhea, menorrhagia, development of frigidity, premature ejaculation, loss of libido, impotence

- ☐ 0 Not present
- ☐ 1 Mild
- ☐ 2 Moderate
- ☐ 3 Severe
- ☐ 4 Very severe

13. **AUTONOMIC SYMPTOMS:** Dry mouth, flushing, pallor, tendency to sweat, giddiness, tension headache, raising of hair

- ☐ 0 Not present
- ☐ 1 Mild
- ☐ 2 Moderate
- ☐ 3 Severe
- ☐ 4 Very severe

14. **BEHAVIOR AT INTERVIEW:** Fidgeting, restlessness or pacing, tremor of hands, furrowed brow, strained face, sighing or rapid respiration, facial pallor, swallowing, belching, brisk tendon jerks, dilated pupils, exophthalmos

- ☐ 0 Not present
- ☐ 1 Mild
- ☐ 2 Moderate
- ☐ 3 Severe
- ☐ 4 Very severe

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Clinical Report Form
Fluoxetine Versus Placebo in Childhood/Adolescent Depression
B1Y-MC-HCJE

COMMENTS : VISIT

NO COMMENTS ☐

Comments should address any clinical report form items that require further explanation. Repeating information from the clinical report form is discouraged.

Comment on all clinically significant lab values that are outside a clinically accepted reference range or clinically significant values that differ importantly from previous values.

If the patient is ending participation in the study at this visit, enter only comments that apply to this visit; then complete the Patient Summary and Study Summary Comments pages.

Print legibly and do not use abbreviations or symbols.

The information reported for this visit is accurate and complete.

_____ _____/_____/_____
Signature MM DD YY

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Clinical Report Form
Fluoxetine Versus Placebo in Childhood/Adolescent Depression
B1Y-MC-HCJE

PATIENT AND VISIT IDENTIFICATION

Patient initials _____ _____ _____
First Middle Last

Visit date _____/_____/_____
MM DD YY

VITAL SIGNS : BLOOD PRESSURE AND HEART RATE

INFORMATION NOT OBTAINED ☐

Position
SI = Sitting

Position	Blood Pressure (mm Hg) Systolic/Diastolic	Heart Rate (bpm)
SI	/	

VITAL SIGNS: TEMPERATURE

INFORMATION NOT OBTAINED ☐

Temperature ___ ___ ___ . ___

Unit of measure (F) Fahrenheit

Method (E) Ear

REMINDER

On the Pre-existing Conditions and Study Adverse Events pages, record new events that occurred since the previous visit and re-evaluate any on-going conditions or events.

On the Concomitant Medication pages, record new medications the patient has taken since the previous visit, any changes to ongoing medications, and a stop date for any medication the patient is no longer taking.

Initials
Date Verified
Initials
Date Keyed
Date Received at Lilly
Reviewed
Inspected
Date

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STUDY DRUG : DATES OF MISSED DOSES

NO MISSED DOSES ☐

Record the date for any day on which the patient missed a full or partial dose of study drug.

	Dates of Missed Doses		
	MM	DD	YY
0.			
1.			
2.			
3.			
4.			
5.			
6.			
7.			
8.			
9.			

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Clinical Report Form
Fluoxetine Versus Placebo in Childhood/Adolescent Depression
B1Y-MC-HCJE

SIDE EFFECTS CHECKLIST

INFORMATION NOT OBTAINED ☐

Since your last visit, have you been bothered with or had any trouble with any of the items listed below? Check the box which best tells how much you were bothered.

	Not at all	Just a little	Pretty much	Very much	Don't know
1. Eating?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
2. Drinking?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
3. Dry mouth and lips?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
4. Wetness in mouth?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
5. Constipation?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
6. Diarrhea?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
7. Stomachaches?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
8. Muscle cramps?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
9. Being sick to your stomach?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
10. Wetting the bed?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
11. Urinating?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
12. Itchy or scratchy skin?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
13. Rashes?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
14. Cold or sniffles?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
15. Headache?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4

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B1Y-MC-HCJE

SIDE EFFECTS CHECKLIST

	Not at all	Just a little	Pretty much	Very much	Don't know
16. Dizziness?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
17. Playing sports?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
18. Shakiness?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
19. Pronouncing words?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
20. Doing things with your hands?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
21. Sitting still?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
22. Tiredness?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
23. Feeling sleepy?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
24. Trouble sleeping?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
25. Bad dreams?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
26. Getting along with parents?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
27. Getting along with kids?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
28. Crying?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
29. Getting mad?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
30. Not being happy?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
31. Being sad?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
32. Paying attention?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4

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Clinical Report Form
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CHILDRENS DEPRESSION RATING SCALE - REVISED

INFORMATION NOT OBTAINED ☐

CHECK THE NUMERIC CODE which best describes the patient.

1. **SCHOOLWORK**:

☐ 1 Performance consistent with ability
☐ 2
☐ 3 Decrease in school performance
☐ 4
☐ 5 Major interference in most subjects
☐ 6
☐ 7 No motivation to perform

2. **CAPACITY TO HAVE FUN**

☐ 1 Interest and activities realistically appropriate for age, personality, and social environment. Shows no appreciable change with present illness.
☐ 2
☐ 3 Describes some activities realistically available several times a week but not on a daily basis. Shows interest but not enthusiasm.
☐ 4
☐ 5 Is easily bored. Complains of "nothing to do." Participates in structured activities with a "going through the motions" attitude. May express interest primarily in activities that are (realistically) unavailable on a daily or weekly basis.
☐ 6
☐ 7 Has no initiative to become involved in any activities. Primarily passive. Watches others play or watches TV but shows little interest. Requires coaxing and/or pushing to get involved in activity. Shows no enthusiasm or real interest. Has difficulty naming activities.

3. **SOCIAL WITHDRAWAL**

☐ 1 Enjoys friendships with peers at school and home
☐ 2
☐ 3 May not actively seek out friendships but waits for others to initiate a relationship or may occasionally reject opportunities to play without a describable alternative
☐ 4
☐ 5 Frequently avoids or refuses opportunities for desirable interaction with others and/or sets up situations where rejection is inevitable.
☐ 6
☐ 7 Does not currently relate to other children. States he or she has "no friends" or actively rejects new or former friends.

4. **SLEEP**

☐ 1 No (or occasional) difficulty. (Goes to sleep within 1/2 hour or less.)
☐ 2
☐ 3 Frequently has mild difficulty with sleep
☐ 4
☐ 5 Moderate difficulty with sleep nearly every night.

5. **APPETITE OR EATING PATTERNS**

☐ 1 No problems or change in eating pattern
☐ 2
☐ 3 Mild change from usual eating habits within onset of current behavioral problem
☐ 4
☐ 5 Is not hungry most of the time or has excessive food intake since onset of current behavioral problems or marked increase in appetite

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CHILDRENS DEPRESSION RATING SCALE - REVISED

CHECK THE NUMERIC CODE which best describes the patient.

6. **EXCESSIVE FATIGUE**

- ☐ 1 No unusual complaints of "feeling tired" during the day
- ☐ 2
- ☐ 3 Complaints of fatigue which seem somewhat excessive and not related to boredom
- ☐ 4
- ☐ 5 Daily complaints of feeling tired
- ☐ 6
- ☐ 7 Complains of feeling tired most of the day. May voluntarily take long naps without feeling refreshed. Interferes with play activities.

7. **PHYSICAL COMPLAINTS**:

- ☐ 1 Occasional complaints
- ☐ 2
- ☐ 3 Complaints appear mildly excessive
- ☐ 4
- ☐ 5 Complains daily. Some interference with the ability of the child to function
- ☐ 6
- ☐ 7 Preoccupied with aches and pains; interferes with play activities several times a week

8. **IRRITABILITY**

- ☐ 1 Rare
- ☐ 2 Occasional
- ☐ 3 Several times a week for short periods
- ☐ 4
- ☐ 5 Several times a week for longer periods
- ☐ 6
- ☐ 7 Constant

9. **GUILT**

- ☐ 1 Does not express any undue feeling of guilt. Appears appropriate to precipitating event.
- ☐ 2
- ☐ 3 Exaggerates guilt and/or shame out of proportion to the event described.
- ☐ 4
- ☐ 5 Feels guilty over things not under his or her control. Guilt is definitely pathological.
- ☐ 6
- ☐ 7 Severe delusions of guilt

10. **SELF-ESTEEM**

- ☐ 1 Describes self in primarily positive terms
- ☐ 2
- ☐ 3 Describes self with one important area where the child feels deficit
- ☐ 4
- ☐ 5 Describes self in preponderance of negative terms or gives bland answers to questions
- ☐ 6
- ☐ 7 Refers to self in derogatory terms. Reports that other children refer to him/her frequently by using derogatory nicknames and child puts self down

11. **DEPRESSED FEELINGS**

- ☐ 1 Occasional feelings of unhappiness which quickly disappear
- ☐ 2
- ☐ 3 Describes sustained periods of unhappiness which appear excessive for events described
- ☐ 4
- ☐ 5 Feels unhappy most of the time without a major precipitating cause
- ☐ 6
- ☐ 7 Feels unhappy all of the time. Accompanied by psychic pain (e.g., "I can't stand it").

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B1Y-MC-HCJE

CHILDRENS DEPRESSION RATING SCALE - REVISED

CHECK THE NUMERIC CODE which best describes the patient.

12. **MORBID IDEATION**

- ☐ 1 None
- ☐ 2
- ☐ 3 Has some morbid thought, all of which relate to a reality event but seem excessive.
- ☐ 4
- ☐ 5 Preoccupied with morbid thoughts several times a week. Morbid thoughts extend beyond external reality
- ☐ 6
- ☐ 7 Preoccupied with death themes or morbid thoughts that are elaborate, extensive or bizarre on a daily basis

13. **SUICIDAL IDEATION**

- ☐ 1 Understands the word "suicide" but does not apply term to self
- ☐ 2 Sharp denial of suicidal thoughts
- ☐ 3 Has thoughts about suicide, usually when angry.
- ☐ 4
- ☐ 5 Has recurrent thoughts of suicide
- ☐ 6
- ☐ 7 Has made suicide attempt within the last month or is actively suicidal

14. **WEEPING**:

- ☐ 1 Normal for age.
- ☐ 2 Suggestive statements that child cries, or feels like crying, more frequently than peers.
- ☐ 3 Child cries slightly more than peers.
- ☐ 4
- ☐ 5 Cries or feels like crying frequently (several times a week). Admits to crying without knowing reason why.
- ☐ 6
- ☐ 7 Cries nearly every day.

15. **DEPRESSED AFFECT:**

- ☐ 1 Definitely not depressed. Facial expression and voice animated during interview.
- ☐ 2 Mild suppression of affect. Some loss of spontaneity.
- ☐ 3 Overall loss of spontaneity. Looks distinctly unhappy during parts of the interview. May still be able to smile when discussing non-threatening areas.
- ☐ 4
- ☐ 5 Moderate restriction of affect throughout most of interview. Has longer and frequent periods of looking distinctly unhappy.
- ☐ 6
- ☐ 7 Severe. Looks sad, withdrawn. Minimal verbal interaction throughout interview. Cries or may appear tearful.

16. **TEMPO OF SPEECH:**

- ☐ 1 Normal
- ☐ 2 Slow
- ☐ 3 Slow: delays interview.
- ☐ 4
- ☐ 5 Severe. Low; marked interference with interview.

17. **HYPOACTIVITY:**

- ☐ 1 None
- ☐ 2
- ☐ 3 Mild. Some body movements.
- ☐ 4
- ☐ 5 Moderate. Definite motor retardation.
- ☐ 6
- ☐ 7 Severe. Motionless throughout interview.

(DNDE)

Total of 1 - 17 _____

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CLINICAL GLOBAL IMPRESSION: EFFICACY INDEX

Using the worksheet below, enter the 2-digit efficacy index rating.

1. Efficacy index rating ___ ___

(DNDE)

EFFICACY INDEX WORKSHEET

Rate this item on the basis of DRUG EFFECT ONLY.

Select the terms that best describe the degrees of therapeutic effect and side effects and record the number from the box where the two items intersect in the blanks above.

THERAPEUTIC EFFECT	SIDE EFFECTS			
	None	Do not significantly interfere with patient's functioning	Significantly interferes with patient's functioning	Outweighs therapeutic effect
MARKED - Vast improvement. Complete or nearly complete remission of all symptoms.	**01**	**02**	**03**	**04**
MODERATE - Decided improvement. Partial remission of symptoms.	**05**	**06**	**07**	**08**
MINIMAL - Slight improvement which doesn't alter status of care of patient.	**09**	**10**	**11**	**12**
UNCHANGED OR WORSE	**13**	**14**	**15**	**16**
Not Assessed = **98**				

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CLINICAL GLOBAL IMPRESSION: SEVERITY

INFORMATION NOT OBTAINED ☐

Considering your total clinical experience with this particular population, how mentally ill is the patient at this time?

- ☐ 1 Normal, not at all ill
- ☐ 2 Borderline ill
- ☐ 3 Mildly ill
- ☐ 4 Moderately ill
- ☐ 5 Markedly ill
- ☐ 6 Severely ill
- ☐ 7 Among the most extremely ill patients

Evaluator's initials _____ _____ _____
First Middle Last

CLINICAL GLOBAL IMPRESSION: IMPROVEMENT

INFORMATION NOT OBTAINED ☐

Rate total improvement, whether or not in your judgement it is due entirely to drug treatment. Compared to the patient's condition at Visit 1, how much has he/she changed?

- ☐ 1 Very much improved
- ☐ 2 Much improved
- ☐ 3 Minimally improved
- ☐ 4 No change
- ☐ 5 Minimally worse
- ☐ 6 Much worse
- ☐ 7 Very much worse

Evaluator's initials _____ _____ _____
First Middle Last

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MONTGOMERY - ASBERG DEPRESSION RATING SCALE (MADRS)

INFORMATION NOT OBTAINED ☐

The rating should be based on a clinical interview moving from broadly phrased questions about symptoms to more detailed ones which allow a precise rating of severity. The rater must decide whether the rating lies on the defined scale steps (0, 2, 4, 6) or between them (1, 3, 5).

Check the box (number) that best characterizes the patient at this time

1. **APPARENT SADNESS**
   Representing despondency, gloom, and despair (more than just ordinary transient low spirits), reflected in speech, facial expression, and posture. Rate by depth and inability to brighten up.

   ☐ 0 No sadness.
   ☐ 1
   ☐ 2 Looks dispirited but does brighten up without difficulty.
   ☐ 3
   ☐ 4 Appears sad and unhappy most of the time.
   ☐ 5
   ☐ 6 Looks miserable all the time. Extremely despondent.

2. **REPORTED SADNESS**
   Represented by reports of depressed mood, regardless of whether it is reflected in appearance or not. Includes low spirits, despondency, or the feeling of being beyond help and without hope. Rate according to intensity, duration, and the extent to which the mood is reported to be influenced by events.

   ☐ 0 Occasional sadness in keeping with the circumstances.
   ☐ 1
   ☐ 2 Sad or low but brightens up without difficulty.
   ☐ 3
   ☐ 4 Pervasive feelings of sadness or gloominess. The mood is still influenced by external circumstances.
   ☐ 5
   ☐ 6 Continuous unvarying sadness, misery or despondency.

3. **INNER TENSION**
   Representing feelings of ill-defined discomfort, edginess, inner turmoil, mental tension mounting to either panic, dread, or anguish. Rate according to intensity, frequency, duration, and the extent of reassurance called for.

   ☐ 0 Placid. Only fleeting inner tension.
   ☐ 1
   ☐ 2 Occasional feelings of edginess and ill-defined discomfort.
   ☐ 3
   ☐ 4 Continuous feelings of inner tension or intermittent panic which the patient can only master with some difficulty.
   ☐ 5
   ☐ 6 Unrelenting dread or anguish. Overwhelming panic.

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MONTGOMERY - ASBERG DEPRESSION RATING SCALE (MADRS)

4. **REDUCED SLEEP**
Representing the experience of reduced duration or depth of sleep compared to the subject's own pattern when well.

- ☐ 0 Sleeps as usual.
- ☐ 1
- ☐ 2 Slight difficulty dropping off to sleep or slightly reduced, light or fitful sleep.
- ☐ 3
- ☐ 4 Sleep reduced or broken by at least two hours.
- ☐ 5
- ☐ 6 Less than two or three hours sleep.

5. **REDUCED APPETITE**
Representing the feeling of a loss of appetite compared with when well. Rate by loss of desire for food or the need to force oneself to eat.

- ☐ 0 Normal or increased appetite
- ☐ 1
- ☐ 2 Slightly reduced appetite.
- ☐ 3
- ☐ 4 No appetite. Food is tasteless.
- ☐ 5
- ☐ 6 Needs persuasion to eat at all.

6. **CONCENTRATION DIFFICULTIES**
Representing difficulties in collecting one's thoughts mounting to incapacitating lack of concentration.

- ☐ 0 No difficulties in concentrating.
- ☐ 1
- ☐ 2 Occasional difficulties in collecting one's thoughts.
- ☐ 3
- ☐ 4 Difficulties in concentrating and sustaining thought which reduces ability to read or hold a conversation.
- ☐ 5
- ☐ 6 Unable to read or converse without great difficulty.

7. **LASSITUDE**
Representing a difficulty getting started or slowness initiating and performing everyday activities.

- ☐ 0 Hardly any difficulty in getting started. No sluggishness.
- ☐ 1
- ☐ 2 Difficulties in starting activities
- ☐ 3
- ☐ 4 Difficulties in starting simple routine activities which are carried out with effort.
- ☐ 5
- ☐ 6 Complete lassitude. Unable to do anything without help.

8. **INABILITY TO FEEL**
Representing the subjective experience of reduced interest in the surroundings, or activities that normally give pleasure. The ability to react with adequate emotion to circumstances or people is reduced.

- ☐ 0 Normal interest in the surroundings and other people.
- ☐ 1
- ☐ 2 Reduced ability to enjoy usual interests.
- ☐ 3
- ☐ 4 Loss of interest in the surroundings. Loss of feelings for friends and acquaintances.
- ☐ 5
- ☐ 6 The experience of being emotionally paralyzed, inability to feel anger, grief, or pleasure and a complete or even painful failure to feel for close relatives and friends.

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MONTGOMERY - ASBERG DEPRESSION RATING SCALE (MADRS)

9. **PESSIMISTIC THOUGHTS**
Representing thoughts of guilt, inferiority, self-reproach, sinfulness, remorse, and ruin

- ☐ 0 No pessimistic thoughts.
- ☐ 1
- ☐ 2 Fluctuating ideas of failure, self-reproach, or self-depreciation.
- ☐ 3
- ☐ 4 Persistent self-accusations, or definite but still rational ideas of guilt, or sin. Increasingly pessimistic about the future.
- ☐ 5
- ☐ 6 Delusions of ruin, remorse, or unredeemable sin. Self-accusations which are absurd and unshakable.

10. **SUICIDAL THOUGHTS**
Representing the feeling that life is not worth living, that a natural death would be welcome, suicidal thoughts, and preparations for suicide. Suicidal attempts should not in themselves influence the rating.

- ☐ 0 Enjoys life or takes it as it comes.
- ☐ 1
- ☐ 2 Weary of life. Only fleeting suicidal thoughts.
- ☐ 3
- ☐ 4 Probably better off dead. Suicidal thoughts are common, and suicide is considered as a possible solution, but without specific plans or intention.
- ☐ 5
- ☐ 6 Explicit plans for suicide when there is an opportunity. Active preparations for suicide.

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B1Y-MC-HCJE

COMMENTS : VISIT

NO COMMENTS ☐

Comments should address any clinical report form items that require further explanation. Repeating information from the clinical report form is discouraged.

Comment on all clinically significant lab values that are outside a clinically accepted reference range or clinically significant values that differ importantly from previous values.

If the patient is ending participation in the study at this visit, enter only comments that apply to this visit; then complete the Patient Summary and Study Summary Comments pages.

Print legibly and do not use abbreviations or symbols.

The information reported for this visit is accurate and complete.

_____ _____/_____/_____
Signature MM DD YY

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PATIENT AND VISIT IDENTIFICATION

Patient initials _____ _____ _____
First Middle Last

Visit date _____/_____/_____
MM DD YY

VITAL SIGNS : BLOOD PRESSURE AND HEART RATE

INFORMATION NOT OBTAINED ☐

Position
SI = Sitting

Position	Blood Pressure (mm Hg) Systolic/Diastolic	Heart Rate (bpm)
SI	/	

VITAL SIGNS: TEMPERATURE

INFORMATION NOT OBTAINED ☐

Temperature ___ ___ ___ . ___

Unit of measure (F) Fahrenheit

Method (E) Ear

REMINDER

On the Pre-existing Conditions and Study Adverse Events pages, record new events that occurred since the previous visit and re-evaluate any on-going conditions or events.

On the Concomitant Medication pages, record new medications the patient has taken since the previous visit, any changes to ongoing medications, and a stop date for any medication the patient is no longer taking.

Initials
Date Verified
Initials
Date Keyed
Date Received at Lilly
Reviewed
Inspected
Date

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STUDY DRUG : DATES OF MISSED DOSES

NO MISSED DOSES ☐

Record the date for any day on which the patient missed a full or partial dose of study drug.

	Dates of Missed Doses		
	MM	DD	YY
0.			
1.			
2.			
3.			
4.			
5.			
6.			
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Fluoxetine Versus Placebo in Childhood/Adolescent Depression
B1Y-MC-HCJE

SIDE EFFECTS CHECKLIST

INFORMATION NOT OBTAINED ☐

Since your last visit, have you been bothered with or had any trouble with any of the items listed below? Check the box which best tells how much you were bothered.

	Not at all	Just a little	Pretty much	Very much	Don't know
1. Eating?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
2. Drinking?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
3. Dry mouth and lips?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
4. Wetness in mouth?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
5. Constipation?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
6. Diarrhea?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
7. Stomachaches?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
8. Muscle cramps?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
9. Being sick to your stomach?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
10. Wetting the bed?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
11. Urinating?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
12. Itchy or scratchy skin?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
13. Rashes?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
14. Cold or sniffles?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
15. Headache?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4

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Clinical Report Form
Fluoxetine Versus Placebo in Childhood/Adolescent Depression
B1Y-MC-HCJE

SIDE EFFECTS CHECKLIST

	Not at all	Just a little	Pretty much	Very much	Don't know
16. Dizziness?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
17. Playing sports?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
18. Shakiness?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
19. Pronouncing words?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
20. Doing things with your hands?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
21. Sitting still?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
22. Tiredness?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
23. Feeling sleepy?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
24. Trouble sleeping?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
25. Bad dreams?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
26. Getting along with parents?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
27. Getting along with kids?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
28. Crying?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
29. Getting mad?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
30. Not being happy?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
31. Being sad?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
32. Paying attention?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4

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Fluoxetine Versus Placebo in Childhood/Adolescent Depression
B1Y-MC-HCJE

CHILDRENS DEPRESSION RATING SCALE - REVISED

INFORMATION NOT OBTAINED ☐

CHECK THE NUMERIC CODE which best describes the patient.

1. **SCHOOLWORK**:

☐ 1 Performance consistent with ability
☐ 2
☐ 3 Decrease in school performance
☐ 4
☐ 5 Major interference in most subjects
☐ 6
☐ 7 No motivation to perform

2. **CAPACITY TO HAVE FUN**

☐ 1 Interest and activities realistically appropriate for age, personality, and social environment. Shows no appreciable change with present illness.
☐ 2
☐ 3 Describes some activities realistically available several times a week but not on a daily basis. Shows interest but not enthusiasm.
☐ 4
☐ 5 Is easily bored. Complains of "nothing to do." Participates in structured activities with a "going through the motions" attitude. May express interest primarily in activities that are (realistically) unavailable on a daily or weekly basis.
☐ 6
☐ 7 Has no initiative to become involved in any activities. Primarily passive. Watches others play or watches TV but shows little interest. Requires coaxing and/or pushing to get involved in activity. Shows no enthusiasm or real interest. Has difficulty naming activities.

3. **SOCIAL WITHDRAWAL**

☐ 1 Enjoys friendships with peers at school and home
☐ 2
☐ 3 May not actively seek out friendships but waits for others to initiate a relationship or may occasionally reject opportunities to play without a describable alternative
☐ 4
☐ 5 Frequently avoids or refuses opportunities for desirable interaction with others and/or sets up situations where rejection is inevitable.
☐ 6
☐ 7 Does not currently relate to other children. States he or she has "no friends" or actively rejects new or former friends.

4. **SLEEP**

☐ 1 No (or occasional) difficulty. (Goes to sleep within 1/2 hour or less.)
☐ 2
☐ 3 Frequently has mild difficulty with sleep
☐ 4
☐ 5 Moderate difficulty with sleep nearly every night.

5. **APPETITE OR EATING PATTERNS**

☐ 1 No problems or change in eating pattern
☐ 2
☐ 3 Mild change from usual eating habits within onset of current behavioral problem
☐ 4
☐ 5 Is not hungry most of the time or has excessive food intake since onset of current behavioral problems or marked increase in appetite

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CHILDRENS DEPRESSION RATING SCALE - REVISED

CHECK THE NUMERIC CODE which best describes the patient.

6. **EXCESSIVE FATIGUE**

- ☐ 1 No unusual complaints of "feeling tired" during the day
- ☐ 2
- ☐ 3 Complaints of fatigue which seem somewhat excessive and not related to boredom
- ☐ 4
- ☐ 5 Daily complaints of feeling tired
- ☐ 6
- ☐ 7 Complains of feeling tired most of the day. May voluntarily take long naps without feeling refreshed. Interferes with play activities.

7. **PHYSICAL COMPLAINTS**:

- ☐ 1 Occasional complaints
- ☐ 2
- ☐ 3 Complaints appear mildly excessive
- ☐ 4
- ☐ 5 Complains daily. Some interference with the ability of the child to function
- ☐ 6
- ☐ 7 Preoccupied with aches and pains; interferes with play activities several times a week

8. **IRRITABILITY**

- ☐ 1 Rare
- ☐ 2 Occasional
- ☐ 3 Several times a week for short periods
- ☐ 4
- ☐ 5 Several times a week for longer periods
- ☐ 6
- ☐ 7 Constant

9. **GUILT**

- ☐ 1 Does not express any undue feeling of guilt. Appears appropriate to precipitating event.
- ☐ 2
- ☐ 3 Exaggerates guilt and/or shame out of proportion to the event described.
- ☐ 4
- ☐ 5 Feels guilty over things not under his or her control. Guilt is definitely pathological.
- ☐ 6
- ☐ 7 Severe delusions of guilt

10. **SELF-ESTEEM**

- ☐ 1 Describes self in primarily positive terms
- ☐ 2
- ☐ 3 Describes self with one important area where the child feels deficit
- ☐ 4
- ☐ 5 Describes self in preponderance of negative terms or gives bland answers to questions
- ☐ 6
- ☐ 7 Refers to self in derogatory terms. Reports that other children refer to him/her frequently by using derogatory nicknames and child puts self down

11. **DEPRESSED FEELINGS**

- ☐ 1 Occasional feelings of unhappiness which quickly disappear
- ☐ 2
- ☐ 3 Describes sustained periods of unhappiness which appear excessive for events described
- ☐ 4
- ☐ 5 Feels unhappy most of the time without a major precipitating cause
- ☐ 6
- ☐ 7 Feels unhappy all of the time. Accompanied by psychic pain (e.g., "I can't stand it").

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Fluoxetine Versus Placebo in Childhood/Adolescent Depression
B1Y-MC-HCJE

CHILDRENS DEPRESSION RATING SCALE - REVISED

CHECK THE NUMERIC CODE which best describes the patient.

12. **MORBID IDEATION**

- ☐ 1 None
- ☐ 2
- ☐ 3 Has some morbid thought, all of which relate to a reality event but seem excessive.
- ☐ 4
- ☐ 5 Preoccupied with morbid thoughts several times a week. Morbid thoughts extend beyond external reality
- ☐ 6
- ☐ 7 Preoccupied with death themes or morbid thoughts that are elaborate, extensive or bizarre on a daily basis

13. **SUICIDAL IDEATION**

- ☐ 1 Understands the word "suicide" but does not apply term to self
- ☐ 2 Sharp denial of suicidal thoughts
- ☐ 3 Has thoughts about suicide, usually when angry.
- ☐ 4
- ☐ 5 Has recurrent thoughts of suicide
- ☐ 6
- ☐ 7 Has made suicide attempt within the last month or is actively suicidal

14. **WEEPING**:

- ☐ 1 Normal for age.
- ☐ 2 Suggestive statements that child cries, or feels like crying, more frequently than peers.
- ☐ 3 Child cries slightly more than peers.
- ☐ 4
- ☐ 5 Cries or feels like crying frequently (several times a week). Admits to crying without knowing reason why.
- ☐ 6
- ☐ 7 Cries nearly every day.

15. **DEPRESSED AFFECT:**

- ☐ 1 Definitely not depressed. Facial expression and voice animated during interview.
- ☐ 2 Mild suppression of affect. Some loss of spontaneity.
- ☐ 3 Overall loss of spontaneity. Looks distinctly unhappy during parts of the interview. May still be able to smile when discussing non-threatening areas.
- ☐ 4
- ☐ 5 Moderate restriction of affect throughout most of interview. Has longer and frequent periods of looking distinctly unhappy.
- ☐ 6
- ☐ 7 Severe. Looks sad, withdrawn. Minimal verbal interaction throughout interview. Cries or may appear tearful.

16. **TEMPO OF SPEECH:**

- ☐ 1 Normal
- ☐ 2 Slow
- ☐ 3 Slow: delays interview.
- ☐ 4
- ☐ 5 Severe. Low; marked interference with interview.

17. **HYPOACTIVITY:**

- ☐ 1 None
- ☐ 2
- ☐ 3 Mild. Some body movements.
- ☐ 4
- ☐ 5 Moderate. Definite motor retardation.
- ☐ 6
- ☐ 7 Severe. Motionless throughout interview.

(DNDE)

Total of 1 - 17 _____

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Fluoxetine Versus Placebo in Childhood/Adolescent Depression
B1Y-MC-HCJE

CLINICAL GLOBAL IMPRESSION: EFFICACY INDEX

Using the worksheet below, enter the 2-digit efficacy index rating.

1. Efficacy index rating ___ ___

(DNDE)

EFFICACY INDEX WORKSHEET

Rate this item on the basis of DRUG EFFECT ONLY.

Select the terms that best describe the degrees of therapeutic effect and side effects and record the number from the box where the two items intersect in the blanks above.

THERAPEUTIC EFFECT	SIDE EFFECTS			
	None	Do not significantly interfere with patient's functioning	Significantly interferes with patient's functioning	Outweighs therapeutic effect
MARKED - Vast improvement. Complete or nearly complete remission of all symptoms.	**01**	**02**	**03**	**04**
MODERATE - Decided improvement. Partial remission of symptoms.	**05**	**06**	**07**	**08**
MINIMAL - Slight improvement which doesn't alter status of care of patient.	**09**	**10**	**11**	**12**
UNCHANGED OR WORSE	**13**	**14**	**15**	**16**
Not Assessed = **98**				

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CLINICAL GLOBAL IMPRESSION: SEVERITY

INFORMATION NOT OBTAINED ☐

Considering your total clinical experience with this particular population, how mentally ill is the patient at this time?

- ☐ 1 Normal, not at all ill
- ☐ 2 Borderline ill
- ☐ 3 Mildly ill
- ☐ 4 Moderately ill
- ☐ 5 Markedly ill
- ☐ 6 Severely ill
- ☐ 7 Among the most extremely ill patients

Evaluator's initials _____ _____ _____
First Middle Last

CLINICAL GLOBAL IMPRESSION: IMPROVEMENT

INFORMATION NOT OBTAINED ☐

Rate total improvement, whether or not in your judgement it is due entirely to drug treatment. Compared to the patient's condition at Visit 1, how much has he/she changed?

- ☐ 1 Very much improved
- ☐ 2 Much improved
- ☐ 3 Minimally improved
- ☐ 4 No change
- ☐ 5 Minimally worse
- ☐ 6 Much worse
- ☐ 7 Very much worse

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MONTGOMERY - ASBERG DEPRESSION RATING SCALE (MADRS)

INFORMATION NOT OBTAINED ☐

The rating should be based on a clinical interview moving from broadly phrased questions about symptoms to more detailed ones which allow a precise rating of severity. The rater must decide whether the rating lies on the defined scale steps (0, 2, 4, 6) or between them (1, 3, 5).

Check the box (number) that best characterizes the patient at this time

1. **APPARENT SADNESS**
   Representing despondency, gloom, and despair (more than just ordinary transient low spirits), reflected in speech, facial expression, and posture. Rate by depth and inability to brighten up.

   ☐ 0 No sadness.
   ☐ 1
   ☐ 2 Looks dispirited but does brighten up without difficulty.
   ☐ 3
   ☐ 4 Appears sad and unhappy most of the time.
   ☐ 5
   ☐ 6 Looks miserable all the time. Extremely despondent.

2. **REPORTED SADNESS**
   Represented by reports of depressed mood, regardless of whether it is reflected in appearance or not. Includes low spirits, despondency, or the feeling of being beyond help and without hope. Rate according to intensity, duration, and the extent to which the mood is reported to be influenced by events.

   ☐ 0 Occasional sadness in keeping with the circumstances.
   ☐ 1
   ☐ 2 Sad or low but brightens up without difficulty.
   ☐ 3
   ☐ 4 Pervasive feelings of sadness or gloominess. The mood is still influenced by external circumstances.
   ☐ 5
   ☐ 6 Continuous unvarying sadness, misery or despondency.

3. **INNER TENSION**
   Representing feelings of ill-defined discomfort, edginess, inner turmoil, mental tension mounting to either panic, dread, or anguish. Rate according to intensity, frequency, duration, and the extent of reassurance called for.

   ☐ 0 Placid. Only fleeting inner tension.
   ☐ 1
   ☐ 2 Occasional feelings of edginess and ill-defined discomfort.
   ☐ 3
   ☐ 4 Continuous feelings of inner tension or intermittent panic which the patient can only master with some difficulty.
   ☐ 5
   ☐ 6 Unrelenting dread or anguish. Overwhelming panic.

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MONTGOMERY - ASBERG DEPRESSION RATING SCALE (MADRS)

4. **REDUCED SLEEP**
Representing the experience of reduced duration or depth of sleep compared to the subject's own pattern when well.

- ☐ 0 Sleeps as usual.
- ☐ 1
- ☐ 2 Slight difficulty dropping off to sleep or slightly reduced, light or fitful sleep.
- ☐ 3
- ☐ 4 Sleep reduced or broken by at least two hours.
- ☐ 5
- ☐ 6 Less than two or three hours sleep.

5. **REDUCED APPETITE**
Representing the feeling of a loss of appetite compared with when well. Rate by loss of desire for food or the need to force oneself to eat.

- ☐ 0 Normal or increased appetite
- ☐ 1
- ☐ 2 Slightly reduced appetite.
- ☐ 3
- ☐ 4 No appetite. Food is tasteless.
- ☐ 5
- ☐ 6 Needs persuasion to eat at all.

6. **CONCENTRATION DIFFICULTIES**
Representing difficulties in collecting one's thoughts mounting to incapacitating lack of concentration.

- ☐ 0 No difficulties in concentrating.
- ☐ 1
- ☐ 2 Occasional difficulties in collecting one's thoughts.
- ☐ 3
- ☐ 4 Difficulties in concentrating and sustaining thought which reduces ability to read or hold a conversation.
- ☐ 5
- ☐ 6 Unable to read or converse without great difficulty.

7. **LASSITUDE**
Representing a difficulty getting started or slowness initiating and performing everyday activities.

- ☐ 0 Hardly any difficulty in getting started. No sluggishness.
- ☐ 1
- ☐ 2 Difficulties in starting activities
- ☐ 3
- ☐ 4 Difficulties in starting simple routine activities which are carried out with effort.
- ☐ 5
- ☐ 6 Complete lassitude. Unable to do anything without help.

8. **INABILITY TO FEEL**
Representing the subjective experience of reduced interest in the surroundings, or activities that normally give pleasure. The ability to react with adequate emotion to circumstances or people is reduced.

- ☐ 0 Normal interest in the surroundings and other people.
- ☐ 1
- ☐ 2 Reduced ability to enjoy usual interests.
- ☐ 3
- ☐ 4 Loss of interest in the surroundings. Loss of feelings for friends and acquaintances.
- ☐ 5
- ☐ 6 The experience of being emotionally paralyzed, inability to feel anger, grief, or pleasure and a complete or even painful failure to feel for close relatives and friends.

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B1Y-MC-HCJE

MONTGOMERY - ASBERG DEPRESSION RATING SCALE (MADRS)

9. **PESSIMISTIC THOUGHTS**
Representing thoughts of guilt, inferiority, self-reproach, sinfulness, remorse, and ruin

- ☐ 0 No pessimistic thoughts.
- ☐ 1
- ☐ 2 Fluctuating ideas of failure, self-reproach, or self-depreciation.
- ☐ 3
- ☐ 4 Persistent self-accusations, or definite but still rational ideas of guilt, or sin. Increasingly pessimistic about the future.
- ☐ 5
- ☐ 6 Delusions of ruin, remorse, or unredeemable sin. Self-accusations which are absurd and unshakable.

10. **SUICIDAL THOUGHTS**
Representing the feeling that life is not worth living, that a natural death would be welcome, suicidal thoughts, and preparations for suicide. Suicidal attempts should not in themselves influence the rating.

- ☐ 0 Enjoys life or takes it as it comes.
- ☐ 1
- ☐ 2 Weary of life. Only fleeting suicidal thoughts.
- ☐ 3
- ☐ 4 Probably better off dead. Suicidal thoughts are common, and suicide is considered as a possible solution, but without specific plans or intention.
- ☐ 5
- ☐ 6 Explicit plans for suicide when there is an opportunity. Active preparations for suicide.

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B1Y-MC-HCJE

CHILDREN'S DEPRESSION INDEX (CDI)

NOTE: Only complete if patient was 8 to 12 years old at Visit 1. If patient was not 8 to 12 years old, check the Information Not Obtained box.

INFORMATION NOT OBTAINED ☐

This lists the feelings and ideas in groups. From each group of three sentences, pick one sentence that describes you **best** for the past two weeks. After you pick a sentence from the first group, go on to the next group. There is no right answer or wrong answer. Just pick the sentence that best describes the way you have been recently. Put an "X" in the box next to your answer.
Remember: pick out the sentences that describe you best **in the past two weeks**.

Item 1

- ☐ 0 I am sad once in a while.
- ☐ 1 I am sad many times.
- ☐ 2 I am sad all the time.

Item 2

- ☐ 2 Nothing will ever work out for me.
- ☐ 1 I am not sure if things will work out for me.
- ☐ 0 Things will work out for me O.K.

Item 3

- ☐ 0 I do most things O.K.
- ☐ 1 I do many things wrong.
- ☐ 2 I do everything wrong.

Item 4

- ☐ 0 I have fun in many things.
- ☐ 1 I have fun in some things.
- ☐ 2 Nothing is fun at all.

Item 5

- ☐ 2 I am bad all the time.
- ☐ 1 I am bad many times.
- ☐ 0 I am bad once in a while.

Item 6

- ☐ 0 I think about bad things happening to me once in a while.
- ☐ 1 I worry that bad things will happen to me.
- ☐ 2 I am sure that terrible things will happen to me.

Item 7

- ☐ 2 I hate myself.
- ☐ 1 I do not like myself.
- ☐ 0 I like myself.

Item 8

- ☐ 2 All bad things are my fault.
- ☐ 1 Many bad things are my fault.
- ☐ 0 Bad things are not usually my fault.

Item 9

- ☐ 0 I do not think about killing myself.
- ☐ 1 I think about killing myself but I would not do it.
- ☐ 2 I want to kill myself.

Item 10

- ☐ 2 I feel like crying every day.
- ☐ 1 I feel like crying many days.
- ☐ 0 I feel like crying once in a while.

Item 11

- ☐ 2 Things bother me all the time.
- ☐ 1 Things bother me many times.
- ☐ 0 Things bother me once in a while.

Item 12

- ☐ 0 I like being with people.
- ☐ 1 I do not like being with people many times.
- ☐ 2 I do not want to be with people at all.

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CHILDREN'S DEPRESSION INDEX (CDI)

Item 13

- ☐ 2 I cannot make up my mind about things.
- ☐ 1 It is hard to make up my mind about things.
- ☐ 0 I make up my mind about things easily.

Item 14

- ☐ 0 I look O.K.
- ☐ 1 There are some bad things about my looks.
- ☐ 2 I look ugly.

Item 15

- ☐ 2 I have to push myself all the time to do my schoolwork.
- ☐ 1 I have to push myself many times to do my schoolwork.
- ☐ 0 Doing schoolwork is not a big problem.

Item 16

- ☐ 2 I have trouble sleeping every night.
- ☐ 1 I have trouble sleeping many nights.
- ☐ 0 I sleep pretty well.

Item 17

- ☐ 0 I am tired once in a while.
- ☐ 1 I am tired many days.
- ☐ 2 I am tired all the time.

Item 18

- ☐ 2 Most days I do not feel like eating.
- ☐ 1 Many days I do not feel like eating.
- ☐ 0 I eat pretty well.

Item 19

- ☐ 0 I do not worry about aches and pains.
- ☐ 1 I worry about aches and pains many times.
- ☐ 2 I worry about aches and pains all the time.

Item 20

- ☐ 0 I do not feel alone.
- ☐ 1 I feel alone many times.
- ☐ 2 I feel alone all the time.

Item 21

- ☐ 2 I never have fun at school.
- ☐ 1 I have fun at school only once in a while.
- ☐ 0 I have fun at school many times.

Item 22

- ☐ 0 I have plenty of friends.
- ☐ 1 I have some friends but I wish I had more.
- ☐ 2 I do not have any friends.

Item 23

- ☐ 0 My schoolwork is alright.
- ☐ 1 My schoolwork is not as good as before.
- ☐ 2 I do very badly in subjects I used to be good in.

Item 24

- ☐ 2 I can never be as good as other kids.
- ☐ 1 I can be as good as other kids if I want to.
- ☐ 0 I am just as good as other kids.

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CHILDREN'S DEPRESSION INDEX (CDI)

Item 25

- ☐ 2 Nobody really loves me.
- ☐ 1 I am not sure if anybody loves me.
- ☐ 0 I am sure that somebody loves me.

Item 26

- ☐ 0 I usually do what I am told.
- ☐ 1 I do not do what I am told most times.
- ☐ 2 I never do what I am told.

Item 27

- ☐ 0 I get along with people.
- ☐ 1 I get into fights many times.
- ☐ 2 I get into fights all the time.

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BECK DEPRESSION INVENTORY

NOTE: Only complete if patient was 13 to 17 years old at Visit 1. If patient was not 13 to 17 years old, check the Information Not Obtained box.

INFORMATION NOT OBTAINED ☐

This questionnaire consists of 21 groups of statements. After reading each group of statements carefully circle the number (0, 1, 2, 3) next to the one statement in each group which best describes the way you have been feeling **the past week, including today**. If several statements within a group seem to apply equally well, circle each one. Be sure to read all the statements in each group before making your choice.

1

0 I do not feel sad.
1 I feel sad.
2 I am sad all the time and I can't snap out of it.
3 I am so sad or unhappy that I can't stand it.

2

0 I am not particularly discouraged about the future.
1 I feel discouraged about the future.
2 I feel I have nothing to look forward to.
3 I feel that the future is hopeless and that things cannot improve.

3

0 I do not feel like a failure.
1 I feel I have failed more than the average person.
2 As I look back on my life, all I can see is a lot of failures.
3 I feel I am a complete failure as a person.

4

0 I get as much satisfaction out of things as I used to.
1 I don't enjoy things the way I used to.
2 I don't get real satisfaction out of anything anymore.
3 I am dissatisfied or bored with everything.

5

0 I don't feel particularly guilty.
1 I feel guilty a good part of the time.
2 I feel quite guilty most of the time.
3 I feel guilty all of the time.

6

0 I don't feel I am being punished.
1 I feel I may be punished.
2 I expect to be punished.
3 I feel I am being punished.

7

0 I don't feel disappointed in myself.
1 I am disappointed in myself.
2 I am disgusted with myself.
3 I hate myself.

8

0 I don't feel I am any worse than anybody else.
1 I am critical of myself for my weaknesses or mistakes.
2 I blame myself all the time for my faults.
3 I blame myself for everything bad that happens.

9

0 I don't have any thoughts of killing myself.
1 I have thoughts of killing myself, but I would not carry them out.
2 I would like to kill myself.
3 I would kill myself if I had the chance.

10

0 I don't cry any more than usual.
1 I cry more now than I used to.
2 I cry all the time now.
3 I used to be able to cry, but now I can't cry even though I want to.

11

0 I am no more irritated now than I ever am.
1 I get annoyed or irritated more easily than I used to.
2 I feel irritated all the time now.
3 I don't get irritated at all by the things that used to irritate me.

12

0 I have not lost interest in other people.
1 I am less interested in other people than I used to be.
2 I have lost most of my interest in other people.
3 I have lost all of my interest in other people.

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BECK DEPRESSION INVENTORY

13

0 I make decisions about as well as I ever could.
1 I put off making decisions more than I used to.
2 I have greater difficulty in making decisions than before.
3 I can't make decisions at all anymore.

14

0 I don't feel I look any worse than I used to.
1 I am worried that I am looking old or unattractive.
2 I feel that there are permanent changes in my appearance that make me look unattractive.
3 I believe that I look ugly.

15

0 I can work about as well as before.
1 It takes an extra effort to get started at doing something.
2 I have to push myself very hard to do anything.
3 I can't do any work at all.

16

0 I can sleep as well as usual.
1 I don't sleep as well as I used to.
2 I wake up 1-2 hours earlier than usual and find it hard to get back to sleep.
3 I wake up several hours earlier than I used to and cannot get back to sleep.

17

0 I don't get more tired than usual.
1 I get tired more easily than I used to.
2 I get tired from doing almost anything.
3 I am too tired to do anything.

18

0 My appetite is no worse than usual.
1 My appetite is not as good as it used to be.
2 My appetite is much worse now.
3 I have no appetite at all anymore.

19

0 I haven't lost much weight, if any, lately.
1 I have lost more than 5 pounds.
2 I have lost more than 10 pounds.
3 I have lost more than 15 pounds.

19a

I am purposely trying to lose weight by eating less.
1 Yes
2 No

20

0 I am no more worried about my health than usual.
1 I am worried about physical problems such as aches and pains; or upset stomach or constipation.
2 I am very worried about physical problems and it's hard to think of much else.
3 I am so worried about my physical problems that I cannot think about anything else.

21

0 I have not noticed any recent change in my interest in sex.
1 I am less interested in sex than I used to be.
2 I am much less interested in sex now.
3 I have lost interest in sex completely.

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HAMILTON ANXIETY SCALE

INFORMATION NOT OBTAINED ☐

For each of the items below, **CHECK ONE BOX** that best describes the patient.

1. **ANXIOUS MOOD:** Worries, anticipation of the worst, fearful anticipation, irritability

   ☐ 0 Not present
   ☐ 1 Mild
   ☐ 2 Moderate
   ☐ 3 Severe
   ☐ 4 Very severe

2. **TENSION**: Feelings of tension, fatigability, startle response, moved to tears easily, trembling, feeling of restlessness, inability to relax

   ☐ 0 Not present
   ☐ 1 Mild
   ☐ 2 Moderate
   ☐ 3 Severe
   ☐ 4 Very severe

3. **FEARS**: Of dark, of strangers, of being alone, of animals, of traffic, of crowds

   ☐ 0 Not present
   ☐ 1 Mild
   ☐ 2 Moderate
   ☐ 3 Severe
   ☐ 4 Very severe

4. **INSOMNIA**: Difficulty in falling asleep, broken sleep, unsatisfying sleep and fatigue on waking, dreams, nightmares, night terrors

   ☐ 0 Not present
   ☐ 1 Mild
   ☐ 2 Moderate
   ☐ 3 Severe
   ☐ 4 Very severe

5. **INTELLECTUAL (COGNITIVE)**: Difficulty in concentration, poor memory

   ☐ 0 Not present
   ☐ 1 Mild
   ☐ 2 Moderate
   ☐ 3 Severe
   ☐ 4 Very severe

6. **DEPRESSED MOOD**: Loss of interest, lack of pleasure in hobbies, depression, early waking, diurnal swing

   ☐ 0 Not present
   ☐ 1 Mild
   ☐ 2 Moderate
   ☐ 3 Severe
   ☐ 4 Very severe

7. **SOMATIC (MUSCULAR)**: Pains and aches, twitchings, stiffness, myoclonic jerks, grinding of teeth, unsteady voice, increased muscular tone

   ☐ 0 Not present
   ☐ 1 Mild
   ☐ 2 Moderate
   ☐ 3 Severe
   ☐ 4 Very severe

8. **SOMATIC (SENSORY)**: Tinnitus, blurring of vision, hot and cold flushes, feeling of weakness, pricking sensation

   ☐ 0 Not present
   ☐ 1 Mild
   ☐ 2 Moderate
   ☐ 3 Severe
   ☐ 4 Very severe

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HAMILTON ANXIETY SCALE

9. **CARDIOVASCULAR SYMPTOMS:** Tachycardia, palpitations, pain in chest, throbbing of vessels, fainting feelings, missing beat

- ☐ 0 Not present
- ☐ 1 Mild
- ☐ 2 Moderate
- ☐ 3 Severe
- ☐ 4 Very severe

10. **RESPIRATORY SYMPTOMS:** Pressure or constriction in chest, choking feelings, sighing, dyspnea

- ☐ 0 Not present
- ☐ 1 Mild
- ☐ 2 Moderate
- ☐ 3 Severe
- ☐ 4 Very severe

11. **GASTROINTESTINAL SYMPTOMS:** Difficulty in swallowing, wind, abdominal pain, burning sensations, abdominal fullness, nausea, vomiting, borborygmi, looseness of bowels, loss of weight, constipation

- ☐ 0 Not present
- ☐ 1 Mild
- ☐ 2 Moderate
- ☐ 3 Severe
- ☐ 4 Very severe

12. **GENITOURINARY SYMPTOMS:** Frequency of micturition, urgency of micturition, amenorrhea, menorrhagia, development of frigidity, premature ejaculation, loss of libido, impotence

- ☐ 0 Not present
- ☐ 1 Mild
- ☐ 2 Moderate
- ☐ 3 Severe
- ☐ 4 Very severe

13. **AUTONOMIC SYMPTOMS:** Dry mouth, flushing, pallor, tendency to sweat, giddiness, tension headache, raising of hair

- ☐ 0 Not present
- ☐ 1 Mild
- ☐ 2 Moderate
- ☐ 3 Severe
- ☐ 4 Very severe

14. **BEHAVIOR AT INTERVIEW:** Fidgeting, restlessness or pacing, tremor of hands, furrowed brow, strained face, sighing or rapid respiration, facial pallor, swallowing, belching, brisk tendon jerks, dilated pupils, exophthalmos

- ☐ 0 Not present
- ☐ 1 Mild
- ☐ 2 Moderate
- ☐ 3 Severe
- ☐ 4 Very severe

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Clinical Report Form
Fluoxetine Versus Placebo in Childhood/Adolescent Depression
B1Y-MC-HCJE

COMMENTS : VISIT

NO COMMENTS ☐

Comments should address any clinical report form items that require further explanation. Repeating information from the clinical report form is discouraged.

Comment on all clinically significant lab values that are outside a clinically accepted reference range or clinically significant values that differ importantly from previous values.

If the patient is ending participation in the study at this visit, enter only comments that apply to this visit; then complete the Patient Summary and Study Summary Comments pages.

Print legibly and do not use abbreviations or symbols.

The information reported for this visit is accurate and complete.

_____ _____/_____/_____
Signature MM DD YY

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B1Y-MC-HCJE

PATIENT AND VISIT IDENTIFICATION

Patient initials _____ _____ _____
First Middle Last

Visit date _____/_____/_____
MM DD YY

VITAL SIGNS : BLOOD PRESSURE AND HEART RATE

INFORMATION NOT OBTAINED ☐

Position
SI = Sitting

Position	Blood Pressure (mm Hg) Systolic/Diastolic	Heart Rate (bpm)
SI	/	

VITAL SIGNS: TEMPERATURE

INFORMATION NOT OBTAINED ☐

Temperature ___ ___ ___ . ___

Unit of measure (F) Fahrenheit

Method (E) Ear

REMINDER

On the Pre-existing Conditions and Study Adverse Events pages, record new events that occurred since the previous visit and re-evaluate any on-going conditions or events.

On the Concomitant Medication pages, record new medications the patient has taken since the previous visit, any changes to ongoing medications, and a stop date for any medication the patient is no longer taking.

Initials
Date Verified
Initials
Date Keyed
Date Received at Lilly
Reviewed
Inspected
Date

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STUDY DRUG : DATES OF MISSED DOSES

NO MISSED DOSES ☐

Record the date for any day on which the patient missed a full or partial dose of study drug.

	Dates of Missed Doses		
	MM	DD	YY
0.			
1.			
2.			
3.			
4.			
5.			
6.			
7.			
8.			
9.			

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B1Y-MC-HCJE

SIDE EFFECTS CHECKLIST

INFORMATION NOT OBTAINED ☐

Since your last visit, have you been bothered with or had any trouble with any of the items listed below? Check the box which best tells how much you were bothered.

	Not at all	Just a little	Pretty much	Very much	Don't know
1. Eating?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
2. Drinking?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
3. Dry mouth and lips?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
4. Wetness in mouth?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
5. Constipation?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
6. Diarrhea?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
7. Stomachaches?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
8. Muscle cramps?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
9. Being sick to your stomach?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
10. Wetting the bed?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
11. Urinating?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
12. Itchy or scratchy skin?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
13. Rashes?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
14. Cold or sniffles?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
15. Headache?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4

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B1Y-MC-HCJE

SIDE EFFECTS CHECKLIST

	Not at all	Just a little	Pretty much	Very much	Don't know
16. Dizziness?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
17. Playing sports?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
18. Shakiness?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
19. Pronouncing words?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
20. Doing things with your hands?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
21. Sitting still?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
22. Tiredness?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
23. Feeling sleepy?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
24. Trouble sleeping?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
25. Bad dreams?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
26. Getting along with parents?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
27. Getting along with kids?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
28. Crying?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
29. Getting mad?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
30. Not being happy?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
31. Being sad?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
32. Paying attention?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4

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CHILDRENS DEPRESSION RATING SCALE - REVISED

INFORMATION NOT OBTAINED ☐

CHECK THE NUMERIC CODE which best describes the patient.

1. **SCHOOLWORK**:

☐ 1 Performance consistent with ability
☐ 2
☐ 3 Decrease in school performance
☐ 4
☐ 5 Major interference in most subjects
☐ 6
☐ 7 No motivation to perform

2. **CAPACITY TO HAVE FUN**

☐ 1 Interest and activities realistically appropriate for age, personality, and social environment. Shows no appreciable change with present illness.
☐ 2
☐ 3 Describes some activities realistically available several times a week but not on a daily basis. Shows interest but not enthusiasm.
☐ 4
☐ 5 Is easily bored. Complains of "nothing to do." Participates in structured activities with a "going through the motions" attitude. May express interest primarily in activities that are (realistically) unavailable on a daily or weekly basis.
☐ 6
☐ 7 Has no initiative to become involved in any activities. Primarily passive. Watches others play or watches TV but shows little interest. Requires coaxing and/or pushing to get involved in activity. Shows no enthusiasm or real interest. Has difficulty naming activities.

3. **SOCIAL WITHDRAWAL**

☐ 1 Enjoys friendships with peers at school and home
☐ 2
☐ 3 May not actively seek out friendships but waits for others to initiate a relationship or may occasionally reject opportunities to play without a describable alternative
☐ 4
☐ 5 Frequently avoids or refuses opportunities for desirable interaction with others and/or sets up situations where rejection is inevitable.
☐ 6
☐ 7 Does not currently relate to other children. States he or she has "no friends" or actively rejects new or former friends.

4. **SLEEP**

☐ 1 No (or occasional) difficulty. (Goes to sleep within 1/2 hour or less.)
☐ 2
☐ 3 Frequently has mild difficulty with sleep
☐ 4
☐ 5 Moderate difficulty with sleep nearly every night.

5. **APPETITE OR EATING PATTERNS**

☐ 1 No problems or change in eating pattern
☐ 2
☐ 3 Mild change from usual eating habits within onset of current behavioral problem
☐ 4
☐ 5 Is not hungry most of the time or has excessive food intake since onset of current behavioral problems or marked increase in appetite

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CHILDRENS DEPRESSION RATING SCALE - REVISED

CHECK THE NUMERIC CODE which best describes the patient.

6. **EXCESSIVE FATIGUE**

- ☐ 1 No unusual complaints of "feeling tired" during the day
- ☐ 2
- ☐ 3 Complaints of fatigue which seem somewhat excessive and not related to boredom
- ☐ 4
- ☐ 5 Daily complaints of feeling tired
- ☐ 6
- ☐ 7 Complains of feeling tired most of the day. May voluntarily take long naps without feeling refreshed. Interferes with play activities.

7. **PHYSICAL COMPLAINTS**:

- ☐ 1 Occasional complaints
- ☐ 2
- ☐ 3 Complaints appear mildly excessive
- ☐ 4
- ☐ 5 Complains daily. Some interference with the ability of the child to function
- ☐ 6
- ☐ 7 Preoccupied with aches and pains; interferes with play activities several times a week

8. **IRRITABILITY**

- ☐ 1 Rare
- ☐ 2 Occasional
- ☐ 3 Several times a week for short periods
- ☐ 4
- ☐ 5 Several times a week for longer periods
- ☐ 6
- ☐ 7 Constant

9. **GUILT**

- ☐ 1 Does not express any undue feeling of guilt. Appears appropriate to precipitating event.
- ☐ 2
- ☐ 3 Exaggerates guilt and/or shame out of proportion to the event described.
- ☐ 4
- ☐ 5 Feels guilty over things not under his or her control. Guilt is definitely pathological.
- ☐ 6
- ☐ 7 Severe delusions of guilt

10. **SELF-ESTEEM**

- ☐ 1 Describes self in primarily positive terms
- ☐ 2
- ☐ 3 Describes self with one important area where the child feels deficit
- ☐ 4
- ☐ 5 Describes self in preponderance of negative terms or gives bland answers to questions
- ☐ 6
- ☐ 7 Refers to self in derogatory terms. Reports that other children refer to him/her frequently by using derogatory nicknames and child puts self down

11. **DEPRESSED FEELINGS**

- ☐ 1 Occasional feelings of unhappiness which quickly disappear
- ☐ 2
- ☐ 3 Describes sustained periods of unhappiness which appear excessive for events described
- ☐ 4
- ☐ 5 Feels unhappy most of the time without a major precipitating cause
- ☐ 6
- ☐ 7 Feels unhappy all of the time. Accompanied by psychic pain (e.g., "I can't stand it").

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CHILDRENS DEPRESSION RATING SCALE - REVISED

CHECK THE NUMERIC CODE which best describes the patient.

12. **MORBID IDEATION**

- ☐ 1 None
- ☐ 2
- ☐ 3 Has some morbid thought, all of which relate to a reality event but seem excessive.
- ☐ 4
- ☐ 5 Preoccupied with morbid thoughts several times a week. Morbid thoughts extend beyond external reality
- ☐ 6
- ☐ 7 Preoccupied with death themes or morbid thoughts that are elaborate, extensive or bizarre on a daily basis

13. **SUICIDAL IDEATION**

- ☐ 1 Understands the word "suicide" but does not apply term to self
- ☐ 2 Sharp denial of suicidal thoughts
- ☐ 3 Has thoughts about suicide, usually when angry.
- ☐ 4
- ☐ 5 Has recurrent thoughts of suicide
- ☐ 6
- ☐ 7 Has made suicide attempt within the last month or is actively suicidal

14. **WEEPING**:

- ☐ 1 Normal for age.
- ☐ 2 Suggestive statements that child cries, or feels like crying, more frequently than peers.
- ☐ 3 Child cries slightly more than peers.
- ☐ 4
- ☐ 5 Cries or feels like crying frequently (several times a week). Admits to crying without knowing reason why.
- ☐ 6
- ☐ 7 Cries nearly every day.

15. **DEPRESSED AFFECT:**

- ☐ 1 Definitely not depressed. Facial expression and voice animated during interview.
- ☐ 2 Mild suppression of affect. Some loss of spontaneity.
- ☐ 3 Overall loss of spontaneity. Looks distinctly unhappy during parts of the interview. May still be able to smile when discussing non-threatening areas.
- ☐ 4
- ☐ 5 Moderate restriction of affect throughout most of interview. Has longer and frequent periods of looking distinctly unhappy.
- ☐ 6
- ☐ 7 Severe. Looks sad, withdrawn. Minimal verbal interaction throughout interview. Cries or may appear tearful.

16. **TEMPO OF SPEECH:**

- ☐ 1 Normal
- ☐ 2 Slow
- ☐ 3 Slow: delays interview.
- ☐ 4
- ☐ 5 Severe. Low; marked interference with interview.

17. **HYPOACTIVITY:**

- ☐ 1 None
- ☐ 2
- ☐ 3 Mild. Some body movements.
- ☐ 4
- ☐ 5 Moderate. Definite motor retardation.
- ☐ 6
- ☐ 7 Severe. Motionless throughout interview.

(DNDE)

Total of 1 - 17 _____

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CLINICAL GLOBAL IMPRESSION: EFFICACY INDEX

Using the worksheet below, enter the 2-digit efficacy index rating.

1. Efficacy index rating ___ ___

(DNDE)

EFFICACY INDEX WORKSHEET

Rate this item on the basis of DRUG EFFECT ONLY.

Select the terms that best describe the degrees of therapeutic effect and side effects and record the number from the box where the two items intersect in the blanks above.

THERAPEUTIC EFFECT	SIDE EFFECTS			
	None	Do not significantly interfere with patient's functioning	Significantly interferes with patient's functioning	Outweighs therapeutic effect
MARKED - Vast improvement. Complete or nearly complete remission of all symptoms.	**01**	**02**	**03**	**04**
MODERATE - Decided improvement. Partial remission of symptoms.	**05**	**06**	**07**	**08**
MINIMAL - Slight improvement which doesn't alter status of care of patient.	**09**	**10**	**11**	**12**
UNCHANGED OR WORSE	**13**	**14**	**15**	**16**
Not Assessed = **98**				

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CLINICAL GLOBAL IMPRESSION: SEVERITY

INFORMATION NOT OBTAINED ☐

Considering your total clinical experience with this particular population, how mentally ill is the patient at this time?

- ☐ 1 Normal, not at all ill
- ☐ 2 Borderline ill
- ☐ 3 Mildly ill
- ☐ 4 Moderately ill
- ☐ 5 Markedly ill
- ☐ 6 Severely ill
- ☐ 7 Among the most extremely ill patients

Evaluator's initials _____ _____ _____
First Middle Last

CLINICAL GLOBAL IMPRESSION: IMPROVEMENT

INFORMATION NOT OBTAINED ☐

Rate total improvement, whether or not in your judgement it is due entirely to drug treatment. Compared to the patient's condition at Visit 1, how much has he/she changed?

- ☐ 1 Very much improved
- ☐ 2 Much improved
- ☐ 3 Minimally improved
- ☐ 4 No change
- ☐ 5 Minimally worse
- ☐ 6 Much worse
- ☐ 7 Very much worse

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MONTGOMERY - ASBERG DEPRESSION RATING SCALE (MADRS)

INFORMATION NOT OBTAINED ☐

The rating should be based on a clinical interview moving from broadly phrased questions about symptoms to more detailed ones which allow a precise rating of severity. The rater must decide whether the rating lies on the defined scale steps (0, 2, 4, 6) or between them (1, 3, 5).

Check the box (number) that best characterizes the patient at this time

1. **APPARENT SADNESS**
   Representing despondency, gloom, and despair (more than just ordinary transient low spirits), reflected in speech, facial expression, and posture. Rate by depth and inability to brighten up.

   ☐ 0 No sadness.
   ☐ 1
   ☐ 2 Looks dispirited but does brighten up without difficulty.
   ☐ 3
   ☐ 4 Appears sad and unhappy most of the time.
   ☐ 5
   ☐ 6 Looks miserable all the time. Extremely despondent.

2. **REPORTED SADNESS**
   Represented by reports of depressed mood, regardless of whether it is reflected in appearance or not. Includes low spirits, despondency, or the feeling of being beyond help and without hope. Rate according to intensity, duration, and the extent to which the mood is reported to be influenced by events.

   ☐ 0 Occasional sadness in keeping with the circumstances.
   ☐ 1
   ☐ 2 Sad or low but brightens up without difficulty.
   ☐ 3
   ☐ 4 Pervasive feelings of sadness or gloominess. The mood is still influenced by external circumstances.
   ☐ 5
   ☐ 6 Continuous unvarying sadness, misery or despondency.

3. **INNER TENSION**
   Representing feelings of ill-defined discomfort, edginess, inner turmoil, mental tension mounting to either panic, dread, or anguish. Rate according to intensity, frequency, duration, and the extent of reassurance called for.

   ☐ 0 Placid. Only fleeting inner tension.
   ☐ 1
   ☐ 2 Occasional feelings of edginess and ill-defined discomfort.
   ☐ 3
   ☐ 4 Continuous feelings of inner tension or intermittent panic which the patient can only master with some difficulty.
   ☐ 5
   ☐ 6 Unrelenting dread or anguish. Overwhelming panic.

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MONTGOMERY - ASBERG DEPRESSION RATING SCALE (MADRS)

4. **REDUCED SLEEP**
Representing the experience of reduced duration or depth of sleep compared to the subject's own pattern when well.

- ☐ 0 Sleeps as usual.
- ☐ 1
- ☐ 2 Slight difficulty dropping off to sleep or slightly reduced, light or fitful sleep.
- ☐ 3
- ☐ 4 Sleep reduced or broken by at least two hours.
- ☐ 5
- ☐ 6 Less than two or three hours sleep.

5. **REDUCED APPETITE**
Representing the feeling of a loss of appetite compared with when well. Rate by loss of desire for food or the need to force oneself to eat.

- ☐ 0 Normal or increased appetite
- ☐ 1
- ☐ 2 Slightly reduced appetite.
- ☐ 3
- ☐ 4 No appetite. Food is tasteless.
- ☐ 5
- ☐ 6 Needs persuasion to eat at all.

6. **CONCENTRATION DIFFICULTIES**
Representing difficulties in collecting one's thoughts mounting to incapacitating lack of concentration.

- ☐ 0 No difficulties in concentrating.
- ☐ 1
- ☐ 2 Occasional difficulties in collecting one's thoughts.
- ☐ 3
- ☐ 4 Difficulties in concentrating and sustaining thought which reduces ability to read or hold a conversation.
- ☐ 5
- ☐ 6 Unable to read or converse without great difficulty.

7. **LASSITUDE**
Representing a difficulty getting started or slowness initiating and performing everyday activities.

- ☐ 0 Hardly any difficulty in getting started. No sluggishness.
- ☐ 1
- ☐ 2 Difficulties in starting activities
- ☐ 3
- ☐ 4 Difficulties in starting simple routine activities which are carried out with effort.
- ☐ 5
- ☐ 6 Complete lassitude. Unable to do anything without help.

8. **INABILITY TO FEEL**
Representing the subjective experience of reduced interest in the surroundings, or activities that normally give pleasure. The ability to react with adequate emotion to circumstances or people is reduced.

- ☐ 0 Normal interest in the surroundings and other people.
- ☐ 1
- ☐ 2 Reduced ability to enjoy usual interests.
- ☐ 3
- ☐ 4 Loss of interest in the surroundings. Loss of feelings for friends and acquaintances.
- ☐ 5
- ☐ 6 The experience of being emotionally paralyzed, inability to feel anger, grief, or pleasure and a complete or even painful failure to feel for close relatives and friends.

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B1Y-MC-HCJE

MONTGOMERY - ASBERG DEPRESSION RATING SCALE (MADRS)

9. **PESSIMISTIC THOUGHTS**
Representing thoughts of guilt, inferiority, self-reproach, sinfulness, remorse, and ruin

- ☐ 0 No pessimistic thoughts.
- ☐ 1
- ☐ 2 Fluctuating ideas of failure, self-reproach, or self-depreciation.
- ☐ 3
- ☐ 4 Persistent self-accusations, or definite but still rational ideas of guilt, or sin. Increasingly pessimistic about the future.
- ☐ 5
- ☐ 6 Delusions of ruin, remorse, or unredeemable sin. Self-accusations which are absurd and unshakable.

10. **SUICIDAL THOUGHTS**
Representing the feeling that life is not worth living, that a natural death would be welcome, suicidal thoughts, and preparations for suicide. Suicidal attempts should not in themselves influence the rating.

- ☐ 0 Enjoys life or takes it as it comes.
- ☐ 1
- ☐ 2 Weary of life. Only fleeting suicidal thoughts.
- ☐ 3
- ☐ 4 Probably better off dead. Suicidal thoughts are common, and suicide is considered as a possible solution, but without specific plans or intention.
- ☐ 5
- ☐ 6 Explicit plans for suicide when there is an opportunity. Active preparations for suicide.

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B1Y-MC-HCJE

COMMENTS : VISIT

NO COMMENTS ☐

Comments should address any clinical report form items that require further explanation. Repeating information from the clinical report form is discouraged.

Comment on all clinically significant lab values that are outside a clinically accepted reference range or clinically significant values that differ importantly from previous values.

If the patient is ending participation in the study at this visit, enter only comments that apply to this visit; then complete the Patient Summary and Study Summary Comments pages.

Print legibly and do not use abbreviations or symbols.

The information reported for this visit is accurate and complete.

_____ _____/_____/_____
Signature MM DD YY

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Clinical Report Form
Fluoxetine Versus Placebo in Childhood/Adolescent Depression
B1Y-MC-HCJE

PATIENT AND VISIT IDENTIFICATION

Patient initials _____ _____ _____
First Middle Last

Visit date _____/_____/_____
MM DD YY

VITAL SIGNS : BLOOD PRESSURE AND HEART RATE

INFORMATION NOT OBTAINED ☐

Position
SI = Sitting

Position	Blood Pressure (mm Hg) Systolic/Diastolic	Heart Rate (bpm)
SI	/	

VITAL SIGNS: TEMPERATURE

INFORMATION NOT OBTAINED ☐

Temperature ___ ___ ___ . ___

Unit of measure (F) Fahrenheit

Method (E) Ear

REMINDER

On the Pre-existing Conditions and Study Adverse Events pages, record new events that occurred since the previous visit and re-evaluate any on-going conditions or events.

On the Concomitant Medication pages, record new medications the patient has taken since the previous visit, any changes to ongoing medications, and a stop date for any medication the patient is no longer taking.

Initials
Date Verified
Initials
Date Keyed
Date Received at Lilly
Reviewed
Inspected
Date

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STUDY DRUG : DATES OF MISSED DOSES

NO MISSED DOSES ☐

Record the date for any day on which the patient missed a full or partial dose of study drug.

	Dates of Missed Doses		
	MM	DD	YY
0.			
1.			
2.			
3.			
4.			
5.			
6.			
7.			
8.			
9.			

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Clinical Report Form
Fluoxetine Versus Placebo in Childhood/Adolescent Depression
B1Y-MC-HCJE

SIDE EFFECTS CHECKLIST

INFORMATION NOT OBTAINED ☐

Since your last visit, have you been bothered with or had any trouble with any of the items listed below? Check the box which best tells how much you were bothered.

	Not at all	Just a little	Pretty much	Very much	Don't know
1. Eating?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
2. Drinking?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
3. Dry mouth and lips?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
4. Wetness in mouth?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
5. Constipation?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
6. Diarrhea?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
7. Stomachaches?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
8. Muscle cramps?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
9. Being sick to your stomach?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
10. Wetting the bed?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
11. Urinating?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
12. Itchy or scratchy skin?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
13. Rashes?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
14. Cold or sniffles?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
15. Headache?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4

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Clinical Report Form
Fluoxetine Versus Placebo in Childhood/Adolescent Depression
B1Y-MC-HCJE

SIDE EFFECTS CHECKLIST

	Not at all	Just a little	Pretty much	Very much	Don't know
16. Dizziness?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
17. Playing sports?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
18. Shakiness?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
19. Pronouncing words?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
20. Doing things with your hands?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
21. Sitting still?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
22. Tiredness?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
23. Feeling sleepy?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
24. Trouble sleeping?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
25. Bad dreams?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
26. Getting along with parents?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
27. Getting along with kids?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
28. Crying?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
29. Getting mad?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
30. Not being happy?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
31. Being sad?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
32. Paying attention?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4

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Clinical Report Form
Fluoxetine Versus Placebo in Childhood/Adolescent Depression
B1Y-MC-HCJE

CHILDRENS DEPRESSION RATING SCALE - REVISED

INFORMATION NOT OBTAINED ☐

CHECK THE NUMERIC CODE which best describes the patient.

1. **SCHOOLWORK**:

☐ 1 Performance consistent with ability
☐ 2
☐ 3 Decrease in school performance
☐ 4
☐ 5 Major interference in most subjects
☐ 6
☐ 7 No motivation to perform

2. **CAPACITY TO HAVE FUN**

☐ 1 Interest and activities realistically appropriate for age, personality, and social environment. Shows no appreciable change with present illness.
☐ 2
☐ 3 Describes some activities realistically available several times a week but not on a daily basis. Shows interest but not enthusiasm.
☐ 4
☐ 5 Is easily bored. Complains of "nothing to do." Participates in structured activities with a "going through the motions" attitude. May express interest primarily in activities that are (realistically) unavailable on a daily or weekly basis.
☐ 6
☐ 7 Has no initiative to become involved in any activities. Primarily passive. Watches others play or watches TV but shows little interest. Requires coaxing and/or pushing to get involved in activity. Shows no enthusiasm or real interest. Has difficulty naming activities.

3. **SOCIAL WITHDRAWAL**

☐ 1 Enjoys friendships with peers at school and home
☐ 2
☐ 3 May not actively seek out friendships but waits for others to initiate a relationship or may occasionally reject opportunities to play without a describable alternative
☐ 4
☐ 5 Frequently avoids or refuses opportunities for desirable interaction with others and/or sets up situations where rejection is inevitable.
☐ 6
☐ 7 Does not currently relate to other children. States he or she has "no friends" or actively rejects new or former friends.

4. **SLEEP**

☐ 1 No (or occasional) difficulty. (Goes to sleep within 1/2 hour or less.)
☐ 2
☐ 3 Frequently has mild difficulty with sleep
☐ 4
☐ 5 Moderate difficulty with sleep nearly every night.

5. **APPETITE OR EATING PATTERNS**

☐ 1 No problems or change in eating pattern
☐ 2
☐ 3 Mild change from usual eating habits within onset of current behavioral problem
☐ 4
☐ 5 Is not hungry most of the time or has excessive food intake since onset of current behavioral problems or marked increase in appetite

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CHILDRENS DEPRESSION RATING SCALE - REVISED

CHECK THE NUMERIC CODE which best describes the patient.

6. **EXCESSIVE FATIGUE**

- ☐ 1 No unusual complaints of "feeling tired" during the day
- ☐ 2
- ☐ 3 Complaints of fatigue which seem somewhat excessive and not related to boredom
- ☐ 4
- ☐ 5 Daily complaints of feeling tired
- ☐ 6
- ☐ 7 Complains of feeling tired most of the day. May voluntarily take long naps without feeling refreshed. Interferes with play activities.

7. **PHYSICAL COMPLAINTS**:

- ☐ 1 Occasional complaints
- ☐ 2
- ☐ 3 Complaints appear mildly excessive
- ☐ 4
- ☐ 5 Complains daily. Some interference with the ability of the child to function
- ☐ 6
- ☐ 7 Preoccupied with aches and pains; interferes with play activities several times a week

8. **IRRITABILITY**

- ☐ 1 Rare
- ☐ 2 Occasional
- ☐ 3 Several times a week for short periods
- ☐ 4
- ☐ 5 Several times a week for longer periods
- ☐ 6
- ☐ 7 Constant

9. **GUILT**

- ☐ 1 Does not express any undue feeling of guilt. Appears appropriate to precipitating event.
- ☐ 2
- ☐ 3 Exaggerates guilt and/or shame out of proportion to the event described.
- ☐ 4
- ☐ 5 Feels guilty over things not under his or her control. Guilt is definitely pathological.
- ☐ 6
- ☐ 7 Severe delusions of guilt

10. **SELF-ESTEEM**

- ☐ 1 Describes self in primarily positive terms
- ☐ 2
- ☐ 3 Describes self with one important area where the child feels deficit
- ☐ 4
- ☐ 5 Describes self in preponderance of negative terms or gives bland answers to questions
- ☐ 6
- ☐ 7 Refers to self in derogatory terms. Reports that other children refer to him/her frequently by using derogatory nicknames and child puts self down

11. **DEPRESSED FEELINGS**

- ☐ 1 Occasional feelings of unhappiness which quickly disappear
- ☐ 2
- ☐ 3 Describes sustained periods of unhappiness which appear excessive for events described
- ☐ 4
- ☐ 5 Feels unhappy most of the time without a major precipitating cause
- ☐ 6
- ☐ 7 Feels unhappy all of the time. Accompanied by psychic pain (e.g., "I can't stand it").

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Fluoxetine Versus Placebo in Childhood/Adolescent Depression
B1Y-MC-HCJE

CHILDRENS DEPRESSION RATING SCALE - REVISED

CHECK THE NUMERIC CODE which best describes the patient.

12. **MORBID IDEATION**

- ☐ 1 None
- ☐ 2
- ☐ 3 Has some morbid thought, all of which relate to a reality event but seem excessive.
- ☐ 4
- ☐ 5 Preoccupied with morbid thoughts several times a week. Morbid thoughts extend beyond external reality
- ☐ 6
- ☐ 7 Preoccupied with death themes or morbid thoughts that are elaborate, extensive or bizarre on a daily basis

13. **SUICIDAL IDEATION**

- ☐ 1 Understands the word "suicide" but does not apply term to self
- ☐ 2 Sharp denial of suicidal thoughts
- ☐ 3 Has thoughts about suicide, usually when angry.
- ☐ 4
- ☐ 5 Has recurrent thoughts of suicide
- ☐ 6
- ☐ 7 Has made suicide attempt within the last month or is actively suicidal

14. **WEEPING**:

- ☐ 1 Normal for age.
- ☐ 2 Suggestive statements that child cries, or feels like crying, more frequently than peers.
- ☐ 3 Child cries slightly more than peers.
- ☐ 4
- ☐ 5 Cries or feels like crying frequently (several times a week). Admits to crying without knowing reason why.
- ☐ 6
- ☐ 7 Cries nearly every day.

15. **DEPRESSED AFFECT:**

- ☐ 1 Definitely not depressed. Facial expression and voice animated during interview.
- ☐ 2 Mild suppression of affect. Some loss of spontaneity.
- ☐ 3 Overall loss of spontaneity. Looks distinctly unhappy during parts of the interview. May still be able to smile when discussing non-threatening areas.
- ☐ 4
- ☐ 5 Moderate restriction of affect throughout most of interview. Has longer and frequent periods of looking distinctly unhappy.
- ☐ 6
- ☐ 7 Severe. Looks sad, withdrawn. Minimal verbal interaction throughout interview. Cries or may appear tearful.

16. **TEMPO OF SPEECH:**

- ☐ 1 Normal
- ☐ 2 Slow
- ☐ 3 Slow: delays interview.
- ☐ 4
- ☐ 5 Severe. Low; marked interference with interview.

17. **HYPOACTIVITY:**

- ☐ 1 None
- ☐ 2
- ☐ 3 Mild. Some body movements.
- ☐ 4
- ☐ 5 Moderate. Definite motor retardation.
- ☐ 6
- ☐ 7 Severe. Motionless throughout interview.

(DNDE)

Total of 1 - 17 _____

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B1Y-MC-HCJE

CLINICAL GLOBAL IMPRESSION: EFFICACY INDEX

Using the worksheet below, enter the 2-digit efficacy index rating.

1. Efficacy index rating ___ ___

(DNDE)

EFFICACY INDEX WORKSHEET

Rate this item on the basis of DRUG EFFECT ONLY.

Select the terms that best describe the degrees of therapeutic effect and side effects and record the number from the box where the two items intersect in the blanks above.

THERAPEUTIC EFFECT	SIDE EFFECTS			
	None	Do not significantly interfere with patient's functioning	Significantly interferes with patient's functioning	Outweighs therapeutic effect
MARKED - Vast improvement. Complete or nearly complete remission of all symptoms.	**01**	**02**	**03**	**04**
MODERATE - Decided improvement. Partial remission of symptoms.	**05**	**06**	**07**	**08**
MINIMAL - Slight improvement which doesn't alter status of care of patient.	**09**	**10**	**11**	**12**
UNCHANGED OR WORSE	**13**	**14**	**15**	**16**
Not Assessed = **98**				

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B1Y-MC-HCJE

CLINICAL GLOBAL IMPRESSION: SEVERITY

INFORMATION NOT OBTAINED ☐

Considering your total clinical experience with this particular population, how mentally ill is the patient at this time?

- ☐ 1 Normal, not at all ill
- ☐ 2 Borderline ill
- ☐ 3 Mildly ill
- ☐ 4 Moderately ill
- ☐ 5 Markedly ill
- ☐ 6 Severely ill
- ☐ 7 Among the most extremely ill patients

Evaluator's initials _____ _____ _____
First Middle Last

CLINICAL GLOBAL IMPRESSION: IMPROVEMENT

INFORMATION NOT OBTAINED ☐

Rate total improvement, whether or not in your judgement it is due entirely to drug treatment. Compared to the patient's condition at Visit 1, how much has he/she changed?

- ☐ 1 Very much improved
- ☐ 2 Much improved
- ☐ 3 Minimally improved
- ☐ 4 No change
- ☐ 5 Minimally worse
- ☐ 6 Much worse
- ☐ 7 Very much worse

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MONTGOMERY - ASBERG DEPRESSION RATING SCALE (MADRS)

INFORMATION NOT OBTAINED ☐

The rating should be based on a clinical interview moving from broadly phrased questions about symptoms to more detailed ones which allow a precise rating of severity. The rater must decide whether the rating lies on the defined scale steps (0, 2, 4, 6) or between them (1, 3, 5).

Check the box (number) that best characterizes the patient at this time

1. **APPARENT SADNESS**
   Representing despondency, gloom, and despair (more than just ordinary transient low spirits), reflected in speech, facial expression, and posture. Rate by depth and inability to brighten up.

   ☐ 0 No sadness.
   ☐ 1
   ☐ 2 Looks dispirited but does brighten up without difficulty.
   ☐ 3
   ☐ 4 Appears sad and unhappy most of the time.
   ☐ 5
   ☐ 6 Looks miserable all the time. Extremely despondent.

2. **REPORTED SADNESS**
   Represented by reports of depressed mood, regardless of whether it is reflected in appearance or not. Includes low spirits, despondency, or the feeling of being beyond help and without hope. Rate according to intensity, duration, and the extent to which the mood is reported to be influenced by events.

   ☐ 0 Occasional sadness in keeping with the circumstances.
   ☐ 1
   ☐ 2 Sad or low but brightens up without difficulty.
   ☐ 3
   ☐ 4 Pervasive feelings of sadness or gloominess. The mood is still influenced by external circumstances.
   ☐ 5
   ☐ 6 Continuous unvarying sadness, misery or despondency.

3. **INNER TENSION**
   Representing feelings of ill-defined discomfort, edginess, inner turmoil, mental tension mounting to either panic, dread, or anguish. Rate according to intensity, frequency, duration, and the extent of reassurance called for.

   ☐ 0 Placid. Only fleeting inner tension.
   ☐ 1
   ☐ 2 Occasional feelings of edginess and ill-defined discomfort.
   ☐ 3
   ☐ 4 Continuous feelings of inner tension or intermittent panic which the patient can only master with some difficulty.
   ☐ 5
   ☐ 6 Unrelenting dread or anguish. Overwhelming panic.

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MONTGOMERY - ASBERG DEPRESSION RATING SCALE (MADRS)

4. **REDUCED SLEEP**
Representing the experience of reduced duration or depth of sleep compared to the subject's own pattern when well.

- ☐ 0 Sleeps as usual.
- ☐ 1
- ☐ 2 Slight difficulty dropping off to sleep or slightly reduced, light or fitful sleep.
- ☐ 3
- ☐ 4 Sleep reduced or broken by at least two hours.
- ☐ 5
- ☐ 6 Less than two or three hours sleep.

5. **REDUCED APPETITE**
Representing the feeling of a loss of appetite compared with when well. Rate by loss of desire for food or the need to force oneself to eat.

- ☐ 0 Normal or increased appetite
- ☐ 1
- ☐ 2 Slightly reduced appetite.
- ☐ 3
- ☐ 4 No appetite. Food is tasteless.
- ☐ 5
- ☐ 6 Needs persuasion to eat at all.

6. **CONCENTRATION DIFFICULTIES**
Representing difficulties in collecting one's thoughts mounting to incapacitating lack of concentration.

- ☐ 0 No difficulties in concentrating.
- ☐ 1
- ☐ 2 Occasional difficulties in collecting one's thoughts.
- ☐ 3
- ☐ 4 Difficulties in concentrating and sustaining thought which reduces ability to read or hold a conversation.
- ☐ 5
- ☐ 6 Unable to read or converse without great difficulty.

7. **LASSITUDE**
Representing a difficulty getting started or slowness initiating and performing everyday activities.

- ☐ 0 Hardly any difficulty in getting started. No sluggishness.
- ☐ 1
- ☐ 2 Difficulties in starting activities
- ☐ 3
- ☐ 4 Difficulties in starting simple routine activities which are carried out with effort.
- ☐ 5
- ☐ 6 Complete lassitude. Unable to do anything without help.

8. **INABILITY TO FEEL**
Representing the subjective experience of reduced interest in the surroundings, or activities that normally give pleasure. The ability to react with adequate emotion to circumstances or people is reduced.

- ☐ 0 Normal interest in the surroundings and other people.
- ☐ 1
- ☐ 2 Reduced ability to enjoy usual interests.
- ☐ 3
- ☐ 4 Loss of interest in the surroundings. Loss of feelings for friends and acquaintances.
- ☐ 5
- ☐ 6 The experience of being emotionally paralyzed, inability to feel anger, grief, or pleasure and a complete or even painful failure to feel for close relatives and friends.

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MONTGOMERY - ASBERG DEPRESSION RATING SCALE (MADRS)

9. **PESSIMISTIC THOUGHTS**
Representing thoughts of guilt, inferiority, self-reproach, sinfulness, remorse, and ruin

- ☐ 0 No pessimistic thoughts.
- ☐ 1
- ☐ 2 Fluctuating ideas of failure, self-reproach, or self-depreciation.
- ☐ 3
- ☐ 4 Persistent self-accusations, or definite but still rational ideas of guilt, or sin. Increasingly pessimistic about the future.
- ☐ 5
- ☐ 6 Delusions of ruin, remorse, or unredeemable sin. Self-accusations which are absurd and unshakable.

10. **SUICIDAL THOUGHTS**
Representing the feeling that life is not worth living, that a natural death would be welcome, suicidal thoughts, and preparations for suicide. Suicidal attempts should not in themselves influence the rating.

- ☐ 0 Enjoys life or takes it as it comes.
- ☐ 1
- ☐ 2 Weary of life. Only fleeting suicidal thoughts.
- ☐ 3
- ☐ 4 Probably better off dead. Suicidal thoughts are common, and suicide is considered as a possible solution, but without specific plans or intention.
- ☐ 5
- ☐ 6 Explicit plans for suicide when there is an opportunity. Active preparations for suicide.

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Clinical Report Form
Fluoxetine Versus Placebo in Childhood/Adolescent Depression
B1Y-MC-HCJE

CHILDREN'S DEPRESSION INDEX (CDI)

NOTE: Only complete if patient was 8 to 12 years old at Visit 1. If patient was not 8 to 12 years old, check the Information Not Obtained box.

INFORMATION NOT OBTAINED ☐

This lists the feelings and ideas in groups. From each group of three sentences, pick one sentence that describes you **best** for the past two weeks. After you pick a sentence from the first group, go on to the next group. There is no right answer or wrong answer. Just pick the sentence that best describes the way you have been recently. Put an "X" in the box next to your answer.
Remember: pick out the sentences that describe you best **in the past two weeks**.

Item 1

- ☐ 0 I am sad once in a while.
- ☐ 1 I am sad many times.
- ☐ 2 I am sad all the time.

Item 2

- ☐ 2 Nothing will ever work out for me.
- ☐ 1 I am not sure if things will work out for me.
- ☐ 0 Things will work out for me O.K.

Item 3

- ☐ 0 I do most things O.K.
- ☐ 1 I do many things wrong.
- ☐ 2 I do everything wrong.

Item 4

- ☐ 0 I have fun in many things.
- ☐ 1 I have fun in some things.
- ☐ 2 Nothing is fun at all.

Item 5

- ☐ 2 I am bad all the time.
- ☐ 1 I am bad many times.
- ☐ 0 I am bad once in a while.

Item 6

- ☐ 0 I think about bad things happening to me once in a while.
- ☐ 1 I worry that bad things will happen to me.
- ☐ 2 I am sure that terrible things will happen to me.

Item 7

- ☐ 2 I hate myself.
- ☐ 1 I do not like myself.
- ☐ 0 I like myself.

Item 8

- ☐ 2 All bad things are my fault.
- ☐ 1 Many bad things are my fault.
- ☐ 0 Bad things are not usually my fault.

Item 9

- ☐ 0 I do not think about killing myself.
- ☐ 1 I think about killing myself but I would not do it.
- ☐ 2 I want to kill myself.

Item 10

- ☐ 2 I feel like crying every day.
- ☐ 1 I feel like crying many days.
- ☐ 0 I feel like crying once in a while.

Item 11

- ☐ 2 Things bother me all the time.
- ☐ 1 Things bother me many times.
- ☐ 0 Things bother me once in a while.

Item 12

- ☐ 0 I like being with people.
- ☐ 1 I do not like being with people many times.
- ☐ 2 I do not want to be with people at all.

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CHILDREN'S DEPRESSION INDEX (CDI)

Item 13

- ☐ 2 I cannot make up my mind about things.
- ☐ 1 It is hard to make up my mind about things.
- ☐ 0 I make up my mind about things easily.

Item 14

- ☐ 0 I look O.K.
- ☐ 1 There are some bad things about my looks.
- ☐ 2 I look ugly.

Item 15

- ☐ 2 I have to push myself all the time to do my schoolwork.
- ☐ 1 I have to push myself many times to do my schoolwork.
- ☐ 0 Doing schoolwork is not a big problem.

Item 16

- ☐ 2 I have trouble sleeping every night.
- ☐ 1 I have trouble sleeping many nights.
- ☐ 0 I sleep pretty well.

Item 17

- ☐ 0 I am tired once in a while.
- ☐ 1 I am tired many days.
- ☐ 2 I am tired all the time.

Item 18

- ☐ 2 Most days I do not feel like eating.
- ☐ 1 Many days I do not feel like eating.
- ☐ 0 I eat pretty well.

Item 19

- ☐ 0 I do not worry about aches and pains.
- ☐ 1 I worry about aches and pains many times.
- ☐ 2 I worry about aches and pains all the time.

Item 20

- ☐ 0 I do not feel alone.
- ☐ 1 I feel alone many times.
- ☐ 2 I feel alone all the time.

Item 21

- ☐ 2 I never have fun at school.
- ☐ 1 I have fun at school only once in a while.
- ☐ 0 I have fun at school many times.

Item 22

- ☐ 0 I have plenty of friends.
- ☐ 1 I have some friends but I wish I had more.
- ☐ 2 I do not have any friends.

Item 23

- ☐ 0 My schoolwork is alright.
- ☐ 1 My schoolwork is not as good as before.
- ☐ 2 I do very badly in subjects I used to be good in.

Item 24

- ☐ 2 I can never be as good as other kids.
- ☐ 1 I can be as good as other kids if I want to.
- ☐ 0 I am just as good as other kids.

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CHILDREN'S DEPRESSION INDEX (CDI)

Item 25

- ☐ 2 Nobody really loves me.
- ☐ 1 I am not sure if anybody loves me.
- ☐ 0 I am sure that somebody loves me.

Item 26

- ☐ 0 I usually do what I am told.
- ☐ 1 I do not do what I am told most times.
- ☐ 2 I never do what I am told.

Item 27

- ☐ 0 I get along with people.
- ☐ 1 I get into fights many times.
- ☐ 2 I get into fights all the time.

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BECK DEPRESSION INVENTORY

NOTE: Only complete if patient was 13 to 17 years old at Visit 1. If patient was not 13 to 17 years old, check the Information Not Obtained box.

INFORMATION NOT OBTAINED ☐

This questionnaire consists of 21 groups of statements. After reading each group of statements carefully circle the number (0, 1, 2, 3) next to the one statement in each group which best describes the way you have been feeling **the past week, including today**. If several statements within a group seem to apply equally well, circle each one. Be sure to read all the statements in each group before making your choice.

1

0 I do not feel sad.
1 I feel sad.
2 I am sad all the time and I can't snap out of it.
3 I am so sad or unhappy that I can't stand it.

2

0 I am not particularly discouraged about the future.
1 I feel discouraged about the future.
2 I feel I have nothing to look forward to.
3 I feel that the future is hopeless and that things cannot improve.

3

0 I do not feel like a failure.
1 I feel I have failed more than the average person.
2 As I look back on my life, all I can see is a lot of failures.
3 I feel I am a complete failure as a person.

4

0 I get as much satisfaction out of things as I used to.
1 I don't enjoy things the way I used to.
2 I don't get real satisfaction out of anything anymore.
3 I am dissatisfied or bored with everything.

5

0 I don't feel particularly guilty.
1 I feel guilty a good part of the time.
2 I feel quite guilty most of the time.
3 I feel guilty all of the time.

6

0 I don't feel I am being punished.
1 I feel I may be punished.
2 I expect to be punished.
3 I feel I am being punished.

7

0 I don't feel disappointed in myself.
1 I am disappointed in myself.
2 I am disgusted with myself.
3 I hate myself.

8

0 I don't feel I am any worse than anybody else.
1 I am critical of myself for my weaknesses or mistakes.
2 I blame myself all the time for my faults.
3 I blame myself for everything bad that happens.

9

0 I don't have any thoughts of killing myself.
1 I have thoughts of killing myself, but I would not carry them out.
2 I would like to kill myself.
3 I would kill myself if I had the chance.

10

0 I don't cry any more than usual.
1 I cry more now than I used to.
2 I cry all the time now.
3 I used to be able to cry, but now I can't cry even though I want to.

11

0 I am no more irritated now than I ever am.
1 I get annoyed or irritated more easily than I used to.
2 I feel irritated all the time now.
3 I don't get irritated at all by the things that used to irritate me.

12

0 I have not lost interest in other people.
1 I am less interested in other people than I used to be.
2 I have lost most of my interest in other people.
3 I have lost all of my interest in other people.

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BECK DEPRESSION INVENTORY

13

0 I make decisions about as well as I ever could.
1 I put off making decisions more than I used to.
2 I have greater difficulty in making decisions than before.
3 I can't make decisions at all anymore.

14

0 I don't feel I look any worse than I used to.
1 I am worried that I am looking old or unattractive.
2 I feel that there are permanent changes in my appearance that make me look unattractive.
3 I believe that I look ugly.

15

0 I can work about as well as before.
1 It takes an extra effort to get started at doing something.
2 I have to push myself very hard to do anything.
3 I can't do any work at all.

16

0 I can sleep as well as usual.
1 I don't sleep as well as I used to.
2 I wake up 1-2 hours earlier than usual and find it hard to get back to sleep.
3 I wake up several hours earlier than I used to and cannot get back to sleep.

17

0 I don't get more tired than usual.
1 I get tired more easily than I used to.
2 I get tired from doing almost anything.
3 I am too tired to do anything.

18

0 My appetite is no worse than usual.
1 My appetite is not as good as it used to be.
2 My appetite is much worse now.
3 I have no appetite at all anymore.

19

0 I haven't lost much weight, if any, lately.
1 I have lost more than 5 pounds.
2 I have lost more than 10 pounds.
3 I have lost more than 15 pounds.

19a

I am purposely trying to lose weight by eating less.
1 Yes
2 No

20

0 I am no more worried about my health than usual.
1 I am worried about physical problems such as aches and pains; or upset stomach or constipation.
2 I am very worried about physical problems and it's hard to think of much else.
3 I am so worried about my physical problems that I cannot think about anything else.

21

0 I have not noticed any recent change in my interest in sex.
1 I am less interested in sex than I used to be.
2 I am much less interested in sex now.
3 I have lost interest in sex completely.

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HAMILTON ANXIETY SCALE

INFORMATION NOT OBTAINED ☐

For each of the items below, **CHECK ONE BOX** that best describes the patient.

1. **ANXIOUS MOOD:** Worries, anticipation of the worst, fearful anticipation, irritability

   ☐ 0 Not present
   ☐ 1 Mild
   ☐ 2 Moderate
   ☐ 3 Severe
   ☐ 4 Very severe

2. **TENSION**: Feelings of tension, fatigability, startle response, moved to tears easily, trembling, feeling of restlessness, inability to relax

   ☐ 0 Not present
   ☐ 1 Mild
   ☐ 2 Moderate
   ☐ 3 Severe
   ☐ 4 Very severe

3. **FEARS**: Of dark, of strangers, of being alone, of animals, of traffic, of crowds

   ☐ 0 Not present
   ☐ 1 Mild
   ☐ 2 Moderate
   ☐ 3 Severe
   ☐ 4 Very severe

4. **INSOMNIA**: Difficulty in falling asleep, broken sleep, unsatisfying sleep and fatigue on waking, dreams, nightmares, night terrors

   ☐ 0 Not present
   ☐ 1 Mild
   ☐ 2 Moderate
   ☐ 3 Severe
   ☐ 4 Very severe

5. **INTELLECTUAL (COGNITIVE)**: Difficulty in concentration, poor memory

   ☐ 0 Not present
   ☐ 1 Mild
   ☐ 2 Moderate
   ☐ 3 Severe
   ☐ 4 Very severe

6. **DEPRESSED MOOD**: Loss of interest, lack of pleasure in hobbies, depression, early waking, diurnal swing

   ☐ 0 Not present
   ☐ 1 Mild
   ☐ 2 Moderate
   ☐ 3 Severe
   ☐ 4 Very severe

7. **SOMATIC (MUSCULAR)**: Pains and aches, twitchings, stiffness, myoclonic jerks, grinding of teeth, unsteady voice, increased muscular tone

   ☐ 0 Not present
   ☐ 1 Mild
   ☐ 2 Moderate
   ☐ 3 Severe
   ☐ 4 Very severe

8. **SOMATIC (SENSORY)**: Tinnitus, blurring of vision, hot and cold flushes, feeling of weakness, pricking sensation

   ☐ 0 Not present
   ☐ 1 Mild
   ☐ 2 Moderate
   ☐ 3 Severe
   ☐ 4 Very severe

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HAMILTON ANXIETY SCALE

9. **CARDIOVASCULAR SYMPTOMS:** Tachycardia, palpitations, pain in chest, throbbing of vessels, fainting feelings, missing beat

- ☐ 0 Not present
- ☐ 1 Mild
- ☐ 2 Moderate
- ☐ 3 Severe
- ☐ 4 Very severe

10. **RESPIRATORY SYMPTOMS:** Pressure or constriction in chest, choking feelings, sighing, dyspnea

- ☐ 0 Not present
- ☐ 1 Mild
- ☐ 2 Moderate
- ☐ 3 Severe
- ☐ 4 Very severe

11. **GASTROINTESTINAL SYMPTOMS:** Difficulty in swallowing, wind, abdominal pain, burning sensations, abdominal fullness, nausea, vomiting, borborygmi, looseness of bowels, loss of weight, constipation

- ☐ 0 Not present
- ☐ 1 Mild
- ☐ 2 Moderate
- ☐ 3 Severe
- ☐ 4 Very severe

12. **GENITOURINARY SYMPTOMS:** Frequency of micturition, urgency of micturition, amenorrhea, menorrhagia, development of frigidity, premature ejaculation, loss of libido, impotence

- ☐ 0 Not present
- ☐ 1 Mild
- ☐ 2 Moderate
- ☐ 3 Severe
- ☐ 4 Very severe

13. **AUTONOMIC SYMPTOMS:** Dry mouth, flushing, pallor, tendency to sweat, giddiness, tension headache, raising of hair

- ☐ 0 Not present
- ☐ 1 Mild
- ☐ 2 Moderate
- ☐ 3 Severe
- ☐ 4 Very severe

14. **BEHAVIOR AT INTERVIEW:** Fidgeting, restlessness or pacing, tremor of hands, furrowed brow, strained face, sighing or rapid respiration, facial pallor, swallowing, belching, brisk tendon jerks, dilated pupils, exophthalmos

- ☐ 0 Not present
- ☐ 1 Mild
- ☐ 2 Moderate
- ☐ 3 Severe
- ☐ 4 Very severe

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COMMENTS : VISIT

NO COMMENTS ☐

Comments should address any clinical report form items that require further explanation. Repeating information from the clinical report form is discouraged.

Comment on all clinically significant lab values that are outside a clinically accepted reference range or clinically significant values that differ importantly from previous values.

If the patient is ending participation in the study at this visit, enter only comments that apply to this visit; then complete the Patient Summary and Study Summary Comments pages.

Print legibly and do not use abbreviations or symbols.

The information reported for this visit is accurate and complete.

_____ _____/_____/_____
Signature MM DD YY

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B1Y-MC-HCJE

PATIENT AND VISIT IDENTIFICATION

Patient initials _____ _____ _____
First Middle Last

Visit date _____/_____/_____
MM DD YY

VITAL SIGNS : BLOOD PRESSURE AND HEART RATE

INFORMATION NOT OBTAINED ☐

Position
SI = Sitting

Position	Blood Pressure (mm Hg) Systolic/Diastolic	Heart Rate (bpm)
SI	/	

VITAL SIGNS: TEMPERATURE

INFORMATION NOT OBTAINED ☐

Temperature ___ ___ ___ . ___

Unit of measure (F) Fahrenheit

Method (E) Ear

REMINDER

On the Pre-existing Conditions and Study Adverse Events pages, record new events that occurred since the previous visit and re-evaluate any on-going conditions or events.

On the Concomitant Medication pages, record new medications the patient has taken since the previous visit, any changes to ongoing medications, and a stop date for any medication the patient is no longer taking.

Initials
Date Verified
Initials
Date Keyed
Date Received at Lilly
Reviewed
Inspected
Date

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STUDY DRUG : DATES OF MISSED DOSES

NO MISSED DOSES ☐

Record the date for any day on which the patient missed a full or partial dose of study drug.

	Dates of Missed Doses		
	MM	DD	YY
0.			
1.			
2.			
3.			
4.			
5.			
6.			
7.			
8.			
9.			

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B1Y-MC-HCJE

SIDE EFFECTS CHECKLIST

INFORMATION NOT OBTAINED ☐

Since your last visit, have you been bothered with or had any trouble with any of the items listed below? Check the box which best tells how much you were bothered.

	Not at all	Just a little	Pretty much	Very much	Don't know
1. Eating?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
2. Drinking?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
3. Dry mouth and lips?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
4. Wetness in mouth?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
5. Constipation?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
6. Diarrhea?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
7. Stomachaches?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
8. Muscle cramps?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
9. Being sick to your stomach?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
10. Wetting the bed?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
11. Urinating?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
12. Itchy or scratchy skin?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
13. Rashes?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
14. Cold or sniffles?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
15. Headache?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4

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B1Y-MC-HCJE

SIDE EFFECTS CHECKLIST

	Not at all	Just a little	Pretty much	Very much	Don't know
16. Dizziness?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
17. Playing sports?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
18. Shakiness?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
19. Pronouncing words?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
20. Doing things with your hands?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
21. Sitting still?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
22. Tiredness?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
23. Feeling sleepy?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
24. Trouble sleeping?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
25. Bad dreams?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
26. Getting along with parents?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
27. Getting along with kids?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
28. Crying?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
29. Getting mad?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
30. Not being happy?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
31. Being sad?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
32. Paying attention?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4

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CHILDRENS DEPRESSION RATING SCALE - REVISED

INFORMATION NOT OBTAINED ☐

CHECK THE NUMERIC CODE which best describes the patient.

1. **SCHOOLWORK**:

☐ 1 Performance consistent with ability
☐ 2
☐ 3 Decrease in school performance
☐ 4
☐ 5 Major interference in most subjects
☐ 6
☐ 7 No motivation to perform

2. **CAPACITY TO HAVE FUN**

☐ 1 Interest and activities realistically appropriate for age, personality, and social environment. Shows no appreciable change with present illness.
☐ 2
☐ 3 Describes some activities realistically available several times a week but not on a daily basis. Shows interest but not enthusiasm.
☐ 4
☐ 5 Is easily bored. Complains of "nothing to do." Participates in structured activities with a "going through the motions" attitude. May express interest primarily in activities that are (realistically) unavailable on a daily or weekly basis.
☐ 6
☐ 7 Has no initiative to become involved in any activities. Primarily passive. Watches others play or watches TV but shows little interest. Requires coaxing and/or pushing to get involved in activity. Shows no enthusiasm or real interest. Has difficulty naming activities.

3. **SOCIAL WITHDRAWAL**

☐ 1 Enjoys friendships with peers at school and home
☐ 2
☐ 3 May not actively seek out friendships but waits for others to initiate a relationship or may occasionally reject opportunities to play without a describable alternative
☐ 4
☐ 5 Frequently avoids or refuses opportunities for desirable interaction with others and/or sets up situations where rejection is inevitable.
☐ 6
☐ 7 Does not currently relate to other children. States he or she has "no friends" or actively rejects new or former friends.

4. **SLEEP**

☐ 1 No (or occasional) difficulty. (Goes to sleep within 1/2 hour or less.)
☐ 2
☐ 3 Frequently has mild difficulty with sleep
☐ 4
☐ 5 Moderate difficulty with sleep nearly every night.

5. **APPETITE OR EATING PATTERNS**

☐ 1 No problems or change in eating pattern
☐ 2
☐ 3 Mild change from usual eating habits within onset of current behavioral problem
☐ 4
☐ 5 Is not hungry most of the time or has excessive food intake since onset of current behavioral problems or marked increase in appetite

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CHILDRENS DEPRESSION RATING SCALE - REVISED

CHECK THE NUMERIC CODE which best describes the patient.

6. **EXCESSIVE FATIGUE**

- ☐ 1 No unusual complaints of "feeling tired" during the day
- ☐ 2
- ☐ 3 Complaints of fatigue which seem somewhat excessive and not related to boredom
- ☐ 4
- ☐ 5 Daily complaints of feeling tired
- ☐ 6
- ☐ 7 Complains of feeling tired most of the day. May voluntarily take long naps without feeling refreshed. Interferes with play activities.

7. **PHYSICAL COMPLAINTS**:

- ☐ 1 Occasional complaints
- ☐ 2
- ☐ 3 Complaints appear mildly excessive
- ☐ 4
- ☐ 5 Complains daily. Some interference with the ability of the child to function
- ☐ 6
- ☐ 7 Preoccupied with aches and pains; interferes with play activities several times a week

8. **IRRITABILITY**

- ☐ 1 Rare
- ☐ 2 Occasional
- ☐ 3 Several times a week for short periods
- ☐ 4
- ☐ 5 Several times a week for longer periods
- ☐ 6
- ☐ 7 Constant

9. **GUILT**

- ☐ 1 Does not express any undue feeling of guilt. Appears appropriate to precipitating event.
- ☐ 2
- ☐ 3 Exaggerates guilt and/or shame out of proportion to the event described.
- ☐ 4
- ☐ 5 Feels guilty over things not under his or her control. Guilt is definitely pathological.
- ☐ 6
- ☐ 7 Severe delusions of guilt

10. **SELF-ESTEEM**

- ☐ 1 Describes self in primarily positive terms
- ☐ 2
- ☐ 3 Describes self with one important area where the child feels deficit
- ☐ 4
- ☐ 5 Describes self in preponderance of negative terms or gives bland answers to questions
- ☐ 6
- ☐ 7 Refers to self in derogatory terms. Reports that other children refer to him/her frequently by using derogatory nicknames and child puts self down

11. **DEPRESSED FEELINGS**

- ☐ 1 Occasional feelings of unhappiness which quickly disappear
- ☐ 2
- ☐ 3 Describes sustained periods of unhappiness which appear excessive for events described
- ☐ 4
- ☐ 5 Feels unhappy most of the time without a major precipitating cause
- ☐ 6
- ☐ 7 Feels unhappy all of the time. Accompanied by psychic pain (e.g., "I can't stand it").

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CHILDRENS DEPRESSION RATING SCALE - REVISED

CHECK THE NUMERIC CODE which best describes the patient.

12. **MORBID IDEATION**

- ☐ 1 None
- ☐ 2
- ☐ 3 Has some morbid thought, all of which relate to a reality event but seem excessive.
- ☐ 4
- ☐ 5 Preoccupied with morbid thoughts several times a week. Morbid thoughts extend beyond external reality
- ☐ 6
- ☐ 7 Preoccupied with death themes or morbid thoughts that are elaborate, extensive or bizarre on a daily basis

13. **SUICIDAL IDEATION**

- ☐ 1 Understands the word "suicide" but does not apply term to self
- ☐ 2 Sharp denial of suicidal thoughts
- ☐ 3 Has thoughts about suicide, usually when angry.
- ☐ 4
- ☐ 5 Has recurrent thoughts of suicide
- ☐ 6
- ☐ 7 Has made suicide attempt within the last month or is actively suicidal

14. **WEEPING**:

- ☐ 1 Normal for age.
- ☐ 2 Suggestive statements that child cries, or feels like crying, more frequently than peers.
- ☐ 3 Child cries slightly more than peers.
- ☐ 4
- ☐ 5 Cries or feels like crying frequently (several times a week). Admits to crying without knowing reason why.
- ☐ 6
- ☐ 7 Cries nearly every day.

15. **DEPRESSED AFFECT:**

- ☐ 1 Definitely not depressed. Facial expression and voice animated during interview.
- ☐ 2 Mild suppression of affect. Some loss of spontaneity.
- ☐ 3 Overall loss of spontaneity. Looks distinctly unhappy during parts of the interview. May still be able to smile when discussing non-threatening areas.
- ☐ 4
- ☐ 5 Moderate restriction of affect throughout most of interview. Has longer and frequent periods of looking distinctly unhappy.
- ☐ 6
- ☐ 7 Severe. Looks sad, withdrawn. Minimal verbal interaction throughout interview. Cries or may appear tearful.

16. **TEMPO OF SPEECH:**

- ☐ 1 Normal
- ☐ 2 Slow
- ☐ 3 Slow: delays interview.
- ☐ 4
- ☐ 5 Severe. Low; marked interference with interview.

17. **HYPOACTIVITY:**

- ☐ 1 None
- ☐ 2
- ☐ 3 Mild. Some body movements.
- ☐ 4
- ☐ 5 Moderate. Definite motor retardation.
- ☐ 6
- ☐ 7 Severe. Motionless throughout interview.

(DNDE)

Total of 1 - 17 _____

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CLINICAL GLOBAL IMPRESSION: EFFICACY INDEX

Using the worksheet below, enter the 2-digit efficacy index rating.

1. Efficacy index rating ___ ___

(DNDE)

EFFICACY INDEX WORKSHEET

Rate this item on the basis of DRUG EFFECT ONLY.

Select the terms that best describe the degrees of therapeutic effect and side effects and record the number from the box where the two items intersect in the blanks above.

THERAPEUTIC EFFECT	SIDE EFFECTS			
	None	Do not significantly interfere with patient's functioning	Significantly interferes with patient's functioning	Outweighs therapeutic effect
MARKED - Vast improvement. Complete or nearly complete remission of all symptoms.	**01**	**02**	**03**	**04**
MODERATE - Decided improvement. Partial remission of symptoms.	**05**	**06**	**07**	**08**
MINIMAL - Slight improvement which doesn't alter status of care of patient.	**09**	**10**	**11**	**12**
UNCHANGED OR WORSE	**13**	**14**	**15**	**16**
Not Assessed = **98**				

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CLINICAL GLOBAL IMPRESSION: SEVERITY

INFORMATION NOT OBTAINED ☐

Considering your total clinical experience with this particular population, how mentally ill is the patient at this time?

- ☐ 1 Normal, not at all ill
- ☐ 2 Borderline ill
- ☐ 3 Mildly ill
- ☐ 4 Moderately ill
- ☐ 5 Markedly ill
- ☐ 6 Severely ill
- ☐ 7 Among the most extremely ill patients

Evaluator's initials _____ _____ _____
First Middle Last

CLINICAL GLOBAL IMPRESSION: IMPROVEMENT

INFORMATION NOT OBTAINED ☐

Rate total improvement, whether or not in your judgement it is due entirely to drug treatment. Compared to the patient's condition at Visit 1, how much has he/she changed?

- ☐ 1 Very much improved
- ☐ 2 Much improved
- ☐ 3 Minimally improved
- ☐ 4 No change
- ☐ 5 Minimally worse
- ☐ 6 Much worse
- ☐ 7 Very much worse

Evaluator's initials _____ _____ _____
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Clinical Report Form
Fluoxetine Versus Placebo in Childhood/Adolescent Depression
B1Y-MC-HCJE

MONTGOMERY - ASBERG DEPRESSION RATING SCALE (MADRS)

INFORMATION NOT OBTAINED ☐

The rating should be based on a clinical interview moving from broadly phrased questions about symptoms to more detailed ones which allow a precise rating of severity. The rater must decide whether the rating lies on the defined scale steps (0, 2, 4, 6) or between them (1, 3, 5).

Check the box (number) that best characterizes the patient at this time

1. **APPARENT SADNESS**
   Representing despondency, gloom, and despair (more than just ordinary transient low spirits), reflected in speech, facial expression, and posture. Rate by depth and inability to brighten up.

   ☐ 0 No sadness.
   ☐ 1
   ☐ 2 Looks dispirited but does brighten up without difficulty.
   ☐ 3
   ☐ 4 Appears sad and unhappy most of the time.
   ☐ 5
   ☐ 6 Looks miserable all the time. Extremely despondent.

2. **REPORTED SADNESS**
   Represented by reports of depressed mood, regardless of whether it is reflected in appearance or not. Includes low spirits, despondency, or the feeling of being beyond help and without hope. Rate according to intensity, duration, and the extent to which the mood is reported to be influenced by events.

   ☐ 0 Occasional sadness in keeping with the circumstances.
   ☐ 1
   ☐ 2 Sad or low but brightens up without difficulty.
   ☐ 3
   ☐ 4 Pervasive feelings of sadness or gloominess. The mood is still influenced by external circumstances.
   ☐ 5
   ☐ 6 Continuous unvarying sadness, misery or despondency.

3. **INNER TENSION**
   Representing feelings of ill-defined discomfort, edginess, inner turmoil, mental tension mounting to either panic, dread, or anguish. Rate according to intensity, frequency, duration, and the extent of reassurance called for.

   ☐ 0 Placid. Only fleeting inner tension.
   ☐ 1
   ☐ 2 Occasional feelings of edginess and ill-defined discomfort.
   ☐ 3
   ☐ 4 Continuous feelings of inner tension or intermittent panic which the patient can only master with some difficulty.
   ☐ 5
   ☐ 6 Unrelenting dread or anguish. Overwhelming panic.

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MONTGOMERY - ASBERG DEPRESSION RATING SCALE (MADRS)

4. **REDUCED SLEEP**
Representing the experience of reduced duration or depth of sleep compared to the subject's own pattern when well.

- ☐ 0 Sleeps as usual.
- ☐ 1
- ☐ 2 Slight difficulty dropping off to sleep or slightly reduced, light or fitful sleep.
- ☐ 3
- ☐ 4 Sleep reduced or broken by at least two hours.
- ☐ 5
- ☐ 6 Less than two or three hours sleep.

5. **REDUCED APPETITE**
Representing the feeling of a loss of appetite compared with when well. Rate by loss of desire for food or the need to force oneself to eat.

- ☐ 0 Normal or increased appetite
- ☐ 1
- ☐ 2 Slightly reduced appetite.
- ☐ 3
- ☐ 4 No appetite. Food is tasteless.
- ☐ 5
- ☐ 6 Needs persuasion to eat at all.

6. **CONCENTRATION DIFFICULTIES**
Representing difficulties in collecting one's thoughts mounting to incapacitating lack of concentration.

- ☐ 0 No difficulties in concentrating.
- ☐ 1
- ☐ 2 Occasional difficulties in collecting one's thoughts.
- ☐ 3
- ☐ 4 Difficulties in concentrating and sustaining thought which reduces ability to read or hold a conversation.
- ☐ 5
- ☐ 6 Unable to read or converse without great difficulty.

7. **LASSITUDE**
Representing a difficulty getting started or slowness initiating and performing everyday activities.

- ☐ 0 Hardly any difficulty in getting started. No sluggishness.
- ☐ 1
- ☐ 2 Difficulties in starting activities
- ☐ 3
- ☐ 4 Difficulties in starting simple routine activities which are carried out with effort.
- ☐ 5
- ☐ 6 Complete lassitude. Unable to do anything without help.

8. **INABILITY TO FEEL**
Representing the subjective experience of reduced interest in the surroundings, or activities that normally give pleasure. The ability to react with adequate emotion to circumstances or people is reduced.

- ☐ 0 Normal interest in the surroundings and other people.
- ☐ 1
- ☐ 2 Reduced ability to enjoy usual interests.
- ☐ 3
- ☐ 4 Loss of interest in the surroundings. Loss of feelings for friends and acquaintances.
- ☐ 5
- ☐ 6 The experience of being emotionally paralyzed, inability to feel anger, grief, or pleasure and a complete or even painful failure to feel for close relatives and friends.

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B1Y-MC-HCJE

MONTGOMERY - ASBERG DEPRESSION RATING SCALE (MADRS)

9. **PESSIMISTIC THOUGHTS**
Representing thoughts of guilt, inferiority, self-reproach, sinfulness, remorse, and ruin

- ☐ 0 No pessimistic thoughts.
- ☐ 1
- ☐ 2 Fluctuating ideas of failure, self-reproach, or self-depreciation.
- ☐ 3
- ☐ 4 Persistent self-accusations, or definite but still rational ideas of guilt, or sin. Increasingly pessimistic about the future.
- ☐ 5
- ☐ 6 Delusions of ruin, remorse, or unredeemable sin. Self-accusations which are absurd and unshakable.

10. **SUICIDAL THOUGHTS**
Representing the feeling that life is not worth living, that a natural death would be welcome, suicidal thoughts, and preparations for suicide. Suicidal attempts should not in themselves influence the rating.

- ☐ 0 Enjoys life or takes it as it comes.
- ☐ 1
- ☐ 2 Weary of life. Only fleeting suicidal thoughts.
- ☐ 3
- ☐ 4 Probably better off dead. Suicidal thoughts are common, and suicide is considered as a possible solution, but without specific plans or intention.
- ☐ 5
- ☐ 6 Explicit plans for suicide when there is an opportunity. Active preparations for suicide.

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Fluoxetine Versus Placebo in Childhood/Adolescent Depression
B1Y-MC-HCJE

COMMENTS : VISIT

NO COMMENTS ☐

Comments should address any clinical report form items that require further explanation. Repeating information from the clinical report form is discouraged.

Comment on all clinically significant lab values that are outside a clinically accepted reference range or clinically significant values that differ importantly from previous values.

If the patient is ending participation in the study at this visit, enter only comments that apply to this visit; then complete the Patient Summary and Study Summary Comments pages.

Print legibly and do not use abbreviations or symbols.

The information reported for this visit is accurate and complete.

_____ _____/_____/_____
Signature MM DD YY

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Fluoxetine Versus Placebo in Childhood/Adolescent Depression
B1Y-MC-HCJE

PATIENT AND VISIT IDENTIFICATION

Patient initials _____ _____ _____
First Middle Last

Visit date _____/_____/_____
MM DD YY

VITAL SIGNS : BLOOD PRESSURE AND HEART RATE

INFORMATION NOT OBTAINED ☐

Position
SI = Sitting

Position	Blood Pressure (mm Hg) Systolic/Diastolic	Heart Rate (bpm)
SI	/	

VITAL SIGNS: TEMPERATURE

INFORMATION NOT OBTAINED ☐

Temperature ___ ___ ___ . ___

Unit of measure (F) Fahrenheit

Method (E) Ear

REMINDER

On the Pre-existing Conditions and Study Adverse Events pages, record new events that occurred since the previous visit and re-evaluate any on-going conditions or events.

On the Concomitant Medication pages, record new medications the patient has taken since the previous visit, any changes to ongoing medications, and a stop date for any medication the patient is no longer taking.

Initials
Date Verified
Initials
Date Keyed
Date Received at Lilly
Reviewed
Inspected
Date

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STUDY DRUG : DATES OF MISSED DOSES

NO MISSED DOSES ☐

Record the date for any day on which the patient missed a full or partial dose of study drug.

	Dates of Missed Doses		
	MM	DD	YY
0.			
1.			
2.			
3.			
4.			
5.			
6.			
7.			
8.			
9.			

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B1Y-MC-HCJE

SIDE EFFECTS CHECKLIST

INFORMATION NOT OBTAINED ☐

Since your last visit, have you been bothered with or had any trouble with any of the items listed below? Check the box which best tells how much you were bothered.

	Not at all	Just a little	Pretty much	Very much	Don't know
1. Eating?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
2. Drinking?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
3. Dry mouth and lips?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
4. Wetness in mouth?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
5. Constipation?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
6. Diarrhea?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
7. Stomachaches?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
8. Muscle cramps?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
9. Being sick to your stomach?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
10. Wetting the bed?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
11. Urinating?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
12. Itchy or scratchy skin?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
13. Rashes?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
14. Cold or sniffles?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
15. Headache?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4

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Fluoxetine Versus Placebo in Childhood/Adolescent Depression
B1Y-MC-HCJE

SIDE EFFECTS CHECKLIST

	Not at all	Just a little	Pretty much	Very much	Don't know
16. Dizziness?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
17. Playing sports?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
18. Shakiness?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
19. Pronouncing words?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
20. Doing things with your hands?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
21. Sitting still?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
22. Tiredness?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
23. Feeling sleepy?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
24. Trouble sleeping?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
25. Bad dreams?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
26. Getting along with parents?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
27. Getting along with kids?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
28. Crying?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
29. Getting mad?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
30. Not being happy?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
31. Being sad?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
32. Paying attention?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4

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Fluoxetine Versus Placebo in Childhood/Adolescent Depression
B1Y-MC-HCJE

CHILDRENS DEPRESSION RATING SCALE - REVISED

INFORMATION NOT OBTAINED ☐

CHECK THE NUMERIC CODE which best describes the patient.

1. **SCHOOLWORK**:

☐ 1 Performance consistent with ability
☐ 2
☐ 3 Decrease in school performance
☐ 4
☐ 5 Major interference in most subjects
☐ 6
☐ 7 No motivation to perform

2. **CAPACITY TO HAVE FUN**

☐ 1 Interest and activities realistically appropriate for age, personality, and social environment. Shows no appreciable change with present illness.
☐ 2
☐ 3 Describes some activities realistically available several times a week but not on a daily basis. Shows interest but not enthusiasm.
☐ 4
☐ 5 Is easily bored. Complains of "nothing to do." Participates in structured activities with a "going through the motions" attitude. May express interest primarily in activities that are (realistically) unavailable on a daily or weekly basis.
☐ 6
☐ 7 Has no initiative to become involved in any activities. Primarily passive. Watches others play or watches TV but shows little interest. Requires coaxing and/or pushing to get involved in activity. Shows no enthusiasm or real interest. Has difficulty naming activities.

3. **SOCIAL WITHDRAWAL**

☐ 1 Enjoys friendships with peers at school and home
☐ 2
☐ 3 May not actively seek out friendships but waits for others to initiate a relationship or may occasionally reject opportunities to play without a describable alternative
☐ 4
☐ 5 Frequently avoids or refuses opportunities for desirable interaction with others and/or sets up situations where rejection is inevitable.
☐ 6
☐ 7 Does not currently relate to other children. States he or she has "no friends" or actively rejects new or former friends.

4. **SLEEP**

☐ 1 No (or occasional) difficulty. (Goes to sleep within 1/2 hour or less.)
☐ 2
☐ 3 Frequently has mild difficulty with sleep
☐ 4
☐ 5 Moderate difficulty with sleep nearly every night.

5. **APPETITE OR EATING PATTERNS**

☐ 1 No problems or change in eating pattern
☐ 2
☐ 3 Mild change from usual eating habits within onset of current behavioral problem
☐ 4
☐ 5 Is not hungry most of the time or has excessive food intake since onset of current behavioral problems or marked increase in appetite

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B1Y-MC-HCJE

CHILDRENS DEPRESSION RATING SCALE - REVISED

CHECK THE NUMERIC CODE which best describes the patient.

6. **EXCESSIVE FATIGUE**

- ☐ 1 No unusual complaints of "feeling tired" during the day
- ☐ 2
- ☐ 3 Complaints of fatigue which seem somewhat excessive and not related to boredom
- ☐ 4
- ☐ 5 Daily complaints of feeling tired
- ☐ 6
- ☐ 7 Complains of feeling tired most of the day. May voluntarily take long naps without feeling refreshed. Interferes with play activities.

7. **PHYSICAL COMPLAINTS**:

- ☐ 1 Occasional complaints
- ☐ 2
- ☐ 3 Complaints appear mildly excessive
- ☐ 4
- ☐ 5 Complains daily. Some interference with the ability of the child to function
- ☐ 6
- ☐ 7 Preoccupied with aches and pains; interferes with play activities several times a week

8. **IRRITABILITY**

- ☐ 1 Rare
- ☐ 2 Occasional
- ☐ 3 Several times a week for short periods
- ☐ 4
- ☐ 5 Several times a week for longer periods
- ☐ 6
- ☐ 7 Constant

9. **GUILT**

- ☐ 1 Does not express any undue feeling of guilt. Appears appropriate to precipitating event.
- ☐ 2
- ☐ 3 Exaggerates guilt and/or shame out of proportion to the event described.
- ☐ 4
- ☐ 5 Feels guilty over things not under his or her control. Guilt is definitely pathological.
- ☐ 6
- ☐ 7 Severe delusions of guilt

10. **SELF-ESTEEM**

- ☐ 1 Describes self in primarily positive terms
- ☐ 2
- ☐ 3 Describes self with one important area where the child feels deficit
- ☐ 4
- ☐ 5 Describes self in preponderance of negative terms or gives bland answers to questions
- ☐ 6
- ☐ 7 Refers to self in derogatory terms. Reports that other children refer to him/her frequently by using derogatory nicknames and child puts self down

11. **DEPRESSED FEELINGS**

- ☐ 1 Occasional feelings of unhappiness which quickly disappear
- ☐ 2
- ☐ 3 Describes sustained periods of unhappiness which appear excessive for events described
- ☐ 4
- ☐ 5 Feels unhappy most of the time without a major precipitating cause
- ☐ 6
- ☐ 7 Feels unhappy all of the time. Accompanied by psychic pain (e.g., "I can't stand it").

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CHILDRENS DEPRESSION RATING SCALE - REVISED

CHECK THE NUMERIC CODE which best describes the patient.

12. **MORBID IDEATION**

- ☐ 1 None
- ☐ 2
- ☐ 3 Has some morbid thought, all of which relate to a reality event but seem excessive.
- ☐ 4
- ☐ 5 Preoccupied with morbid thoughts several times a week. Morbid thoughts extend beyond external reality
- ☐ 6
- ☐ 7 Preoccupied with death themes or morbid thoughts that are elaborate, extensive or bizarre on a daily basis

13. **SUICIDAL IDEATION**

- ☐ 1 Understands the word "suicide" but does not apply term to self
- ☐ 2 Sharp denial of suicidal thoughts
- ☐ 3 Has thoughts about suicide, usually when angry.
- ☐ 4
- ☐ 5 Has recurrent thoughts of suicide
- ☐ 6
- ☐ 7 Has made suicide attempt within the last month or is actively suicidal

14. **WEEPING**:

- ☐ 1 Normal for age.
- ☐ 2 Suggestive statements that child cries, or feels like crying, more frequently than peers.
- ☐ 3 Child cries slightly more than peers.
- ☐ 4
- ☐ 5 Cries or feels like crying frequently (several times a week). Admits to crying without knowing reason why.
- ☐ 6
- ☐ 7 Cries nearly every day.

15. **DEPRESSED AFFECT:**

- ☐ 1 Definitely not depressed. Facial expression and voice animated during interview.
- ☐ 2 Mild suppression of affect. Some loss of spontaneity.
- ☐ 3 Overall loss of spontaneity. Looks distinctly unhappy during parts of the interview. May still be able to smile when discussing non-threatening areas.
- ☐ 4
- ☐ 5 Moderate restriction of affect throughout most of interview. Has longer and frequent periods of looking distinctly unhappy.
- ☐ 6
- ☐ 7 Severe. Looks sad, withdrawn. Minimal verbal interaction throughout interview. Cries or may appear tearful.

16. **TEMPO OF SPEECH:**

- ☐ 1 Normal
- ☐ 2 Slow
- ☐ 3 Slow: delays interview.
- ☐ 4
- ☐ 5 Severe. Low; marked interference with interview.

17. **HYPOACTIVITY:**

- ☐ 1 None
- ☐ 2
- ☐ 3 Mild. Some body movements.
- ☐ 4
- ☐ 5 Moderate. Definite motor retardation.
- ☐ 6
- ☐ 7 Severe. Motionless throughout interview.

(DNDE)

Total of 1 - 17 _____

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B1Y-MC-HCJE

CLINICAL GLOBAL IMPRESSION: EFFICACY INDEX

Using the worksheet below, enter the 2-digit efficacy index rating.

1. Efficacy index rating ___ ___

(DNDE)

EFFICACY INDEX WORKSHEET

Rate this item on the basis of DRUG EFFECT ONLY.

Select the terms that best describe the degrees of therapeutic effect and side effects and record the number from the box where the two items intersect in the blanks above.

THERAPEUTIC EFFECT	SIDE EFFECTS			
	None	Do not significantly interfere with patient's functioning	Significantly interferes with patient's functioning	Outweighs therapeutic effect
MARKED - Vast improvement. Complete or nearly complete remission of all symptoms.	**01**	**02**	**03**	**04**
MODERATE - Decided improvement. Partial remission of symptoms.	**05**	**06**	**07**	**08**
MINIMAL - Slight improvement which doesn't alter status of care of patient.	**09**	**10**	**11**	**12**
UNCHANGED OR WORSE	**13**	**14**	**15**	**16**
Not Assessed = **98**				

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CLINICAL GLOBAL IMPRESSION: SEVERITY

INFORMATION NOT OBTAINED ☐

Considering your total clinical experience with this particular population, how mentally ill is the patient at this time?

- ☐ 1 Normal, not at all ill
- ☐ 2 Borderline ill
- ☐ 3 Mildly ill
- ☐ 4 Moderately ill
- ☐ 5 Markedly ill
- ☐ 6 Severely ill
- ☐ 7 Among the most extremely ill patients

Evaluator's initials _____ _____ _____
First Middle Last

CLINICAL GLOBAL IMPRESSION: IMPROVEMENT

INFORMATION NOT OBTAINED ☐

Rate total improvement, whether or not in your judgement it is due entirely to drug treatment. Compared to the patient's condition at Visit 1, how much has he/she changed?

- ☐ 1 Very much improved
- ☐ 2 Much improved
- ☐ 3 Minimally improved
- ☐ 4 No change
- ☐ 5 Minimally worse
- ☐ 6 Much worse
- ☐ 7 Very much worse

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MONTGOMERY - ASBERG DEPRESSION RATING SCALE (MADRS)

INFORMATION NOT OBTAINED ☐

The rating should be based on a clinical interview moving from broadly phrased questions about symptoms to more detailed ones which allow a precise rating of severity. The rater must decide whether the rating lies on the defined scale steps (0, 2, 4, 6) or between them (1, 3, 5).

Check the box (number) that best characterizes the patient at this time

1. **APPARENT SADNESS**
   Representing despondency, gloom, and despair (more than just ordinary transient low spirits), reflected in speech, facial expression, and posture. Rate by depth and inability to brighten up.

   ☐ 0 No sadness.
   ☐ 1
   ☐ 2 Looks dispirited but does brighten up without difficulty.
   ☐ 3
   ☐ 4 Appears sad and unhappy most of the time.
   ☐ 5
   ☐ 6 Looks miserable all the time. Extremely despondent.

2. **REPORTED SADNESS**
   Represented by reports of depressed mood, regardless of whether it is reflected in appearance or not. Includes low spirits, despondency, or the feeling of being beyond help and without hope. Rate according to intensity, duration, and the extent to which the mood is reported to be influenced by events.

   ☐ 0 Occasional sadness in keeping with the circumstances.
   ☐ 1
   ☐ 2 Sad or low but brightens up without difficulty.
   ☐ 3
   ☐ 4 Pervasive feelings of sadness or gloominess. The mood is still influenced by external circumstances.
   ☐ 5
   ☐ 6 Continuous unvarying sadness, misery or despondency.

3. **INNER TENSION**
   Representing feelings of ill-defined discomfort, edginess, inner turmoil, mental tension mounting to either panic, dread, or anguish. Rate according to intensity, frequency, duration, and the extent of reassurance called for.

   ☐ 0 Placid. Only fleeting inner tension.
   ☐ 1
   ☐ 2 Occasional feelings of edginess and ill-defined discomfort.
   ☐ 3
   ☐ 4 Continuous feelings of inner tension or intermittent panic which the patient can only master with some difficulty.
   ☐ 5
   ☐ 6 Unrelenting dread or anguish. Overwhelming panic.

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MONTGOMERY - ASBERG DEPRESSION RATING SCALE (MADRS)

4. **REDUCED SLEEP**
Representing the experience of reduced duration or depth of sleep compared to the subject's own pattern when well.

- ☐ 0 Sleeps as usual.
- ☐ 1
- ☐ 2 Slight difficulty dropping off to sleep or slightly reduced, light or fitful sleep.
- ☐ 3
- ☐ 4 Sleep reduced or broken by at least two hours.
- ☐ 5
- ☐ 6 Less than two or three hours sleep.

5. **REDUCED APPETITE**
Representing the feeling of a loss of appetite compared with when well. Rate by loss of desire for food or the need to force oneself to eat.

- ☐ 0 Normal or increased appetite
- ☐ 1
- ☐ 2 Slightly reduced appetite.
- ☐ 3
- ☐ 4 No appetite. Food is tasteless.
- ☐ 5
- ☐ 6 Needs persuasion to eat at all.

6. **CONCENTRATION DIFFICULTIES**
Representing difficulties in collecting one's thoughts mounting to incapacitating lack of concentration.

- ☐ 0 No difficulties in concentrating.
- ☐ 1
- ☐ 2 Occasional difficulties in collecting one's thoughts.
- ☐ 3
- ☐ 4 Difficulties in concentrating and sustaining thought which reduces ability to read or hold a conversation.
- ☐ 5
- ☐ 6 Unable to read or converse without great difficulty.

7. **LASSITUDE**
Representing a difficulty getting started or slowness initiating and performing everyday activities.

- ☐ 0 Hardly any difficulty in getting started. No sluggishness.
- ☐ 1
- ☐ 2 Difficulties in starting activities
- ☐ 3
- ☐ 4 Difficulties in starting simple routine activities which are carried out with effort.
- ☐ 5
- ☐ 6 Complete lassitude. Unable to do anything without help.

8. **INABILITY TO FEEL**
Representing the subjective experience of reduced interest in the surroundings, or activities that normally give pleasure. The ability to react with adequate emotion to circumstances or people is reduced.

- ☐ 0 Normal interest in the surroundings and other people.
- ☐ 1
- ☐ 2 Reduced ability to enjoy usual interests.
- ☐ 3
- ☐ 4 Loss of interest in the surroundings. Loss of feelings for friends and acquaintances.
- ☐ 5
- ☐ 6 The experience of being emotionally paralyzed, inability to feel anger, grief, or pleasure and a complete or even painful failure to feel for close relatives and friends.

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B1Y-MC-HCJE

MONTGOMERY - ASBERG DEPRESSION RATING SCALE (MADRS)

9. **PESSIMISTIC THOUGHTS**
Representing thoughts of guilt, inferiority, self-reproach, sinfulness, remorse, and ruin

- ☐ 0 No pessimistic thoughts.
- ☐ 1
- ☐ 2 Fluctuating ideas of failure, self-reproach, or self-depreciation.
- ☐ 3
- ☐ 4 Persistent self-accusations, or definite but still rational ideas of guilt, or sin. Increasingly pessimistic about the future.
- ☐ 5
- ☐ 6 Delusions of ruin, remorse, or unredeemable sin. Self-accusations which are absurd and unshakable.

10. **SUICIDAL THOUGHTS**
Representing the feeling that life is not worth living, that a natural death would be welcome, suicidal thoughts, and preparations for suicide. Suicidal attempts should not in themselves influence the rating.

- ☐ 0 Enjoys life or takes it as it comes.
- ☐ 1
- ☐ 2 Weary of life. Only fleeting suicidal thoughts.
- ☐ 3
- ☐ 4 Probably better off dead. Suicidal thoughts are common, and suicide is considered as a possible solution, but without specific plans or intention.
- ☐ 5
- ☐ 6 Explicit plans for suicide when there is an opportunity. Active preparations for suicide.

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Clinical Report Form
Fluoxetine Versus Placebo in Childhood/Adolescent Depression
B1Y-MC-HCJE

CHILDREN'S DEPRESSION INDEX (CDI)

NOTE: Only complete if patient was 8 to 12 years old at Visit 1. If patient was not 8 to 12 years old, check the Information Not Obtained box.

INFORMATION NOT OBTAINED ☐

This lists the feelings and ideas in groups. From each group of three sentences, pick one sentence that describes you **best** for the past two weeks. After you pick a sentence from the first group, go on to the next group. There is no right answer or wrong answer. Just pick the sentence that best describes the way you have been recently. Put an "X" in the box next to your answer.
Remember: pick out the sentences that describe you best **in the past two weeks**.

Item 1

- ☐ 0 I am sad once in a while.
- ☐ 1 I am sad many times.
- ☐ 2 I am sad all the time.

Item 2

- ☐ 2 Nothing will ever work out for me.
- ☐ 1 I am not sure if things will work out for me.
- ☐ 0 Things will work out for me O.K.

Item 3

- ☐ 0 I do most things O.K.
- ☐ 1 I do many things wrong.
- ☐ 2 I do everything wrong.

Item 4

- ☐ 0 I have fun in many things.
- ☐ 1 I have fun in some things.
- ☐ 2 Nothing is fun at all.

Item 5

- ☐ 2 I am bad all the time.
- ☐ 1 I am bad many times.
- ☐ 0 I am bad once in a while.

Item 6

- ☐ 0 I think about bad things happening to me once in a while.
- ☐ 1 I worry that bad things will happen to me.
- ☐ 2 I am sure that terrible things will happen to me.

Item 7

- ☐ 2 I hate myself.
- ☐ 1 I do not like myself.
- ☐ 0 I like myself.

Item 8

- ☐ 2 All bad things are my fault.
- ☐ 1 Many bad things are my fault.
- ☐ 0 Bad things are not usually my fault.

Item 9

- ☐ 0 I do not think about killing myself.
- ☐ 1 I think about killing myself but I would not do it.
- ☐ 2 I want to kill myself.

Item 10

- ☐ 2 I feel like crying every day.
- ☐ 1 I feel like crying many days.
- ☐ 0 I feel like crying once in a while.

Item 11

- ☐ 2 Things bother me all the time.
- ☐ 1 Things bother me many times.
- ☐ 0 Things bother me once in a while.

Item 12

- ☐ 0 I like being with people.
- ☐ 1 I do not like being with people many times.
- ☐ 2 I do not want to be with people at all.

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CHILDREN'S DEPRESSION INDEX (CDI)

Item 13

- ☐ 2 I cannot make up my mind about things.
- ☐ 1 It is hard to make up my mind about things.
- ☐ 0 I make up my mind about things easily.

Item 14

- ☐ 0 I look O.K.
- ☐ 1 There are some bad things about my looks.
- ☐ 2 I look ugly.

Item 15

- ☐ 2 I have to push myself all the time to do my schoolwork.
- ☐ 1 I have to push myself many times to do my schoolwork.
- ☐ 0 Doing schoolwork is not a big problem.

Item 16

- ☐ 2 I have trouble sleeping every night.
- ☐ 1 I have trouble sleeping many nights.
- ☐ 0 I sleep pretty well.

Item 17

- ☐ 0 I am tired once in a while.
- ☐ 1 I am tired many days.
- ☐ 2 I am tired all the time.

Item 18

- ☐ 2 Most days I do not feel like eating.
- ☐ 1 Many days I do not feel like eating.
- ☐ 0 I eat pretty well.

Item 19

- ☐ 0 I do not worry about aches and pains.
- ☐ 1 I worry about aches and pains many times.
- ☐ 2 I worry about aches and pains all the time.

Item 20

- ☐ 0 I do not feel alone.
- ☐ 1 I feel alone many times.
- ☐ 2 I feel alone all the time.

Item 21

- ☐ 2 I never have fun at school.
- ☐ 1 I have fun at school only once in a while.
- ☐ 0 I have fun at school many times.

Item 22

- ☐ 0 I have plenty of friends.
- ☐ 1 I have some friends but I wish I had more.
- ☐ 2 I do not have any friends.

Item 23

- ☐ 0 My schoolwork is alright.
- ☐ 1 My schoolwork is not as good as before.
- ☐ 2 I do very badly in subjects I used to be good in.

Item 24

- ☐ 2 I can never be as good as other kids.
- ☐ 1 I can be as good as other kids if I want to.
- ☐ 0 I am just as good as other kids.

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CHILDREN'S DEPRESSION INDEX (CDI)

Item 25

- ☐ 2 Nobody really loves me.
- ☐ 1 I am not sure if anybody loves me.
- ☐ 0 I am sure that somebody loves me.

Item 26

- ☐ 0 I usually do what I am told.
- ☐ 1 I do not do what I am told most times.
- ☐ 2 I never do what I am told.

Item 27

- ☐ 0 I get along with people.
- ☐ 1 I get into fights many times.
- ☐ 2 I get into fights all the time.

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BECK DEPRESSION INVENTORY

NOTE: Only complete if patient was 13 to 17 years old at Visit 1. If patient was not 13 to 17 years old, check the Information Not Obtained box.

INFORMATION NOT OBTAINED ☐

This questionnaire consists of 21 groups of statements. After reading each group of statements carefully circle the number (0, 1, 2, 3) next to the one statement in each group which best describes the way you have been feeling **the past week, including today**. If several statements within a group seem to apply equally well, circle each one. Be sure to read all the statements in each group before making your choice.

1

0 I do not feel sad.
1 I feel sad.
2 I am sad all the time and I can't snap out of it.
3 I am so sad or unhappy that I can't stand it.

2

0 I am not particularly discouraged about the future.
1 I feel discouraged about the future.
2 I feel I have nothing to look forward to.
3 I feel that the future is hopeless and that things cannot improve.

3

0 I do not feel like a failure.
1 I feel I have failed more than the average person.
2 As I look back on my life, all I can see is a lot of failures.
3 I feel I am a complete failure as a person.

4

0 I get as much satisfaction out of things as I used to.
1 I don't enjoy things the way I used to.
2 I don't get real satisfaction out of anything anymore.
3 I am dissatisfied or bored with everything.

5

0 I don't feel particularly guilty.
1 I feel guilty a good part of the time.
2 I feel quite guilty most of the time.
3 I feel guilty all of the time.

6

0 I don't feel I am being punished.
1 I feel I may be punished.
2 I expect to be punished.
3 I feel I am being punished.

7

0 I don't feel disappointed in myself.
1 I am disappointed in myself.
2 I am disgusted with myself.
3 I hate myself.

8

0 I don't feel I am any worse than anybody else.
1 I am critical of myself for my weaknesses or mistakes.
2 I blame myself all the time for my faults.
3 I blame myself for everything bad that happens.

9

0 I don't have any thoughts of killing myself.
1 I have thoughts of killing myself, but I would not carry them out.
2 I would like to kill myself.
3 I would kill myself if I had the chance.

10

0 I don't cry any more than usual.
1 I cry more now than I used to.
2 I cry all the time now.
3 I used to be able to cry, but now I can't cry even though I want to.

11

0 I am no more irritated now than I ever am.
1 I get annoyed or irritated more easily than I used to.
2 I feel irritated all the time now.
3 I don't get irritated at all by the things that used to irritate me.

12

0 I have not lost interest in other people.
1 I am less interested in other people than I used to be.
2 I have lost most of my interest in other people.
3 I have lost all of my interest in other people.

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BECK DEPRESSION INVENTORY

13

0 I make decisions about as well as I ever could.
1 I put off making decisions more than I used to.
2 I have greater difficulty in making decisions than before.
3 I can't make decisions at all anymore.

14

0 I don't feel I look any worse than I used to.
1 I am worried that I am looking old or unattractive.
2 I feel that there are permanent changes in my appearance that make me look unattractive.
3 I believe that I look ugly.

15

0 I can work about as well as before.
1 It takes an extra effort to get started at doing something.
2 I have to push myself very hard to do anything.
3 I can't do any work at all.

16

0 I can sleep as well as usual.
1 I don't sleep as well as I used to.
2 I wake up 1-2 hours earlier than usual and find it hard to get back to sleep.
3 I wake up several hours earlier than I used to and cannot get back to sleep.

17

0 I don't get more tired than usual.
1 I get tired more easily than I used to.
2 I get tired from doing almost anything.
3 I am too tired to do anything.

18

0 My appetite is no worse than usual.
1 My appetite is not as good as it used to be.
2 My appetite is much worse now.
3 I have no appetite at all anymore.

19

0 I haven't lost much weight, if any, lately.
1 I have lost more than 5 pounds.
2 I have lost more than 10 pounds.
3 I have lost more than 15 pounds.

19a

I am purposely trying to lose weight by eating less.
1 Yes
2 No

20

0 I am no more worried about my health than usual.
1 I am worried about physical problems such as aches and pains; or upset stomach or constipation.
2 I am very worried about physical problems and it's hard to think of much else.
3 I am so worried about my physical problems that I cannot think about anything else.

21

0 I have not noticed any recent change in my interest in sex.
1 I am less interested in sex than I used to be.
2 I am much less interested in sex now.
3 I have lost interest in sex completely.

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Clinical Report Form
Fluoxetine Versus Placebo in Childhood/Adolescent Depression
B1Y-MC-HCJE

HAMILTON ANXIETY SCALE

INFORMATION NOT OBTAINED ☐

For each of the items below, **CHECK ONE BOX** that best describes the patient.

1. **ANXIOUS MOOD:** Worries, anticipation of the worst, fearful anticipation, irritability

   ☐ 0 Not present
   ☐ 1 Mild
   ☐ 2 Moderate
   ☐ 3 Severe
   ☐ 4 Very severe

2. **TENSION**: Feelings of tension, fatigability, startle response, moved to tears easily, trembling, feeling of restlessness, inability to relax

   ☐ 0 Not present
   ☐ 1 Mild
   ☐ 2 Moderate
   ☐ 3 Severe
   ☐ 4 Very severe

3. **FEARS**: Of dark, of strangers, of being alone, of animals, of traffic, of crowds

   ☐ 0 Not present
   ☐ 1 Mild
   ☐ 2 Moderate
   ☐ 3 Severe
   ☐ 4 Very severe

4. **INSOMNIA**: Difficulty in falling asleep, broken sleep, unsatisfying sleep and fatigue on waking, dreams, nightmares, night terrors

   ☐ 0 Not present
   ☐ 1 Mild
   ☐ 2 Moderate
   ☐ 3 Severe
   ☐ 4 Very severe

5. **INTELLECTUAL (COGNITIVE)**: Difficulty in concentration, poor memory

   ☐ 0 Not present
   ☐ 1 Mild
   ☐ 2 Moderate
   ☐ 3 Severe
   ☐ 4 Very severe

6. **DEPRESSED MOOD**: Loss of interest, lack of pleasure in hobbies, depression, early waking, diurnal swing

   ☐ 0 Not present
   ☐ 1 Mild
   ☐ 2 Moderate
   ☐ 3 Severe
   ☐ 4 Very severe

7. **SOMATIC (MUSCULAR)**: Pains and aches, twitchings, stiffness, myoclonic jerks, grinding of teeth, unsteady voice, increased muscular tone

   ☐ 0 Not present
   ☐ 1 Mild
   ☐ 2 Moderate
   ☐ 3 Severe
   ☐ 4 Very severe

8. **SOMATIC (SENSORY)**: Tinnitus, blurring of vision, hot and cold flushes, feeling of weakness, pricking sensation

   ☐ 0 Not present
   ☐ 1 Mild
   ☐ 2 Moderate
   ☐ 3 Severe
   ☐ 4 Very severe

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HAMILTON ANXIETY SCALE

9. **CARDIOVASCULAR SYMPTOMS:** Tachycardia, palpitations, pain in chest, throbbing of vessels, fainting feelings, missing beat

- ☐ 0 Not present
- ☐ 1 Mild
- ☐ 2 Moderate
- ☐ 3 Severe
- ☐ 4 Very severe

10. **RESPIRATORY SYMPTOMS:** Pressure or constriction in chest, choking feelings, sighing, dyspnea

- ☐ 0 Not present
- ☐ 1 Mild
- ☐ 2 Moderate
- ☐ 3 Severe
- ☐ 4 Very severe

11. **GASTROINTESTINAL SYMPTOMS:** Difficulty in swallowing, wind, abdominal pain, burning sensations, abdominal fullness, nausea, vomiting, borborygmi, looseness of bowels, loss of weight, constipation

- ☐ 0 Not present
- ☐ 1 Mild
- ☐ 2 Moderate
- ☐ 3 Severe
- ☐ 4 Very severe

12. **GENITOURINARY SYMPTOMS:** Frequency of micturition, urgency of micturition, amenorrhea, menorrhagia, development of frigidity, premature ejaculation, loss of libido, impotence

- ☐ 0 Not present
- ☐ 1 Mild
- ☐ 2 Moderate
- ☐ 3 Severe
- ☐ 4 Very severe

13. **AUTONOMIC SYMPTOMS:** Dry mouth, flushing, pallor, tendency to sweat, giddiness, tension headache, raising of hair

- ☐ 0 Not present
- ☐ 1 Mild
- ☐ 2 Moderate
- ☐ 3 Severe
- ☐ 4 Very severe

14. **BEHAVIOR AT INTERVIEW:** Fidgeting, restlessness or pacing, tremor of hands, furrowed brow, strained face, sighing or rapid respiration, facial pallor, swallowing, belching, brisk tendon jerks, dilated pupils, exophthalmos

- ☐ 0 Not present
- ☐ 1 Mild
- ☐ 2 Moderate
- ☐ 3 Severe
- ☐ 4 Very severe

Evaluator's Initials _____ _____ _____
First Middle Last

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Clinical Report Form
Fluoxetine Versus Placebo in Childhood/Adolescent Depression
B1Y-MC-HCJE

COMMENTS : VISIT

NO COMMENTS ☐

Comments should address any clinical report form items that require further explanation. Repeating information from the clinical report form is discouraged.

Comment on all clinically significant lab values that are outside a clinically accepted reference range or clinically significant values that differ importantly from previous values.

If the patient is ending participation in the study at this visit, enter only comments that apply to this visit; then complete the Patient Summary and Study Summary Comments pages.

Print legibly and do not use abbreviations or symbols.

The information reported for this visit is accurate and complete.

_____ _____/_____/_____
Signature MM DD YY

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Clinical Report Form
Fluoxetine Versus Placebo in Childhood/Adolescent Depression
B1Y-MC-HCJE

PATIENT AND VISIT IDENTIFICATION

Patient initials _____ _____ _____
First Middle Last

Visit date _____/_____/_____
MM DD YY

VITAL SIGNS : BLOOD PRESSURE AND HEART RATE

INFORMATION NOT OBTAINED ☐

Position
SI = Sitting

Position	Blood Pressure (mm Hg) Systolic/Diastolic	Heart Rate (bpm)
SI	/	

VITAL SIGNS: TEMPERATURE

INFORMATION NOT OBTAINED ☐

Temperature ___ ___ ___ . ___

Unit of measure (F) Fahrenheit

Method (E) Ear

REMINDER

On the Pre-existing Conditions and Study Adverse Events pages, record new events that occurred since the previous visit and re-evaluate any on-going conditions or events.

On the Concomitant Medication pages, record new medications the patient has taken since the previous visit, any changes to ongoing medications, and a stop date for any medication the patient is no longer taking.

Initials
Date Verified
Initials
Date Keyed
Date Received at Lilly
Reviewed
Inspected
Date

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B1Y-MC-HCJE

STUDY DRUG : DATES OF MISSED DOSES

NO MISSED DOSES ☐

Record the date for any day on which the patient missed a full or partial dose of study drug.

	Dates of Missed Doses		
	MM	DD	YY
0.			
1.			
2.			
3.			
4.			
5.			
6.			
7.			
8.			
9.			

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Fluoxetine Versus Placebo in Childhood/Adolescent Depression
B1Y-MC-HCJE

SIDE EFFECTS CHECKLIST

INFORMATION NOT OBTAINED ☐

Since your last visit, have you been bothered with or had any trouble with any of the items listed below? Check the box which best tells how much you were bothered.

	Not at all	Just a little	Pretty much	Very much	Don't know
1. Eating?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
2. Drinking?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
3. Dry mouth and lips?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
4. Wetness in mouth?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
5. Constipation?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
6. Diarrhea?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
7. Stomachaches?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
8. Muscle cramps?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
9. Being sick to your stomach?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
10. Wetting the bed?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
11. Urinating?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
12. Itchy or scratchy skin?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
13. Rashes?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
14. Cold or sniffles?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
15. Headache?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4

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Fluoxetine Versus Placebo in Childhood/Adolescent Depression
B1Y-MC-HCJE

SIDE EFFECTS CHECKLIST

	Not at all	Just a little	Pretty much	Very much	Don't know
16. Dizziness?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
17. Playing sports?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
18. Shakiness?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
19. Pronouncing words?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
20. Doing things with your hands?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
21. Sitting still?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
22. Tiredness?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
23. Feeling sleepy?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
24. Trouble sleeping?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
25. Bad dreams?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
26. Getting along with parents?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
27. Getting along with kids?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
28. Crying?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
29. Getting mad?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
30. Not being happy?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
31. Being sad?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
32. Paying attention?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4

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Clinical Report Form
Fluoxetine Versus Placebo in Childhood/Adolescent Depression
B1Y-MC-HCJE

CHILDRENS DEPRESSION RATING SCALE - REVISED

INFORMATION NOT OBTAINED ☐

CHECK THE NUMERIC CODE which best describes the patient.

1. **SCHOOLWORK**:

☐ 1 Performance consistent with ability
☐ 2
☐ 3 Decrease in school performance
☐ 4
☐ 5 Major interference in most subjects
☐ 6
☐ 7 No motivation to perform

2. **CAPACITY TO HAVE FUN**

☐ 1 Interest and activities realistically appropriate for age, personality, and social environment. Shows no appreciable change with present illness.
☐ 2
☐ 3 Describes some activities realistically available several times a week but not on a daily basis. Shows interest but not enthusiasm.
☐ 4
☐ 5 Is easily bored. Complains of "nothing to do." Participates in structured activities with a "going through the motions" attitude. May express interest primarily in activities that are (realistically) unavailable on a daily or weekly basis.
☐ 6
☐ 7 Has no initiative to become involved in any activities. Primarily passive. Watches others play or watches TV but shows little interest. Requires coaxing and/or pushing to get involved in activity. Shows no enthusiasm or real interest. Has difficulty naming activities.

3. **SOCIAL WITHDRAWAL**

☐ 1 Enjoys friendships with peers at school and home
☐ 2
☐ 3 May not actively seek out friendships but waits for others to initiate a relationship or may occasionally reject opportunities to play without a describable alternative
☐ 4
☐ 5 Frequently avoids or refuses opportunities for desirable interaction with others and/or sets up situations where rejection is inevitable.
☐ 6
☐ 7 Does not currently relate to other children. States he or she has "no friends" or actively rejects new or former friends.

4. **SLEEP**

☐ 1 No (or occasional) difficulty. (Goes to sleep within 1/2 hour or less.)
☐ 2
☐ 3 Frequently has mild difficulty with sleep
☐ 4
☐ 5 Moderate difficulty with sleep nearly every night.

5. **APPETITE OR EATING PATTERNS**

☐ 1 No problems or change in eating pattern
☐ 2
☐ 3 Mild change from usual eating habits within onset of current behavioral problem
☐ 4
☐ 5 Is not hungry most of the time or has excessive food intake since onset of current behavioral problems or marked increase in appetite

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Fluoxetine Versus Placebo in Childhood/Adolescent Depression
B1Y-MC-HCJE

CHILDRENS DEPRESSION RATING SCALE - REVISED

CHECK THE NUMERIC CODE which best describes the patient.

6. **EXCESSIVE FATIGUE**

- ☐ 1 No unusual complaints of "feeling tired" during the day
- ☐ 2
- ☐ 3 Complaints of fatigue which seem somewhat excessive and not related to boredom
- ☐ 4
- ☐ 5 Daily complaints of feeling tired
- ☐ 6
- ☐ 7 Complains of feeling tired most of the day. May voluntarily take long naps without feeling refreshed. Interferes with play activities.

7. **PHYSICAL COMPLAINTS**:

- ☐ 1 Occasional complaints
- ☐ 2
- ☐ 3 Complaints appear mildly excessive
- ☐ 4
- ☐ 5 Complains daily. Some interference with the ability of the child to function
- ☐ 6
- ☐ 7 Preoccupied with aches and pains; interferes with play activities several times a week

8. **IRRITABILITY**

- ☐ 1 Rare
- ☐ 2 Occasional
- ☐ 3 Several times a week for short periods
- ☐ 4
- ☐ 5 Several times a week for longer periods
- ☐ 6
- ☐ 7 Constant

9. **GUILT**

- ☐ 1 Does not express any undue feeling of guilt. Appears appropriate to precipitating event.
- ☐ 2
- ☐ 3 Exaggerates guilt and/or shame out of proportion to the event described.
- ☐ 4
- ☐ 5 Feels guilty over things not under his or her control. Guilt is definitely pathological.
- ☐ 6
- ☐ 7 Severe delusions of guilt

10. **SELF-ESTEEM**

- ☐ 1 Describes self in primarily positive terms
- ☐ 2
- ☐ 3 Describes self with one important area where the child feels deficit
- ☐ 4
- ☐ 5 Describes self in preponderance of negative terms or gives bland answers to questions
- ☐ 6
- ☐ 7 Refers to self in derogatory terms. Reports that other children refer to him/her frequently by using derogatory nicknames and child puts self down

11. **DEPRESSED FEELINGS**

- ☐ 1 Occasional feelings of unhappiness which quickly disappear
- ☐ 2
- ☐ 3 Describes sustained periods of unhappiness which appear excessive for events described
- ☐ 4
- ☐ 5 Feels unhappy most of the time without a major precipitating cause
- ☐ 6
- ☐ 7 Feels unhappy all of the time. Accompanied by psychic pain (e.g., "I can't stand it").

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Fluoxetine Versus Placebo in Childhood/Adolescent Depression
B1Y-MC-HCJE

CHILDRENS DEPRESSION RATING SCALE - REVISED

CHECK THE NUMERIC CODE which best describes the patient.

12. **MORBID IDEATION**

- ☐ 1 None
- ☐ 2
- ☐ 3 Has some morbid thought, all of which relate to a reality event but seem excessive.
- ☐ 4
- ☐ 5 Preoccupied with morbid thoughts several times a week. Morbid thoughts extend beyond external reality
- ☐ 6
- ☐ 7 Preoccupied with death themes or morbid thoughts that are elaborate, extensive or bizarre on a daily basis

13. **SUICIDAL IDEATION**

- ☐ 1 Understands the word "suicide" but does not apply term to self
- ☐ 2 Sharp denial of suicidal thoughts
- ☐ 3 Has thoughts about suicide, usually when angry.
- ☐ 4
- ☐ 5 Has recurrent thoughts of suicide
- ☐ 6
- ☐ 7 Has made suicide attempt within the last month or is actively suicidal

14. **WEEPING**:

- ☐ 1 Normal for age.
- ☐ 2 Suggestive statements that child cries, or feels like crying, more frequently than peers.
- ☐ 3 Child cries slightly more than peers.
- ☐ 4
- ☐ 5 Cries or feels like crying frequently (several times a week). Admits to crying without knowing reason why.
- ☐ 6
- ☐ 7 Cries nearly every day.

15. **DEPRESSED AFFECT:**

- ☐ 1 Definitely not depressed. Facial expression and voice animated during interview.
- ☐ 2 Mild suppression of affect. Some loss of spontaneity.
- ☐ 3 Overall loss of spontaneity. Looks distinctly unhappy during parts of the interview. May still be able to smile when discussing non-threatening areas.
- ☐ 4
- ☐ 5 Moderate restriction of affect throughout most of interview. Has longer and frequent periods of looking distinctly unhappy.
- ☐ 6
- ☐ 7 Severe. Looks sad, withdrawn. Minimal verbal interaction throughout interview. Cries or may appear tearful.

16. **TEMPO OF SPEECH:**

- ☐ 1 Normal
- ☐ 2 Slow
- ☐ 3 Slow: delays interview.
- ☐ 4
- ☐ 5 Severe. Low; marked interference with interview.

17. **HYPOACTIVITY:**

- ☐ 1 None
- ☐ 2
- ☐ 3 Mild. Some body movements.
- ☐ 4
- ☐ 5 Moderate. Definite motor retardation.
- ☐ 6
- ☐ 7 Severe. Motionless throughout interview.

(DNDE)

Total of 1 - 17 _____

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CLINICAL GLOBAL IMPRESSION: EFFICACY INDEX

Using the worksheet below, enter the 2-digit efficacy index rating.

1. Efficacy index rating ___ ___

(DNDE)

EFFICACY INDEX WORKSHEET

Rate this item on the basis of DRUG EFFECT ONLY.

Select the terms that best describe the degrees of therapeutic effect and side effects and record the number from the box where the two items intersect in the blanks above.

THERAPEUTIC EFFECT	SIDE EFFECTS			
	None	Do not significantly interfere with patient's functioning	Significantly interferes with patient's functioning	Outweighs therapeutic effect
MARKED - Vast improvement. Complete or nearly complete remission of all symptoms.	**01**	**02**	**03**	**04**
MODERATE - Decided improvement. Partial remission of symptoms.	**05**	**06**	**07**	**08**
MINIMAL - Slight improvement which doesn't alter status of care of patient.	**09**	**10**	**11**	**12**
UNCHANGED OR WORSE	**13**	**14**	**15**	**16**
Not Assessed = **98**				

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CLINICAL GLOBAL IMPRESSION: SEVERITY

INFORMATION NOT OBTAINED ☐

Considering your total clinical experience with this particular population, how mentally ill is the patient at this time?

- ☐ 1 Normal, not at all ill
- ☐ 2 Borderline ill
- ☐ 3 Mildly ill
- ☐ 4 Moderately ill
- ☐ 5 Markedly ill
- ☐ 6 Severely ill
- ☐ 7 Among the most extremely ill patients

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CLINICAL GLOBAL IMPRESSION: IMPROVEMENT

INFORMATION NOT OBTAINED ☐

Rate total improvement, whether or not in your judgement it is due entirely to drug treatment. Compared to the patient's condition at Visit 1, how much has he/she changed?

- ☐ 1 Very much improved
- ☐ 2 Much improved
- ☐ 3 Minimally improved
- ☐ 4 No change
- ☐ 5 Minimally worse
- ☐ 6 Much worse
- ☐ 7 Very much worse

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MONTGOMERY - ASBERG DEPRESSION RATING SCALE (MADRS)

INFORMATION NOT OBTAINED ☐

The rating should be based on a clinical interview moving from broadly phrased questions about symptoms to more detailed ones which allow a precise rating of severity. The rater must decide whether the rating lies on the defined scale steps (0, 2, 4, 6) or between them (1, 3, 5).

Check the box (number) that best characterizes the patient at this time

1. **APPARENT SADNESS**
   Representing despondency, gloom, and despair (more than just ordinary transient low spirits), reflected in speech, facial expression, and posture. Rate by depth and inability to brighten up.

   ☐ 0 No sadness.
   ☐ 1
   ☐ 2 Looks dispirited but does brighten up without difficulty.
   ☐ 3
   ☐ 4 Appears sad and unhappy most of the time.
   ☐ 5
   ☐ 6 Looks miserable all the time. Extremely despondent.

2. **REPORTED SADNESS**
   Represented by reports of depressed mood, regardless of whether it is reflected in appearance or not. Includes low spirits, despondency, or the feeling of being beyond help and without hope. Rate according to intensity, duration, and the extent to which the mood is reported to be influenced by events.

   ☐ 0 Occasional sadness in keeping with the circumstances.
   ☐ 1
   ☐ 2 Sad or low but brightens up without difficulty.
   ☐ 3
   ☐ 4 Pervasive feelings of sadness or gloominess. The mood is still influenced by external circumstances.
   ☐ 5
   ☐ 6 Continuous unvarying sadness, misery or despondency.

3. **INNER TENSION**
   Representing feelings of ill-defined discomfort, edginess, inner turmoil, mental tension mounting to either panic, dread, or anguish. Rate according to intensity, frequency, duration, and the extent of reassurance called for.

   ☐ 0 Placid. Only fleeting inner tension.
   ☐ 1
   ☐ 2 Occasional feelings of edginess and ill-defined discomfort.
   ☐ 3
   ☐ 4 Continuous feelings of inner tension or intermittent panic which the patient can only master with some difficulty.
   ☐ 5
   ☐ 6 Unrelenting dread or anguish. Overwhelming panic.

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MONTGOMERY - ASBERG DEPRESSION RATING SCALE (MADRS)

4. **REDUCED SLEEP**
Representing the experience of reduced duration or depth of sleep compared to the subject's own pattern when well.

- ☐ 0 Sleeps as usual.
- ☐ 1
- ☐ 2 Slight difficulty dropping off to sleep or slightly reduced, light or fitful sleep.
- ☐ 3
- ☐ 4 Sleep reduced or broken by at least two hours.
- ☐ 5
- ☐ 6 Less than two or three hours sleep.

5. **REDUCED APPETITE**
Representing the feeling of a loss of appetite compared with when well. Rate by loss of desire for food or the need to force oneself to eat.

- ☐ 0 Normal or increased appetite
- ☐ 1
- ☐ 2 Slightly reduced appetite.
- ☐ 3
- ☐ 4 No appetite. Food is tasteless.
- ☐ 5
- ☐ 6 Needs persuasion to eat at all.

6. **CONCENTRATION DIFFICULTIES**
Representing difficulties in collecting one's thoughts mounting to incapacitating lack of concentration.

- ☐ 0 No difficulties in concentrating.
- ☐ 1
- ☐ 2 Occasional difficulties in collecting one's thoughts.
- ☐ 3
- ☐ 4 Difficulties in concentrating and sustaining thought which reduces ability to read or hold a conversation.
- ☐ 5
- ☐ 6 Unable to read or converse without great difficulty.

7. **LASSITUDE**
Representing a difficulty getting started or slowness initiating and performing everyday activities.

- ☐ 0 Hardly any difficulty in getting started. No sluggishness.
- ☐ 1
- ☐ 2 Difficulties in starting activities
- ☐ 3
- ☐ 4 Difficulties in starting simple routine activities which are carried out with effort.
- ☐ 5
- ☐ 6 Complete lassitude. Unable to do anything without help.

8. **INABILITY TO FEEL**
Representing the subjective experience of reduced interest in the surroundings, or activities that normally give pleasure. The ability to react with adequate emotion to circumstances or people is reduced.

- ☐ 0 Normal interest in the surroundings and other people.
- ☐ 1
- ☐ 2 Reduced ability to enjoy usual interests.
- ☐ 3
- ☐ 4 Loss of interest in the surroundings. Loss of feelings for friends and acquaintances.
- ☐ 5
- ☐ 6 The experience of being emotionally paralyzed, inability to feel anger, grief, or pleasure and a complete or even painful failure to feel for close relatives and friends.

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MONTGOMERY - ASBERG DEPRESSION RATING SCALE (MADRS)

9. **PESSIMISTIC THOUGHTS**
Representing thoughts of guilt, inferiority, self-reproach, sinfulness, remorse, and ruin

- ☐ 0 No pessimistic thoughts.
- ☐ 1
- ☐ 2 Fluctuating ideas of failure, self-reproach, or self-depreciation.
- ☐ 3
- ☐ 4 Persistent self-accusations, or definite but still rational ideas of guilt, or sin. Increasingly pessimistic about the future.
- ☐ 5
- ☐ 6 Delusions of ruin, remorse, or unredeemable sin. Self-accusations which are absurd and unshakable.

10. **SUICIDAL THOUGHTS**
Representing the feeling that life is not worth living, that a natural death would be welcome, suicidal thoughts, and preparations for suicide. Suicidal attempts should not in themselves influence the rating.

- ☐ 0 Enjoys life or takes it as it comes.
- ☐ 1
- ☐ 2 Weary of life. Only fleeting suicidal thoughts.
- ☐ 3
- ☐ 4 Probably better off dead. Suicidal thoughts are common, and suicide is considered as a possible solution, but without specific plans or intention.
- ☐ 5
- ☐ 6 Explicit plans for suicide when there is an opportunity. Active preparations for suicide.

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CHILDREN'S DEPRESSION INDEX (CDI)

NOTE: Only complete if patient was 8 to 12 years old at Visit 1. If patient was not 8 to 12 years old, check the Information Not Obtained box.

INFORMATION NOT OBTAINED ☐

This lists the feelings and ideas in groups. From each group of three sentences, pick one sentence that describes you **best** for the past two weeks. After you pick a sentence from the first group, go on to the next group. There is no right answer or wrong answer. Just pick the sentence that best describes the way you have been recently. Put an "X" in the box next to your answer.
Remember: pick out the sentences that describe you best **in the past two weeks**.

Item 1

- ☐ 0 I am sad once in a while.
- ☐ 1 I am sad many times.
- ☐ 2 I am sad all the time.

Item 2

- ☐ 2 Nothing will ever work out for me.
- ☐ 1 I am not sure if things will work out for me.
- ☐ 0 Things will work out for me O.K.

Item 3

- ☐ 0 I do most things O.K.
- ☐ 1 I do many things wrong.
- ☐ 2 I do everything wrong.

Item 4

- ☐ 0 I have fun in many things.
- ☐ 1 I have fun in some things.
- ☐ 2 Nothing is fun at all.

Item 5

- ☐ 2 I am bad all the time.
- ☐ 1 I am bad many times.
- ☐ 0 I am bad once in a while.

Item 6

- ☐ 0 I think about bad things happening to me once in a while.
- ☐ 1 I worry that bad things will happen to me.
- ☐ 2 I am sure that terrible things will happen to me.

Item 7

- ☐ 2 I hate myself.
- ☐ 1 I do not like myself.
- ☐ 0 I like myself.

Item 8

- ☐ 2 All bad things are my fault.
- ☐ 1 Many bad things are my fault.
- ☐ 0 Bad things are not usually my fault.

Item 9

- ☐ 0 I do not think about killing myself.
- ☐ 1 I think about killing myself but I would not do it.
- ☐ 2 I want to kill myself.

Item 10

- ☐ 2 I feel like crying every day.
- ☐ 1 I feel like crying many days.
- ☐ 0 I feel like crying once in a while.

Item 11

- ☐ 2 Things bother me all the time.
- ☐ 1 Things bother me many times.
- ☐ 0 Things bother me once in a while.

Item 12

- ☐ 0 I like being with people.
- ☐ 1 I do not like being with people many times.
- ☐ 2 I do not want to be with people at all.

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CHILDREN'S DEPRESSION INDEX (CDI)

Item 13

- ☐ 2 I cannot make up my mind about things.
- ☐ 1 It is hard to make up my mind about things.
- ☐ 0 I make up my mind about things easily.

Item 14

- ☐ 0 I look O.K.
- ☐ 1 There are some bad things about my looks.
- ☐ 2 I look ugly.

Item 15

- ☐ 2 I have to push myself all the time to do my schoolwork.
- ☐ 1 I have to push myself many times to do my schoolwork.
- ☐ 0 Doing schoolwork is not a big problem.

Item 16

- ☐ 2 I have trouble sleeping every night.
- ☐ 1 I have trouble sleeping many nights.
- ☐ 0 I sleep pretty well.

Item 17

- ☐ 0 I am tired once in a while.
- ☐ 1 I am tired many days.
- ☐ 2 I am tired all the time.

Item 18

- ☐ 2 Most days I do not feel like eating.
- ☐ 1 Many days I do not feel like eating.
- ☐ 0 I eat pretty well.

Item 19

- ☐ 0 I do not worry about aches and pains.
- ☐ 1 I worry about aches and pains many times.
- ☐ 2 I worry about aches and pains all the time.

Item 20

- ☐ 0 I do not feel alone.
- ☐ 1 I feel alone many times.
- ☐ 2 I feel alone all the time.

Item 21

- ☐ 2 I never have fun at school.
- ☐ 1 I have fun at school only once in a while.
- ☐ 0 I have fun at school many times.

Item 22

- ☐ 0 I have plenty of friends.
- ☐ 1 I have some friends but I wish I had more.
- ☐ 2 I do not have any friends.

Item 23

- ☐ 0 My schoolwork is alright.
- ☐ 1 My schoolwork is not as good as before.
- ☐ 2 I do very badly in subjects I used to be good in.

Item 24

- ☐ 2 I can never be as good as other kids.
- ☐ 1 I can be as good as other kids if I want to.
- ☐ 0 I am just as good as other kids.

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CHILDREN'S DEPRESSION INDEX (CDI)

Item 25

- ☐ 2 Nobody really loves me.
- ☐ 1 I am not sure if anybody loves me.
- ☐ 0 I am sure that somebody loves me.

Item 26

- ☐ 0 I usually do what I am told.
- ☐ 1 I do not do what I am told most times.
- ☐ 2 I never do what I am told.

Item 27

- ☐ 0 I get along with people.
- ☐ 1 I get into fights many times.
- ☐ 2 I get into fights all the time.

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BECK DEPRESSION INVENTORY

NOTE: Only complete if patient was 13 to 17 years old at Visit 1. If patient was not 13 to 17 years old, check the Information Not Obtained box.

INFORMATION NOT OBTAINED ☐

This questionnaire consists of 21 groups of statements. After reading each group of statements carefully circle the number (0, 1, 2, 3) next to the one statement in each group which best describes the way you have been feeling **the past week, including today**. If several statements within a group seem to apply equally well, circle each one. Be sure to read all the statements in each group before making your choice.

1

0 I do not feel sad.
1 I feel sad.
2 I am sad all the time and I can't snap out of it.
3 I am so sad or unhappy that I can't stand it.

2

0 I am not particularly discouraged about the future.
1 I feel discouraged about the future.
2 I feel I have nothing to look forward to.
3 I feel that the future is hopeless and that things cannot improve.

3

0 I do not feel like a failure.
1 I feel I have failed more than the average person.
2 As I look back on my life, all I can see is a lot of failures.
3 I feel I am a complete failure as a person.

4

0 I get as much satisfaction out of things as I used to.
1 I don't enjoy things the way I used to.
2 I don't get real satisfaction out of anything anymore.
3 I am dissatisfied or bored with everything.

5

0 I don't feel particularly guilty.
1 I feel guilty a good part of the time.
2 I feel quite guilty most of the time.
3 I feel guilty all of the time.

6

0 I don't feel I am being punished.
1 I feel I may be punished.
2 I expect to be punished.
3 I feel I am being punished.

7

0 I don't feel disappointed in myself.
1 I am disappointed in myself.
2 I am disgusted with myself.
3 I hate myself.

8

0 I don't feel I am any worse than anybody else.
1 I am critical of myself for my weaknesses or mistakes.
2 I blame myself all the time for my faults.
3 I blame myself for everything bad that happens.

9

0 I don't have any thoughts of killing myself.
1 I have thoughts of killing myself, but I would not carry them out.
2 I would like to kill myself.
3 I would kill myself if I had the chance.

10

0 I don't cry any more than usual.
1 I cry more now than I used to.
2 I cry all the time now.
3 I used to be able to cry, but now I can't cry even though I want to.

11

0 I am no more irritated now than I ever am.
1 I get annoyed or irritated more easily than I used to.
2 I feel irritated all the time now.
3 I don't get irritated at all by the things that used to irritate me.

12

0 I have not lost interest in other people.
1 I am less interested in other people than I used to be.
2 I have lost most of my interest in other people.
3 I have lost all of my interest in other people.

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BECK DEPRESSION INVENTORY

13

0 I make decisions about as well as I ever could.
1 I put off making decisions more than I used to.
2 I have greater difficulty in making decisions than before.
3 I can't make decisions at all anymore.

14

0 I don't feel I look any worse than I used to.
1 I am worried that I am looking old or unattractive.
2 I feel that there are permanent changes in my appearance that make me look unattractive.
3 I believe that I look ugly.

15

0 I can work about as well as before.
1 It takes an extra effort to get started at doing something.
2 I have to push myself very hard to do anything.
3 I can't do any work at all.

16

0 I can sleep as well as usual.
1 I don't sleep as well as I used to.
2 I wake up 1-2 hours earlier than usual and find it hard to get back to sleep.
3 I wake up several hours earlier than I used to and cannot get back to sleep.

17

0 I don't get more tired than usual.
1 I get tired more easily than I used to.
2 I get tired from doing almost anything.
3 I am too tired to do anything.

18

0 My appetite is no worse than usual.
1 My appetite is not as good as it used to be.
2 My appetite is much worse now.
3 I have no appetite at all anymore.

19

0 I haven't lost much weight, if any, lately.
1 I have lost more than 5 pounds.
2 I have lost more than 10 pounds.
3 I have lost more than 15 pounds.

19a

I am purposely trying to lose weight by eating less.
1 Yes
2 No

20

0 I am no more worried about my health than usual.
1 I am worried about physical problems such as aches and pains; or upset stomach or constipation.
2 I am very worried about physical problems and it's hard to think of much else.
3 I am so worried about my physical problems that I cannot think about anything else.

21

0 I have not noticed any recent change in my interest in sex.
1 I am less interested in sex than I used to be.
2 I am much less interested in sex now.
3 I have lost interest in sex completely.

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HAMILTON ANXIETY SCALE

INFORMATION NOT OBTAINED ☐

For each of the items below, **CHECK ONE BOX** that best describes the patient.

1. **ANXIOUS MOOD:** Worries, anticipation of the worst, fearful anticipation, irritability

   ☐ 0 Not present
   ☐ 1 Mild
   ☐ 2 Moderate
   ☐ 3 Severe
   ☐ 4 Very severe

2. **TENSION**: Feelings of tension, fatigability, startle response, moved to tears easily, trembling, feeling of restlessness, inability to relax

   ☐ 0 Not present
   ☐ 1 Mild
   ☐ 2 Moderate
   ☐ 3 Severe
   ☐ 4 Very severe

3. **FEARS**: Of dark, of strangers, of being alone, of animals, of traffic, of crowds

   ☐ 0 Not present
   ☐ 1 Mild
   ☐ 2 Moderate
   ☐ 3 Severe
   ☐ 4 Very severe

4. **INSOMNIA**: Difficulty in falling asleep, broken sleep, unsatisfying sleep and fatigue on waking, dreams, nightmares, night terrors

   ☐ 0 Not present
   ☐ 1 Mild
   ☐ 2 Moderate
   ☐ 3 Severe
   ☐ 4 Very severe

5. **INTELLECTUAL (COGNITIVE)**: Difficulty in concentration, poor memory

   ☐ 0 Not present
   ☐ 1 Mild
   ☐ 2 Moderate
   ☐ 3 Severe
   ☐ 4 Very severe

6. **DEPRESSED MOOD**: Loss of interest, lack of pleasure in hobbies, depression, early waking, diurnal swing

   ☐ 0 Not present
   ☐ 1 Mild
   ☐ 2 Moderate
   ☐ 3 Severe
   ☐ 4 Very severe

7. **SOMATIC (MUSCULAR)**: Pains and aches, twitchings, stiffness, myoclonic jerks, grinding of teeth, unsteady voice, increased muscular tone

   ☐ 0 Not present
   ☐ 1 Mild
   ☐ 2 Moderate
   ☐ 3 Severe
   ☐ 4 Very severe

8. **SOMATIC (SENSORY)**: Tinnitus, blurring of vision, hot and cold flushes, feeling of weakness, pricking sensation

   ☐ 0 Not present
   ☐ 1 Mild
   ☐ 2 Moderate
   ☐ 3 Severe
   ☐ 4 Very severe

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HAMILTON ANXIETY SCALE

9. **CARDIOVASCULAR SYMPTOMS:** Tachycardia, palpitations, pain in chest, throbbing of vessels, fainting feelings, missing beat

- ☐ 0 Not present
- ☐ 1 Mild
- ☐ 2 Moderate
- ☐ 3 Severe
- ☐ 4 Very severe

10. **RESPIRATORY SYMPTOMS:** Pressure or constriction in chest, choking feelings, sighing, dyspnea

- ☐ 0 Not present
- ☐ 1 Mild
- ☐ 2 Moderate
- ☐ 3 Severe
- ☐ 4 Very severe

11. **GASTROINTESTINAL SYMPTOMS:** Difficulty in swallowing, wind, abdominal pain, burning sensations, abdominal fullness, nausea, vomiting, borborygmi, looseness of bowels, loss of weight, constipation

- ☐ 0 Not present
- ☐ 1 Mild
- ☐ 2 Moderate
- ☐ 3 Severe
- ☐ 4 Very severe

12. **GENITOURINARY SYMPTOMS:** Frequency of micturition, urgency of micturition, amenorrhea, menorrhagia, development of frigidity, premature ejaculation, loss of libido, impotence

- ☐ 0 Not present
- ☐ 1 Mild
- ☐ 2 Moderate
- ☐ 3 Severe
- ☐ 4 Very severe

13. **AUTONOMIC SYMPTOMS:** Dry mouth, flushing, pallor, tendency to sweat, giddiness, tension headache, raising of hair

- ☐ 0 Not present
- ☐ 1 Mild
- ☐ 2 Moderate
- ☐ 3 Severe
- ☐ 4 Very severe

14. **BEHAVIOR AT INTERVIEW:** Fidgeting, restlessness or pacing, tremor of hands, furrowed brow, strained face, sighing or rapid respiration, facial pallor, swallowing, belching, brisk tendon jerks, dilated pupils, exophthalmos

- ☐ 0 Not present
- ☐ 1 Mild
- ☐ 2 Moderate
- ☐ 3 Severe
- ☐ 4 Very severe

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B1Y-MC-HCJE

COMMENTS : VISIT

NO COMMENTS ☐

Comments should address any clinical report form items that require further explanation. Repeating information from the clinical report form is discouraged.

Comment on all clinically significant lab values that are outside a clinically accepted reference range or clinically significant values that differ importantly from previous values.

If the patient is ending participation in the study at this visit, enter only comments that apply to this visit; then complete the Patient Summary and Study Summary Comments pages.

Print legibly and do not use abbreviations or symbols.

The information reported for this visit is accurate and complete.

_____ _____/_____/_____
Signature MM DD YY

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Clinical Report Form
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PATIENT AND VISIT IDENTIFICATION

Patient initials _____ _____ _____
First Middle Last

Visit date _____/_____/_____
MM DD YY

VITAL SIGNS : BLOOD PRESSURE AND HEART RATE

INFORMATION NOT OBTAINED ☐

Position
SI = Sitting

Position	Blood Pressure (mm Hg) Systolic/Diastolic	Heart Rate (bpm)
SI	/	

VITAL SIGNS: TEMPERATURE

INFORMATION NOT OBTAINED ☐

Temperature ___ ___ ___ . ___

Unit of measure (F) Fahrenheit

Method (E) Ear

REMINDER

On the Pre-existing Conditions and Study Adverse Events pages, record new events that occurred since the previous visit and re-evaluate any on-going conditions or events.

On the Concomitant Medication pages, record new medications the patient has taken since the previous visit, any changes to ongoing medications, and a stop date for any medication the patient is no longer taking.

Initials
Date Verified
Initials
Date Keyed
Date Received at Lilly
Reviewed
Inspected
Date

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STUDY DRUG : DATES OF MISSED DOSES

NO MISSED DOSES ☐

Record the date for any day on which the patient missed a full or partial dose of study drug.

	Dates of Missed Doses		
	MM	DD	YY
0.			
1.			
2.			
3.			
4.			
5.			
6.			
7.			
8.			
9.			

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Clinical Report Form
Fluoxetine Versus Placebo in Childhood/Adolescent Depression
B1Y-MC-HCJE

SIDE EFFECTS CHECKLIST

INFORMATION NOT OBTAINED ☐

Since your last visit, have you been bothered with or had any trouble with any of the items listed below? Check the box which best tells how much you were bothered.

	Not at all	Just a little	Pretty much	Very much	Don't know
1. Eating?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
2. Drinking?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
3. Dry mouth and lips?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
4. Wetness in mouth?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
5. Constipation?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
6. Diarrhea?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
7. Stomachaches?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
8. Muscle cramps?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
9. Being sick to your stomach?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
10. Wetting the bed?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
11. Urinating?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
12. Itchy or scratchy skin?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
13. Rashes?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
14. Cold or sniffles?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
15. Headache?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4

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Clinical Report Form
Fluoxetine Versus Placebo in Childhood/Adolescent Depression
B1Y-MC-HCJE

SIDE EFFECTS CHECKLIST

	Not at all	Just a little	Pretty much	Very much	Don't know
16. Dizziness?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
17. Playing sports?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
18. Shakiness?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
19. Pronouncing words?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
20. Doing things with your hands?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
21. Sitting still?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
22. Tiredness?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
23. Feeling sleepy?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
24. Trouble sleeping?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
25. Bad dreams?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
26. Getting along with parents?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
27. Getting along with kids?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
28. Crying?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
29. Getting mad?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
30. Not being happy?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
31. Being sad?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
32. Paying attention?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4

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Fluoxetine Versus Placebo in Childhood/Adolescent Depression
B1Y-MC-HCJE

CHILDRENS DEPRESSION RATING SCALE - REVISED

INFORMATION NOT OBTAINED ☐

CHECK THE NUMERIC CODE which best describes the patient.

1. **SCHOOLWORK**:

☐ 1 Performance consistent with ability
☐ 2
☐ 3 Decrease in school performance
☐ 4
☐ 5 Major interference in most subjects
☐ 6
☐ 7 No motivation to perform

2. **CAPACITY TO HAVE FUN**

☐ 1 Interest and activities realistically appropriate for age, personality, and social environment. Shows no appreciable change with present illness.
☐ 2
☐ 3 Describes some activities realistically available several times a week but not on a daily basis. Shows interest but not enthusiasm.
☐ 4
☐ 5 Is easily bored. Complains of "nothing to do." Participates in structured activities with a "going through the motions" attitude. May express interest primarily in activities that are (realistically) unavailable on a daily or weekly basis.
☐ 6
☐ 7 Has no initiative to become involved in any activities. Primarily passive. Watches others play or watches TV but shows little interest. Requires coaxing and/or pushing to get involved in activity. Shows no enthusiasm or real interest. Has difficulty naming activities.

3. **SOCIAL WITHDRAWAL**

☐ 1 Enjoys friendships with peers at school and home
☐ 2
☐ 3 May not actively seek out friendships but waits for others to initiate a relationship or may occasionally reject opportunities to play without a describable alternative
☐ 4
☐ 5 Frequently avoids or refuses opportunities for desirable interaction with others and/or sets up situations where rejection is inevitable.
☐ 6
☐ 7 Does not currently relate to other children. States he or she has "no friends" or actively rejects new or former friends.

4. **SLEEP**

☐ 1 No (or occasional) difficulty. (Goes to sleep within 1/2 hour or less.)
☐ 2
☐ 3 Frequently has mild difficulty with sleep
☐ 4
☐ 5 Moderate difficulty with sleep nearly every night.

5. **APPETITE OR EATING PATTERNS**

☐ 1 No problems or change in eating pattern
☐ 2
☐ 3 Mild change from usual eating habits within onset of current behavioral problem
☐ 4
☐ 5 Is not hungry most of the time or has excessive food intake since onset of current behavioral problems or marked increase in appetite

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CHILDRENS DEPRESSION RATING SCALE - REVISED

CHECK THE NUMERIC CODE which best describes the patient.

6. **EXCESSIVE FATIGUE**

- ☐ 1 No unusual complaints of "feeling tired" during the day
- ☐ 2
- ☐ 3 Complaints of fatigue which seem somewhat excessive and not related to boredom
- ☐ 4
- ☐ 5 Daily complaints of feeling tired
- ☐ 6
- ☐ 7 Complains of feeling tired most of the day. May voluntarily take long naps without feeling refreshed. Interferes with play activities.

7. **PHYSICAL COMPLAINTS**:

- ☐ 1 Occasional complaints
- ☐ 2
- ☐ 3 Complaints appear mildly excessive
- ☐ 4
- ☐ 5 Complains daily. Some interference with the ability of the child to function
- ☐ 6
- ☐ 7 Preoccupied with aches and pains; interferes with play activities several times a week

8. **IRRITABILITY**

- ☐ 1 Rare
- ☐ 2 Occasional
- ☐ 3 Several times a week for short periods
- ☐ 4
- ☐ 5 Several times a week for longer periods
- ☐ 6
- ☐ 7 Constant

9. **GUILT**

- ☐ 1 Does not express any undue feeling of guilt. Appears appropriate to precipitating event.
- ☐ 2
- ☐ 3 Exaggerates guilt and/or shame out of proportion to the event described.
- ☐ 4
- ☐ 5 Feels guilty over things not under his or her control. Guilt is definitely pathological.
- ☐ 6
- ☐ 7 Severe delusions of guilt

10. **SELF-ESTEEM**

- ☐ 1 Describes self in primarily positive terms
- ☐ 2
- ☐ 3 Describes self with one important area where the child feels deficit
- ☐ 4
- ☐ 5 Describes self in preponderance of negative terms or gives bland answers to questions
- ☐ 6
- ☐ 7 Refers to self in derogatory terms. Reports that other children refer to him/her frequently by using derogatory nicknames and child puts self down

11. **DEPRESSED FEELINGS**

- ☐ 1 Occasional feelings of unhappiness which quickly disappear
- ☐ 2
- ☐ 3 Describes sustained periods of unhappiness which appear excessive for events described
- ☐ 4
- ☐ 5 Feels unhappy most of the time without a major precipitating cause
- ☐ 6
- ☐ 7 Feels unhappy all of the time. Accompanied by psychic pain (e.g., "I can't stand it").

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CHILDRENS DEPRESSION RATING SCALE - REVISED

CHECK THE NUMERIC CODE which best describes the patient.

12. **MORBID IDEATION**

- ☐ 1 None
- ☐ 2
- ☐ 3 Has some morbid thought, all of which relate to a reality event but seem excessive.
- ☐ 4
- ☐ 5 Preoccupied with morbid thoughts several times a week. Morbid thoughts extend beyond external reality
- ☐ 6
- ☐ 7 Preoccupied with death themes or morbid thoughts that are elaborate, extensive or bizarre on a daily basis

13. **SUICIDAL IDEATION**

- ☐ 1 Understands the word "suicide" but does not apply term to self
- ☐ 2 Sharp denial of suicidal thoughts
- ☐ 3 Has thoughts about suicide, usually when angry.
- ☐ 4
- ☐ 5 Has recurrent thoughts of suicide
- ☐ 6
- ☐ 7 Has made suicide attempt within the last month or is actively suicidal

14. **WEEPING**:

- ☐ 1 Normal for age.
- ☐ 2 Suggestive statements that child cries, or feels like crying, more frequently than peers.
- ☐ 3 Child cries slightly more than peers.
- ☐ 4
- ☐ 5 Cries or feels like crying frequently (several times a week). Admits to crying without knowing reason why.
- ☐ 6
- ☐ 7 Cries nearly every day.

15. **DEPRESSED AFFECT:**

- ☐ 1 Definitely not depressed. Facial expression and voice animated during interview.
- ☐ 2 Mild suppression of affect. Some loss of spontaneity.
- ☐ 3 Overall loss of spontaneity. Looks distinctly unhappy during parts of the interview. May still be able to smile when discussing non-threatening areas.
- ☐ 4
- ☐ 5 Moderate restriction of affect throughout most of interview. Has longer and frequent periods of looking distinctly unhappy.
- ☐ 6
- ☐ 7 Severe. Looks sad, withdrawn. Minimal verbal interaction throughout interview. Cries or may appear tearful.

16. **TEMPO OF SPEECH:**

- ☐ 1 Normal
- ☐ 2 Slow
- ☐ 3 Slow: delays interview.
- ☐ 4
- ☐ 5 Severe. Low; marked interference with interview.

17. **HYPOACTIVITY:**

- ☐ 1 None
- ☐ 2
- ☐ 3 Mild. Some body movements.
- ☐ 4
- ☐ 5 Moderate. Definite motor retardation.
- ☐ 6
- ☐ 7 Severe. Motionless throughout interview.

(DNDE)

Total of 1 - 17 _____

Evaluator's initials _____ _____ _____
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CLINICAL GLOBAL IMPRESSION: EFFICACY INDEX

Using the worksheet below, enter the 2-digit efficacy index rating.

1. Efficacy index rating ___ ___

(DNDE)

EFFICACY INDEX WORKSHEET

Rate this item on the basis of DRUG EFFECT ONLY.

Select the terms that best describe the degrees of therapeutic effect and side effects and record the number from the box where the two items intersect in the blanks above.

THERAPEUTIC EFFECT	SIDE EFFECTS			
	None	Do not significantly interfere with patient's functioning	Significantly interferes with patient's functioning	Outweighs therapeutic effect
MARKED - Vast improvement. Complete or nearly complete remission of all symptoms.	**01**	**02**	**03**	**04**
MODERATE - Decided improvement. Partial remission of symptoms.	**05**	**06**	**07**	**08**
MINIMAL - Slight improvement which doesn't alter status of care of patient.	**09**	**10**	**11**	**12**
UNCHANGED OR WORSE	**13**	**14**	**15**	**16**
Not Assessed = **98**				

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B1Y-MC-HCJE

CLINICAL GLOBAL IMPRESSION: SEVERITY

INFORMATION NOT OBTAINED ☐

Considering your total clinical experience with this particular population, how mentally ill is the patient at this time?

- ☐ 1 Normal, not at all ill
- ☐ 2 Borderline ill
- ☐ 3 Mildly ill
- ☐ 4 Moderately ill
- ☐ 5 Markedly ill
- ☐ 6 Severely ill
- ☐ 7 Among the most extremely ill patients

Evaluator's initials _____ _____ _____
First Middle Last

CLINICAL GLOBAL IMPRESSION: IMPROVEMENT

INFORMATION NOT OBTAINED ☐

Rate total improvement, whether or not in your judgement it is due entirely to drug treatment. Compared to the patient's condition at Visit 1, how much has he/she changed?

- ☐ 1 Very much improved
- ☐ 2 Much improved
- ☐ 3 Minimally improved
- ☐ 4 No change
- ☐ 5 Minimally worse
- ☐ 6 Much worse
- ☐ 7 Very much worse

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Clinical Report Form
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B1Y-MC-HCJE

MONTGOMERY - ASBERG DEPRESSION RATING SCALE (MADRS)

INFORMATION NOT OBTAINED ☐

The rating should be based on a clinical interview moving from broadly phrased questions about symptoms to more detailed ones which allow a precise rating of severity. The rater must decide whether the rating lies on the defined scale steps (0, 2, 4, 6) or between them (1, 3, 5).

Check the box (number) that best characterizes the patient at this time

1. **APPARENT SADNESS**
   Representing despondency, gloom, and despair (more than just ordinary transient low spirits), reflected in speech, facial expression, and posture. Rate by depth and inability to brighten up.

   ☐ 0 No sadness.
   ☐ 1
   ☐ 2 Looks dispirited but does brighten up without difficulty.
   ☐ 3
   ☐ 4 Appears sad and unhappy most of the time.
   ☐ 5
   ☐ 6 Looks miserable all the time. Extremely despondent.

2. **REPORTED SADNESS**
   Represented by reports of depressed mood, regardless of whether it is reflected in appearance or not. Includes low spirits, despondency, or the feeling of being beyond help and without hope. Rate according to intensity, duration, and the extent to which the mood is reported to be influenced by events.

   ☐ 0 Occasional sadness in keeping with the circumstances.
   ☐ 1
   ☐ 2 Sad or low but brightens up without difficulty.
   ☐ 3
   ☐ 4 Pervasive feelings of sadness or gloominess. The mood is still influenced by external circumstances.
   ☐ 5
   ☐ 6 Continuous unvarying sadness, misery or despondency.

3. **INNER TENSION**
   Representing feelings of ill-defined discomfort, edginess, inner turmoil, mental tension mounting to either panic, dread, or anguish. Rate according to intensity, frequency, duration, and the extent of reassurance called for.

   ☐ 0 Placid. Only fleeting inner tension.
   ☐ 1
   ☐ 2 Occasional feelings of edginess and ill-defined discomfort.
   ☐ 3
   ☐ 4 Continuous feelings of inner tension or intermittent panic which the patient can only master with some difficulty.
   ☐ 5
   ☐ 6 Unrelenting dread or anguish. Overwhelming panic.

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MONTGOMERY - ASBERG DEPRESSION RATING SCALE (MADRS)

4. **REDUCED SLEEP**
Representing the experience of reduced duration or depth of sleep compared to the subject's own pattern when well.

- ☐ 0 Sleeps as usual.
- ☐ 1
- ☐ 2 Slight difficulty dropping off to sleep or slightly reduced, light or fitful sleep.
- ☐ 3
- ☐ 4 Sleep reduced or broken by at least two hours.
- ☐ 5
- ☐ 6 Less than two or three hours sleep.

5. **REDUCED APPETITE**
Representing the feeling of a loss of appetite compared with when well. Rate by loss of desire for food or the need to force oneself to eat.

- ☐ 0 Normal or increased appetite
- ☐ 1
- ☐ 2 Slightly reduced appetite.
- ☐ 3
- ☐ 4 No appetite. Food is tasteless.
- ☐ 5
- ☐ 6 Needs persuasion to eat at all.

6. **CONCENTRATION DIFFICULTIES**
Representing difficulties in collecting one's thoughts mounting to incapacitating lack of concentration.

- ☐ 0 No difficulties in concentrating.
- ☐ 1
- ☐ 2 Occasional difficulties in collecting one's thoughts.
- ☐ 3
- ☐ 4 Difficulties in concentrating and sustaining thought which reduces ability to read or hold a conversation.
- ☐ 5
- ☐ 6 Unable to read or converse without great difficulty.

7. **LASSITUDE**
Representing a difficulty getting started or slowness initiating and performing everyday activities.

- ☐ 0 Hardly any difficulty in getting started. No sluggishness.
- ☐ 1
- ☐ 2 Difficulties in starting activities
- ☐ 3
- ☐ 4 Difficulties in starting simple routine activities which are carried out with effort.
- ☐ 5
- ☐ 6 Complete lassitude. Unable to do anything without help.

8. **INABILITY TO FEEL**
Representing the subjective experience of reduced interest in the surroundings, or activities that normally give pleasure. The ability to react with adequate emotion to circumstances or people is reduced.

- ☐ 0 Normal interest in the surroundings and other people.
- ☐ 1
- ☐ 2 Reduced ability to enjoy usual interests.
- ☐ 3
- ☐ 4 Loss of interest in the surroundings. Loss of feelings for friends and acquaintances.
- ☐ 5
- ☐ 6 The experience of being emotionally paralyzed, inability to feel anger, grief, or pleasure and a complete or even painful failure to feel for close relatives and friends.

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B1Y-MC-HCJE

MONTGOMERY - ASBERG DEPRESSION RATING SCALE (MADRS)

9. **PESSIMISTIC THOUGHTS**
Representing thoughts of guilt, inferiority, self-reproach, sinfulness, remorse, and ruin

- ☐ 0 No pessimistic thoughts.
- ☐ 1
- ☐ 2 Fluctuating ideas of failure, self-reproach, or self-depreciation.
- ☐ 3
- ☐ 4 Persistent self-accusations, or definite but still rational ideas of guilt, or sin. Increasingly pessimistic about the future.
- ☐ 5
- ☐ 6 Delusions of ruin, remorse, or unredeemable sin. Self-accusations which are absurd and unshakable.

10. **SUICIDAL THOUGHTS**
Representing the feeling that life is not worth living, that a natural death would be welcome, suicidal thoughts, and preparations for suicide. Suicidal attempts should not in themselves influence the rating.

- ☐ 0 Enjoys life or takes it as it comes.
- ☐ 1
- ☐ 2 Weary of life. Only fleeting suicidal thoughts.
- ☐ 3
- ☐ 4 Probably better off dead. Suicidal thoughts are common, and suicide is considered as a possible solution, but without specific plans or intention.
- ☐ 5
- ☐ 6 Explicit plans for suicide when there is an opportunity. Active preparations for suicide.

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First Middle Last

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Clinical Report Form
Fluoxetine Versus Placebo in Childhood/Adolescent Depression
B1Y-MC-HCJE

COMMENTS : VISIT

NO COMMENTS ☐

Comments should address any clinical report form items that require further explanation. Repeating information from the clinical report form is discouraged.

Comment on all clinically significant lab values that are outside a clinically accepted reference range or clinically significant values that differ importantly from previous values.

If the patient is ending participation in the study at this visit, enter only comments that apply to this visit; then complete the Patient Summary and Study Summary Comments pages.

Print legibly and do not use abbreviations or symbols.

The information reported for this visit is accurate and complete.

_____ _____/_____/_____
Signature MM DD YY

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Clinical Report Form
Fluoxetine Versus Placebo in Childhood/Adolescent Depression
B1Y-MC-HCJE

PATIENT AND VISIT IDENTIFICATION

Patient initials _____ _____ _____
First Middle Last

Visit date _____/_____/_____
MM DD YY

VITAL SIGNS : BLOOD PRESSURE AND HEART RATE

INFORMATION NOT OBTAINED ☐

Position
SI = Sitting

Position	Blood Pressure (mm Hg) Systolic/Diastolic	Heart Rate (bpm)
SI	/	

VITAL SIGNS: TEMPERATURE

INFORMATION NOT OBTAINED ☐

Temperature ___ ___ ___ . ___

Unit of measure (F) Fahrenheit

Method (E) Ear

REMINDER

On the Pre-existing Conditions and Study Adverse Events pages, record new events that occurred since the previous visit and re-evaluate any on-going conditions or events.

On the Concomitant Medication pages, record new medications the patient has taken since the previous visit, any changes to ongoing medications, and a stop date for any medication the patient is no longer taking.

Initials
Date Verified
Initials
Date Keyed
Date Received at Lilly
Reviewed
Inspected
Date

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STUDY DRUG : DATES OF MISSED DOSES

NO MISSED DOSES ☐

Record the date for any day on which the patient missed a full or partial dose of study drug.

	Dates of Missed Doses		
	MM	DD	YY
0.			
1.			
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Clinical Report Form
Fluoxetine Versus Placebo in Childhood/Adolescent Depression
B1Y-MC-HCJE

SIDE EFFECTS CHECKLIST

INFORMATION NOT OBTAINED ☐

Since your last visit, have you been bothered with or had any trouble with any of the items listed below? Check the box which best tells how much you were bothered.

	Not at all	Just a little	Pretty much	Very much	Don't know
1. Eating?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
2. Drinking?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
3. Dry mouth and lips?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
4. Wetness in mouth?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
5. Constipation?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
6. Diarrhea?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
7. Stomachaches?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
8. Muscle cramps?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
9. Being sick to your stomach?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
10. Wetting the bed?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
11. Urinating?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
12. Itchy or scratchy skin?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
13. Rashes?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
14. Cold or sniffles?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
15. Headache?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4

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Clinical Report Form
Fluoxetine Versus Placebo in Childhood/Adolescent Depression
B1Y-MC-HCJE

SIDE EFFECTS CHECKLIST

	Not at all	Just a little	Pretty much	Very much	Don't know
16. Dizziness?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
17. Playing sports?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
18. Shakiness?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
19. Pronouncing words?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
20. Doing things with your hands?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
21. Sitting still?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
22. Tiredness?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
23. Feeling sleepy?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
24. Trouble sleeping?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
25. Bad dreams?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
26. Getting along with parents?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
27. Getting along with kids?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
28. Crying?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
29. Getting mad?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
30. Not being happy?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
31. Being sad?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
32. Paying attention?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4

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B1Y-MC-HCJE

CHILDRENS DEPRESSION RATING SCALE - REVISED

INFORMATION NOT OBTAINED ☐

CHECK THE NUMERIC CODE which best describes the patient.

1. **SCHOOLWORK**:

☐ 1 Performance consistent with ability
☐ 2
☐ 3 Decrease in school performance
☐ 4
☐ 5 Major interference in most subjects
☐ 6
☐ 7 No motivation to perform

2. **CAPACITY TO HAVE FUN**

☐ 1 Interest and activities realistically appropriate for age, personality, and social environment. Shows no appreciable change with present illness.
☐ 2
☐ 3 Describes some activities realistically available several times a week but not on a daily basis. Shows interest but not enthusiasm.
☐ 4
☐ 5 Is easily bored. Complains of "nothing to do." Participates in structured activities with a "going through the motions" attitude. May express interest primarily in activities that are (realistically) unavailable on a daily or weekly basis.
☐ 6
☐ 7 Has no initiative to become involved in any activities. Primarily passive. Watches others play or watches TV but shows little interest. Requires coaxing and/or pushing to get involved in activity. Shows no enthusiasm or real interest. Has difficulty naming activities.

3. **SOCIAL WITHDRAWAL**

☐ 1 Enjoys friendships with peers at school and home
☐ 2
☐ 3 May not actively seek out friendships but waits for others to initiate a relationship or may occasionally reject opportunities to play without a describable alternative
☐ 4
☐ 5 Frequently avoids or refuses opportunities for desirable interaction with others and/or sets up situations where rejection is inevitable.
☐ 6
☐ 7 Does not currently relate to other children. States he or she has "no friends" or actively rejects new or former friends.

4. **SLEEP**

☐ 1 No (or occasional) difficulty. (Goes to sleep within 1/2 hour or less.)
☐ 2
☐ 3 Frequently has mild difficulty with sleep
☐ 4
☐ 5 Moderate difficulty with sleep nearly every night.

5. **APPETITE OR EATING PATTERNS**

☐ 1 No problems or change in eating pattern
☐ 2
☐ 3 Mild change from usual eating habits within onset of current behavioral problem
☐ 4
☐ 5 Is not hungry most of the time or has excessive food intake since onset of current behavioral problems or marked increase in appetite

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B1Y-MC-HCJE

CHILDRENS DEPRESSION RATING SCALE - REVISED

CHECK THE NUMERIC CODE which best describes the patient.

6. **EXCESSIVE FATIGUE**

- ☐ 1 No unusual complaints of "feeling tired" during the day
- ☐ 2
- ☐ 3 Complaints of fatigue which seem somewhat excessive and not related to boredom
- ☐ 4
- ☐ 5 Daily complaints of feeling tired
- ☐ 6
- ☐ 7 Complains of feeling tired most of the day. May voluntarily take long naps without feeling refreshed. Interferes with play activities.

7. **PHYSICAL COMPLAINTS**:

- ☐ 1 Occasional complaints
- ☐ 2
- ☐ 3 Complaints appear mildly excessive
- ☐ 4
- ☐ 5 Complains daily. Some interference with the ability of the child to function
- ☐ 6
- ☐ 7 Preoccupied with aches and pains; interferes with play activities several times a week

8. **IRRITABILITY**

- ☐ 1 Rare
- ☐ 2 Occasional
- ☐ 3 Several times a week for short periods
- ☐ 4
- ☐ 5 Several times a week for longer periods
- ☐ 6
- ☐ 7 Constant

9. **GUILT**

- ☐ 1 Does not express any undue feeling of guilt. Appears appropriate to precipitating event.
- ☐ 2
- ☐ 3 Exaggerates guilt and/or shame out of proportion to the event described.
- ☐ 4
- ☐ 5 Feels guilty over things not under his or her control. Guilt is definitely pathological.
- ☐ 6
- ☐ 7 Severe delusions of guilt

10. **SELF-ESTEEM**

- ☐ 1 Describes self in primarily positive terms
- ☐ 2
- ☐ 3 Describes self with one important area where the child feels deficit
- ☐ 4
- ☐ 5 Describes self in preponderance of negative terms or gives bland answers to questions
- ☐ 6
- ☐ 7 Refers to self in derogatory terms. Reports that other children refer to him/her frequently by using derogatory nicknames and child puts self down

11. **DEPRESSED FEELINGS**

- ☐ 1 Occasional feelings of unhappiness which quickly disappear
- ☐ 2
- ☐ 3 Describes sustained periods of unhappiness which appear excessive for events described
- ☐ 4
- ☐ 5 Feels unhappy most of the time without a major precipitating cause
- ☐ 6
- ☐ 7 Feels unhappy all of the time. Accompanied by psychic pain (e.g., "I can't stand it").

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CHILDRENS DEPRESSION RATING SCALE - REVISED

CHECK THE NUMERIC CODE which best describes the patient.

12. **MORBID IDEATION**

- ☐ 1 None
- ☐ 2
- ☐ 3 Has some morbid thought, all of which relate to a reality event but seem excessive.
- ☐ 4
- ☐ 5 Preoccupied with morbid thoughts several times a week. Morbid thoughts extend beyond external reality
- ☐ 6
- ☐ 7 Preoccupied with death themes or morbid thoughts that are elaborate, extensive or bizarre on a daily basis

13. **SUICIDAL IDEATION**

- ☐ 1 Understands the word "suicide" but does not apply term to self
- ☐ 2 Sharp denial of suicidal thoughts
- ☐ 3 Has thoughts about suicide, usually when angry.
- ☐ 4
- ☐ 5 Has recurrent thoughts of suicide
- ☐ 6
- ☐ 7 Has made suicide attempt within the last month or is actively suicidal

14. **WEEPING**:

- ☐ 1 Normal for age.
- ☐ 2 Suggestive statements that child cries, or feels like crying, more frequently than peers.
- ☐ 3 Child cries slightly more than peers.
- ☐ 4
- ☐ 5 Cries or feels like crying frequently (several times a week). Admits to crying without knowing reason why.
- ☐ 6
- ☐ 7 Cries nearly every day.

15. **DEPRESSED AFFECT:**

- ☐ 1 Definitely not depressed. Facial expression and voice animated during interview.
- ☐ 2 Mild suppression of affect. Some loss of spontaneity.
- ☐ 3 Overall loss of spontaneity. Looks distinctly unhappy during parts of the interview. May still be able to smile when discussing non-threatening areas.
- ☐ 4
- ☐ 5 Moderate restriction of affect throughout most of interview. Has longer and frequent periods of looking distinctly unhappy.
- ☐ 6
- ☐ 7 Severe. Looks sad, withdrawn. Minimal verbal interaction throughout interview. Cries or may appear tearful.

16. **TEMPO OF SPEECH:**

- ☐ 1 Normal
- ☐ 2 Slow
- ☐ 3 Slow: delays interview.
- ☐ 4
- ☐ 5 Severe. Low; marked interference with interview.

17. **HYPOACTIVITY:**

- ☐ 1 None
- ☐ 2
- ☐ 3 Mild. Some body movements.
- ☐ 4
- ☐ 5 Moderate. Definite motor retardation.
- ☐ 6
- ☐ 7 Severe. Motionless throughout interview.

(DNDE)

Total of 1 - 17 _____

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First Middle Last

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Fluoxetine Versus Placebo in Childhood/Adolescent Depression
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CLINICAL GLOBAL IMPRESSION: EFFICACY INDEX

Using the worksheet below, enter the 2-digit efficacy index rating.

1. Efficacy index rating ___ ___

(DNDE)

EFFICACY INDEX WORKSHEET

Rate this item on the basis of DRUG EFFECT ONLY.

Select the terms that best describe the degrees of therapeutic effect and side effects and record the number from the box where the two items intersect in the blanks above.

THERAPEUTIC EFFECT	SIDE EFFECTS			
	None	Do not significantly interfere with patient's functioning	Significantly interferes with patient's functioning	Outweighs therapeutic effect
MARKED - Vast improvement. Complete or nearly complete remission of all symptoms.	**01**	**02**	**03**	**04**
MODERATE - Decided improvement. Partial remission of symptoms.	**05**	**06**	**07**	**08**
MINIMAL - Slight improvement which doesn't alter status of care of patient.	**09**	**10**	**11**	**12**
UNCHANGED OR WORSE	**13**	**14**	**15**	**16**
Not Assessed = **98**				

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Fluoxetine Versus Placebo in Childhood/Adolescent Depression
B1Y-MC-HCJE

CLINICAL GLOBAL IMPRESSION: SEVERITY

INFORMATION NOT OBTAINED ☐

Considering your total clinical experience with this particular population, how mentally ill is the patient at this time?

- ☐ 1 Normal, not at all ill
- ☐ 2 Borderline ill
- ☐ 3 Mildly ill
- ☐ 4 Moderately ill
- ☐ 5 Markedly ill
- ☐ 6 Severely ill
- ☐ 7 Among the most extremely ill patients

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CLINICAL GLOBAL IMPRESSION: IMPROVEMENT

INFORMATION NOT OBTAINED ☐

Rate total improvement, whether or not in your judgement it is due entirely to drug treatment. Compared to the patient's condition at Visit 1, how much has he/she changed?

- ☐ 1 Very much improved
- ☐ 2 Much improved
- ☐ 3 Minimally improved
- ☐ 4 No change
- ☐ 5 Minimally worse
- ☐ 6 Much worse
- ☐ 7 Very much worse

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B1Y-MC-HCJE

MONTGOMERY - ASBERG DEPRESSION RATING SCALE (MADRS)

INFORMATION NOT OBTAINED ☐

The rating should be based on a clinical interview moving from broadly phrased questions about symptoms to more detailed ones which allow a precise rating of severity. The rater must decide whether the rating lies on the defined scale steps (0, 2, 4, 6) or between them (1, 3, 5).

Check the box (number) that best characterizes the patient at this time

1. **APPARENT SADNESS**
   Representing despondency, gloom, and despair (more than just ordinary transient low spirits), reflected in speech, facial expression, and posture. Rate by depth and inability to brighten up.

   ☐ 0 No sadness.
   ☐ 1
   ☐ 2 Looks dispirited but does brighten up without difficulty.
   ☐ 3
   ☐ 4 Appears sad and unhappy most of the time.
   ☐ 5
   ☐ 6 Looks miserable all the time. Extremely despondent.

2. **REPORTED SADNESS**
   Represented by reports of depressed mood, regardless of whether it is reflected in appearance or not. Includes low spirits, despondency, or the feeling of being beyond help and without hope. Rate according to intensity, duration, and the extent to which the mood is reported to be influenced by events.

   ☐ 0 Occasional sadness in keeping with the circumstances.
   ☐ 1
   ☐ 2 Sad or low but brightens up without difficulty.
   ☐ 3
   ☐ 4 Pervasive feelings of sadness or gloominess. The mood is still influenced by external circumstances.
   ☐ 5
   ☐ 6 Continuous unvarying sadness, misery or despondency.

3. **INNER TENSION**
   Representing feelings of ill-defined discomfort, edginess, inner turmoil, mental tension mounting to either panic, dread, or anguish. Rate according to intensity, frequency, duration, and the extent of reassurance called for.

   ☐ 0 Placid. Only fleeting inner tension.
   ☐ 1
   ☐ 2 Occasional feelings of edginess and ill-defined discomfort.
   ☐ 3
   ☐ 4 Continuous feelings of inner tension or intermittent panic which the patient can only master with some difficulty.
   ☐ 5
   ☐ 6 Unrelenting dread or anguish. Overwhelming panic.

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MONTGOMERY - ASBERG DEPRESSION RATING SCALE (MADRS)

4. **REDUCED SLEEP**
Representing the experience of reduced duration or depth of sleep compared to the subject's own pattern when well.

- ☐ 0 Sleeps as usual.
- ☐ 1
- ☐ 2 Slight difficulty dropping off to sleep or slightly reduced, light or fitful sleep.
- ☐ 3
- ☐ 4 Sleep reduced or broken by at least two hours.
- ☐ 5
- ☐ 6 Less than two or three hours sleep.

5. **REDUCED APPETITE**
Representing the feeling of a loss of appetite compared with when well. Rate by loss of desire for food or the need to force oneself to eat.

- ☐ 0 Normal or increased appetite
- ☐ 1
- ☐ 2 Slightly reduced appetite.
- ☐ 3
- ☐ 4 No appetite. Food is tasteless.
- ☐ 5
- ☐ 6 Needs persuasion to eat at all.

6. **CONCENTRATION DIFFICULTIES**
Representing difficulties in collecting one's thoughts mounting to incapacitating lack of concentration.

- ☐ 0 No difficulties in concentrating.
- ☐ 1
- ☐ 2 Occasional difficulties in collecting one's thoughts.
- ☐ 3
- ☐ 4 Difficulties in concentrating and sustaining thought which reduces ability to read or hold a conversation.
- ☐ 5
- ☐ 6 Unable to read or converse without great difficulty.

7. **LASSITUDE**
Representing a difficulty getting started or slowness initiating and performing everyday activities.

- ☐ 0 Hardly any difficulty in getting started. No sluggishness.
- ☐ 1
- ☐ 2 Difficulties in starting activities
- ☐ 3
- ☐ 4 Difficulties in starting simple routine activities which are carried out with effort.
- ☐ 5
- ☐ 6 Complete lassitude. Unable to do anything without help.

8. **INABILITY TO FEEL**
Representing the subjective experience of reduced interest in the surroundings, or activities that normally give pleasure. The ability to react with adequate emotion to circumstances or people is reduced.

- ☐ 0 Normal interest in the surroundings and other people.
- ☐ 1
- ☐ 2 Reduced ability to enjoy usual interests.
- ☐ 3
- ☐ 4 Loss of interest in the surroundings. Loss of feelings for friends and acquaintances.
- ☐ 5
- ☐ 6 The experience of being emotionally paralyzed, inability to feel anger, grief, or pleasure and a complete or even painful failure to feel for close relatives and friends.

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B1Y-MC-HCJE

MONTGOMERY - ASBERG DEPRESSION RATING SCALE (MADRS)

9. **PESSIMISTIC THOUGHTS**
Representing thoughts of guilt, inferiority, self-reproach, sinfulness, remorse, and ruin

- ☐ 0 No pessimistic thoughts.
- ☐ 1
- ☐ 2 Fluctuating ideas of failure, self-reproach, or self-depreciation.
- ☐ 3
- ☐ 4 Persistent self-accusations, or definite but still rational ideas of guilt, or sin. Increasingly pessimistic about the future.
- ☐ 5
- ☐ 6 Delusions of ruin, remorse, or unredeemable sin. Self-accusations which are absurd and unshakable.

10. **SUICIDAL THOUGHTS**
Representing the feeling that life is not worth living, that a natural death would be welcome, suicidal thoughts, and preparations for suicide. Suicidal attempts should not in themselves influence the rating.

- ☐ 0 Enjoys life or takes it as it comes.
- ☐ 1
- ☐ 2 Weary of life. Only fleeting suicidal thoughts.
- ☐ 3
- ☐ 4 Probably better off dead. Suicidal thoughts are common, and suicide is considered as a possible solution, but without specific plans or intention.
- ☐ 5
- ☐ 6 Explicit plans for suicide when there is an opportunity. Active preparations for suicide.

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Clinical Report Form
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CHILDREN'S DEPRESSION INDEX (CDI)

NOTE: Only complete if patient was 8 to 12 years old at Visit 1. If patient was not 8 to 12 years old, check the Information Not Obtained box.

INFORMATION NOT OBTAINED ☐

This lists the feelings and ideas in groups. From each group of three sentences, pick one sentence that describes you **best** for the past two weeks. After you pick a sentence from the first group, go on to the next group. There is no right answer or wrong answer. Just pick the sentence that best describes the way you have been recently. Put an "X" in the box next to your answer.
Remember: pick out the sentences that describe you best **in the past two weeks**.

Item 1

- ☐ 0 I am sad once in a while.
- ☐ 1 I am sad many times.
- ☐ 2 I am sad all the time.

Item 2

- ☐ 2 Nothing will ever work out for me.
- ☐ 1 I am not sure if things will work out for me.
- ☐ 0 Things will work out for me O.K.

Item 3

- ☐ 0 I do most things O.K.
- ☐ 1 I do many things wrong.
- ☐ 2 I do everything wrong.

Item 4

- ☐ 0 I have fun in many things.
- ☐ 1 I have fun in some things.
- ☐ 2 Nothing is fun at all.

Item 5

- ☐ 2 I am bad all the time.
- ☐ 1 I am bad many times.
- ☐ 0 I am bad once in a while.

Item 6

- ☐ 0 I think about bad things happening to me once in a while.
- ☐ 1 I worry that bad things will happen to me.
- ☐ 2 I am sure that terrible things will happen to me.

Item 7

- ☐ 2 I hate myself.
- ☐ 1 I do not like myself.
- ☐ 0 I like myself.

Item 8

- ☐ 2 All bad things are my fault.
- ☐ 1 Many bad things are my fault.
- ☐ 0 Bad things are not usually my fault.

Item 9

- ☐ 0 I do not think about killing myself.
- ☐ 1 I think about killing myself but I would not do it.
- ☐ 2 I want to kill myself.

Item 10

- ☐ 2 I feel like crying every day.
- ☐ 1 I feel like crying many days.
- ☐ 0 I feel like crying once in a while.

Item 11

- ☐ 2 Things bother me all the time.
- ☐ 1 Things bother me many times.
- ☐ 0 Things bother me once in a while.

Item 12

- ☐ 0 I like being with people.
- ☐ 1 I do not like being with people many times.
- ☐ 2 I do not want to be with people at all.

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CHILDREN'S DEPRESSION INDEX (CDI)

Item 13

- ☐ 2 I cannot make up my mind about things.
- ☐ 1 It is hard to make up my mind about things.
- ☐ 0 I make up my mind about things easily.

Item 14

- ☐ 0 I look O.K.
- ☐ 1 There are some bad things about my looks.
- ☐ 2 I look ugly.

Item 15

- ☐ 2 I have to push myself all the time to do my schoolwork.
- ☐ 1 I have to push myself many times to do my schoolwork.
- ☐ 0 Doing schoolwork is not a big problem.

Item 16

- ☐ 2 I have trouble sleeping every night.
- ☐ 1 I have trouble sleeping many nights.
- ☐ 0 I sleep pretty well.

Item 17

- ☐ 0 I am tired once in a while.
- ☐ 1 I am tired many days.
- ☐ 2 I am tired all the time.

Item 18

- ☐ 2 Most days I do not feel like eating.
- ☐ 1 Many days I do not feel like eating.
- ☐ 0 I eat pretty well.

Item 19

- ☐ 0 I do not worry about aches and pains.
- ☐ 1 I worry about aches and pains many times.
- ☐ 2 I worry about aches and pains all the time.

Item 20

- ☐ 0 I do not feel alone.
- ☐ 1 I feel alone many times.
- ☐ 2 I feel alone all the time.

Item 21

- ☐ 2 I never have fun at school.
- ☐ 1 I have fun at school only once in a while.
- ☐ 0 I have fun at school many times.

Item 22

- ☐ 0 I have plenty of friends.
- ☐ 1 I have some friends but I wish I had more.
- ☐ 2 I do not have any friends.

Item 23

- ☐ 0 My schoolwork is alright.
- ☐ 1 My schoolwork is not as good as before.
- ☐ 2 I do very badly in subjects I used to be good in.

Item 24

- ☐ 2 I can never be as good as other kids.
- ☐ 1 I can be as good as other kids if I want to.
- ☐ 0 I am just as good as other kids.

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CHILDREN'S DEPRESSION INDEX (CDI)

Item 25

- ☐ 2 Nobody really loves me.
- ☐ 1 I am not sure if anybody loves me.
- ☐ 0 I am sure that somebody loves me.

Item 26

- ☐ 0 I usually do what I am told.
- ☐ 1 I do not do what I am told most times.
- ☐ 2 I never do what I am told.

Item 27

- ☐ 0 I get along with people.
- ☐ 1 I get into fights many times.
- ☐ 2 I get into fights all the time.

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BECK DEPRESSION INVENTORY

NOTE: Only complete if patient was 13 to 17 years old at Visit 1. If patient was not 13 to 17 years old, check the Information Not Obtained box.

INFORMATION NOT OBTAINED ☐

This questionnaire consists of 21 groups of statements. After reading each group of statements carefully circle the number (0, 1, 2, 3) next to the one statement in each group which best describes the way you have been feeling **the past week, including today**. If several statements within a group seem to apply equally well, circle each one. Be sure to read all the statements in each group before making your choice.

1

0 I do not feel sad.
1 I feel sad.
2 I am sad all the time and I can't snap out of it.
3 I am so sad or unhappy that I can't stand it.

2

0 I am not particularly discouraged about the future.
1 I feel discouraged about the future.
2 I feel I have nothing to look forward to.
3 I feel that the future is hopeless and that things cannot improve.

3

0 I do not feel like a failure.
1 I feel I have failed more than the average person.
2 As I look back on my life, all I can see is a lot of failures.
3 I feel I am a complete failure as a person.

4

0 I get as much satisfaction out of things as I used to.
1 I don't enjoy things the way I used to.
2 I don't get real satisfaction out of anything anymore.
3 I am dissatisfied or bored with everything.

5

0 I don't feel particularly guilty.
1 I feel guilty a good part of the time.
2 I feel quite guilty most of the time.
3 I feel guilty all of the time.

6

0 I don't feel I am being punished.
1 I feel I may be punished.
2 I expect to be punished.
3 I feel I am being punished.

7

0 I don't feel disappointed in myself.
1 I am disappointed in myself.
2 I am disgusted with myself.
3 I hate myself.

8

0 I don't feel I am any worse than anybody else.
1 I am critical of myself for my weaknesses or mistakes.
2 I blame myself all the time for my faults.
3 I blame myself for everything bad that happens.

9

0 I don't have any thoughts of killing myself.
1 I have thoughts of killing myself, but I would not carry them out.
2 I would like to kill myself.
3 I would kill myself if I had the chance.

10

0 I don't cry any more than usual.
1 I cry more now than I used to.
2 I cry all the time now.
3 I used to be able to cry, but now I can't cry even though I want to.

11

0 I am no more irritated now than I ever am.
1 I get annoyed or irritated more easily than I used to.
2 I feel irritated all the time now.
3 I don't get irritated at all by the things that used to irritate me.

12

0 I have not lost interest in other people.
1 I am less interested in other people than I used to be.
2 I have lost most of my interest in other people.
3 I have lost all of my interest in other people.

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BECK DEPRESSION INVENTORY

13

0 I make decisions about as well as I ever could.
1 I put off making decisions more than I used to.
2 I have greater difficulty in making decisions than before.
3 I can't make decisions at all anymore.

14

0 I don't feel I look any worse than I used to.
1 I am worried that I am looking old or unattractive.
2 I feel that there are permanent changes in my appearance that make me look unattractive.
3 I believe that I look ugly.

15

0 I can work about as well as before.
1 It takes an extra effort to get started at doing something.
2 I have to push myself very hard to do anything.
3 I can't do any work at all.

16

0 I can sleep as well as usual.
1 I don't sleep as well as I used to.
2 I wake up 1-2 hours earlier than usual and find it hard to get back to sleep.
3 I wake up several hours earlier than I used to and cannot get back to sleep.

17

0 I don't get more tired than usual.
1 I get tired more easily than I used to.
2 I get tired from doing almost anything.
3 I am too tired to do anything.

18

0 My appetite is no worse than usual.
1 My appetite is not as good as it used to be.
2 My appetite is much worse now.
3 I have no appetite at all anymore.

19

0 I haven't lost much weight, if any, lately.
1 I have lost more than 5 pounds.
2 I have lost more than 10 pounds.
3 I have lost more than 15 pounds.

19a

I am purposely trying to lose weight by eating less.
1 Yes
2 No

20

0 I am no more worried about my health than usual.
1 I am worried about physical problems such as aches and pains; or upset stomach or constipation.
2 I am very worried about physical problems and it's hard to think of much else.
3 I am so worried about my physical problems that I cannot think about anything else.

21

0 I have not noticed any recent change in my interest in sex.
1 I am less interested in sex than I used to be.
2 I am much less interested in sex now.
3 I have lost interest in sex completely.

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HAMILTON ANXIETY SCALE

INFORMATION NOT OBTAINED ☐

For each of the items below, **CHECK ONE BOX** that best describes the patient.

1. **ANXIOUS MOOD:** Worries, anticipation of the worst, fearful anticipation, irritability

   ☐ 0 Not present
   ☐ 1 Mild
   ☐ 2 Moderate
   ☐ 3 Severe
   ☐ 4 Very severe

2. **TENSION**: Feelings of tension, fatigability, startle response, moved to tears easily, trembling, feeling of restlessness, inability to relax

   ☐ 0 Not present
   ☐ 1 Mild
   ☐ 2 Moderate
   ☐ 3 Severe
   ☐ 4 Very severe

3. **FEARS**: Of dark, of strangers, of being alone, of animals, of traffic, of crowds

   ☐ 0 Not present
   ☐ 1 Mild
   ☐ 2 Moderate
   ☐ 3 Severe
   ☐ 4 Very severe

4. **INSOMNIA**: Difficulty in falling asleep, broken sleep, unsatisfying sleep and fatigue on waking, dreams, nightmares, night terrors

   ☐ 0 Not present
   ☐ 1 Mild
   ☐ 2 Moderate
   ☐ 3 Severe
   ☐ 4 Very severe

5. **INTELLECTUAL (COGNITIVE)**: Difficulty in concentration, poor memory

   ☐ 0 Not present
   ☐ 1 Mild
   ☐ 2 Moderate
   ☐ 3 Severe
   ☐ 4 Very severe

6. **DEPRESSED MOOD**: Loss of interest, lack of pleasure in hobbies, depression, early waking, diurnal swing

   ☐ 0 Not present
   ☐ 1 Mild
   ☐ 2 Moderate
   ☐ 3 Severe
   ☐ 4 Very severe

7. **SOMATIC (MUSCULAR)**: Pains and aches, twitchings, stiffness, myoclonic jerks, grinding of teeth, unsteady voice, increased muscular tone

   ☐ 0 Not present
   ☐ 1 Mild
   ☐ 2 Moderate
   ☐ 3 Severe
   ☐ 4 Very severe

8. **SOMATIC (SENSORY)**: Tinnitus, blurring of vision, hot and cold flushes, feeling of weakness, pricking sensation

   ☐ 0 Not present
   ☐ 1 Mild
   ☐ 2 Moderate
   ☐ 3 Severe
   ☐ 4 Very severe

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HAMILTON ANXIETY SCALE

9. **CARDIOVASCULAR SYMPTOMS:** Tachycardia, palpitations, pain in chest, throbbing of vessels, fainting feelings, missing beat

- ☐ 0 Not present
- ☐ 1 Mild
- ☐ 2 Moderate
- ☐ 3 Severe
- ☐ 4 Very severe

10. **RESPIRATORY SYMPTOMS:** Pressure or constriction in chest, choking feelings, sighing, dyspnea

- ☐ 0 Not present
- ☐ 1 Mild
- ☐ 2 Moderate
- ☐ 3 Severe
- ☐ 4 Very severe

11. **GASTROINTESTINAL SYMPTOMS:** Difficulty in swallowing, wind, abdominal pain, burning sensations, abdominal fullness, nausea, vomiting, borborygmi, looseness of bowels, loss of weight, constipation

- ☐ 0 Not present
- ☐ 1 Mild
- ☐ 2 Moderate
- ☐ 3 Severe
- ☐ 4 Very severe

12. **GENITOURINARY SYMPTOMS:** Frequency of micturition, urgency of micturition, amenorrhea, menorrhagia, development of frigidity, premature ejaculation, loss of libido, impotence

- ☐ 0 Not present
- ☐ 1 Mild
- ☐ 2 Moderate
- ☐ 3 Severe
- ☐ 4 Very severe

13. **AUTONOMIC SYMPTOMS:** Dry mouth, flushing, pallor, tendency to sweat, giddiness, tension headache, raising of hair

- ☐ 0 Not present
- ☐ 1 Mild
- ☐ 2 Moderate
- ☐ 3 Severe
- ☐ 4 Very severe

14. **BEHAVIOR AT INTERVIEW:** Fidgeting, restlessness or pacing, tremor of hands, furrowed brow, strained face, sighing or rapid respiration, facial pallor, swallowing, belching, brisk tendon jerks, dilated pupils, exophthalmos

- ☐ 0 Not present
- ☐ 1 Mild
- ☐ 2 Moderate
- ☐ 3 Severe
- ☐ 4 Very severe

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COMMENTS : VISIT

NO COMMENTS ☐

Comments should address any clinical report form items that require further explanation. Repeating information from the clinical report form is discouraged.

Comment on all clinically significant lab values that are outside a clinically accepted reference range or clinically significant values that differ importantly from previous values.

If the patient is ending participation in the study at this visit, enter only comments that apply to this visit; then complete the Patient Summary and Study Summary Comments pages.

Print legibly and do not use abbreviations or symbols.

The information reported for this visit is accurate and complete.

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Signature MM DD YY

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PATIENT AND VISIT IDENTIFICATION

Patient initials _____ _____ _____
First Middle Last

Visit date _____/_____/_____
MM DD YY

VITAL SIGNS : BLOOD PRESSURE AND HEART RATE

INFORMATION NOT OBTAINED ☐

Position
SI = Sitting

Position	Blood Pressure (mm Hg) Systolic/Diastolic	Heart Rate (bpm)
SI	/	

VITAL SIGNS: TEMPERATURE

INFORMATION NOT OBTAINED ☐

Temperature ___ ___ ___ . ___

Unit of measure (F) Fahrenheit

Method (E) Ear

REMINDER

On the Pre-existing Conditions and Study Adverse Events pages, record new events that occurred since the previous visit and re-evaluate any on-going conditions or events.

On the Concomitant Medication pages, record new medications the patient has taken since the previous visit, any changes to ongoing medications, and a stop date for any medication the patient is no longer taking.

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Date Verified
Initials
Date Keyed
Date Received at Lilly
Reviewed
Inspected
Date

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B1Y-MC-HCJE

STUDY DRUG : DATES OF MISSED DOSES

NO MISSED DOSES ☐

Record the date for any day on which the patient missed a full or partial dose of study drug.

	Dates of Missed Doses		
	MM	DD	YY
0.			
1.			
2.			
3.			
4.			
5.			
6.			
7.			
8.			
9.			

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SIDE EFFECTS CHECKLIST

INFORMATION NOT OBTAINED ☐

Since your last visit, have you been bothered with or had any trouble with any of the items listed below? Check the box which best tells how much you were bothered.

	Not at all	Just a little	Pretty much	Very much	Don't know
1. Eating?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
2. Drinking?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
3. Dry mouth and lips?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
4. Wetness in mouth?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
5. Constipation?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
6. Diarrhea?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
7. Stomachaches?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
8. Muscle cramps?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
9. Being sick to your stomach?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
10. Wetting the bed?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
11. Urinating?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
12. Itchy or scratchy skin?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
13. Rashes?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
14. Cold or sniffles?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
15. Headache?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4

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SIDE EFFECTS CHECKLIST

	Not at all	Just a little	Pretty much	Very much	Don't know
16. Dizziness?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
17. Playing sports?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
18. Shakiness?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
19. Pronouncing words?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
20. Doing things with your hands?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
21. Sitting still?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
22. Tiredness?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
23. Feeling sleepy?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
24. Trouble sleeping?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
25. Bad dreams?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
26. Getting along with parents?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
27. Getting along with kids?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
28. Crying?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
29. Getting mad?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
30. Not being happy?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
31. Being sad?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
32. Paying attention?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4

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Clinical Report Form
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CHILDRENS DEPRESSION RATING SCALE - REVISED

INFORMATION NOT OBTAINED ☐

CHECK THE NUMERIC CODE which best describes the patient.

1. **SCHOOLWORK**:

☐ 1 Performance consistent with ability
☐ 2
☐ 3 Decrease in school performance
☐ 4
☐ 5 Major interference in most subjects
☐ 6
☐ 7 No motivation to perform

2. **CAPACITY TO HAVE FUN**

☐ 1 Interest and activities realistically appropriate for age, personality, and social environment. Shows no appreciable change with present illness.
☐ 2
☐ 3 Describes some activities realistically available several times a week but not on a daily basis. Shows interest but not enthusiasm.
☐ 4
☐ 5 Is easily bored. Complains of "nothing to do." Participates in structured activities with a "going through the motions" attitude. May express interest primarily in activities that are (realistically) unavailable on a daily or weekly basis.
☐ 6
☐ 7 Has no initiative to become involved in any activities. Primarily passive. Watches others play or watches TV but shows little interest. Requires coaxing and/or pushing to get involved in activity. Shows no enthusiasm or real interest. Has difficulty naming activities.

3. **SOCIAL WITHDRAWAL**

☐ 1 Enjoys friendships with peers at school and home
☐ 2
☐ 3 May not actively seek out friendships but waits for others to initiate a relationship or may occasionally reject opportunities to play without a describable alternative
☐ 4
☐ 5 Frequently avoids or refuses opportunities for desirable interaction with others and/or sets up situations where rejection is inevitable.
☐ 6
☐ 7 Does not currently relate to other children. States he or she has "no friends" or actively rejects new or former friends.

4. **SLEEP**

☐ 1 No (or occasional) difficulty. (Goes to sleep within 1/2 hour or less.)
☐ 2
☐ 3 Frequently has mild difficulty with sleep
☐ 4
☐ 5 Moderate difficulty with sleep nearly every night.

5. **APPETITE OR EATING PATTERNS**

☐ 1 No problems or change in eating pattern
☐ 2
☐ 3 Mild change from usual eating habits within onset of current behavioral problem
☐ 4
☐ 5 Is not hungry most of the time or has excessive food intake since onset of current behavioral problems or marked increase in appetite

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CHILDRENS DEPRESSION RATING SCALE - REVISED

CHECK THE NUMERIC CODE which best describes the patient.

6. **EXCESSIVE FATIGUE**

- ☐ 1 No unusual complaints of "feeling tired" during the day
- ☐ 2
- ☐ 3 Complaints of fatigue which seem somewhat excessive and not related to boredom
- ☐ 4
- ☐ 5 Daily complaints of feeling tired
- ☐ 6
- ☐ 7 Complains of feeling tired most of the day. May voluntarily take long naps without feeling refreshed. Interferes with play activities.

7. **PHYSICAL COMPLAINTS**:

- ☐ 1 Occasional complaints
- ☐ 2
- ☐ 3 Complaints appear mildly excessive
- ☐ 4
- ☐ 5 Complains daily. Some interference with the ability of the child to function
- ☐ 6
- ☐ 7 Preoccupied with aches and pains; interferes with play activities several times a week

8. **IRRITABILITY**

- ☐ 1 Rare
- ☐ 2 Occasional
- ☐ 3 Several times a week for short periods
- ☐ 4
- ☐ 5 Several times a week for longer periods
- ☐ 6
- ☐ 7 Constant

9. **GUILT**

- ☐ 1 Does not express any undue feeling of guilt. Appears appropriate to precipitating event.
- ☐ 2
- ☐ 3 Exaggerates guilt and/or shame out of proportion to the event described.
- ☐ 4
- ☐ 5 Feels guilty over things not under his or her control. Guilt is definitely pathological.
- ☐ 6
- ☐ 7 Severe delusions of guilt

10. **SELF-ESTEEM**

- ☐ 1 Describes self in primarily positive terms
- ☐ 2
- ☐ 3 Describes self with one important area where the child feels deficit
- ☐ 4
- ☐ 5 Describes self in preponderance of negative terms or gives bland answers to questions
- ☐ 6
- ☐ 7 Refers to self in derogatory terms. Reports that other children refer to him/her frequently by using derogatory nicknames and child puts self down

11. **DEPRESSED FEELINGS**

- ☐ 1 Occasional feelings of unhappiness which quickly disappear
- ☐ 2
- ☐ 3 Describes sustained periods of unhappiness which appear excessive for events described
- ☐ 4
- ☐ 5 Feels unhappy most of the time without a major precipitating cause
- ☐ 6
- ☐ 7 Feels unhappy all of the time. Accompanied by psychic pain (e.g., "I can't stand it").

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CHILDRENS DEPRESSION RATING SCALE - REVISED

CHECK THE NUMERIC CODE which best describes the patient.

12. **MORBID IDEATION**

- ☐ 1 None
- ☐ 2
- ☐ 3 Has some morbid thought, all of which relate to a reality event but seem excessive.
- ☐ 4
- ☐ 5 Preoccupied with morbid thoughts several times a week. Morbid thoughts extend beyond external reality
- ☐ 6
- ☐ 7 Preoccupied with death themes or morbid thoughts that are elaborate, extensive or bizarre on a daily basis

13. **SUICIDAL IDEATION**

- ☐ 1 Understands the word "suicide" but does not apply term to self
- ☐ 2 Sharp denial of suicidal thoughts
- ☐ 3 Has thoughts about suicide, usually when angry.
- ☐ 4
- ☐ 5 Has recurrent thoughts of suicide
- ☐ 6
- ☐ 7 Has made suicide attempt within the last month or is actively suicidal

14. **WEEPING**:

- ☐ 1 Normal for age.
- ☐ 2 Suggestive statements that child cries, or feels like crying, more frequently than peers.
- ☐ 3 Child cries slightly more than peers.
- ☐ 4
- ☐ 5 Cries or feels like crying frequently (several times a week). Admits to crying without knowing reason why.
- ☐ 6
- ☐ 7 Cries nearly every day.

15. **DEPRESSED AFFECT:**

- ☐ 1 Definitely not depressed. Facial expression and voice animated during interview.
- ☐ 2 Mild suppression of affect. Some loss of spontaneity.
- ☐ 3 Overall loss of spontaneity. Looks distinctly unhappy during parts of the interview. May still be able to smile when discussing non-threatening areas.
- ☐ 4
- ☐ 5 Moderate restriction of affect throughout most of interview. Has longer and frequent periods of looking distinctly unhappy.
- ☐ 6
- ☐ 7 Severe. Looks sad, withdrawn. Minimal verbal interaction throughout interview. Cries or may appear tearful.

16. **TEMPO OF SPEECH:**

- ☐ 1 Normal
- ☐ 2 Slow
- ☐ 3 Slow: delays interview.
- ☐ 4
- ☐ 5 Severe. Low; marked interference with interview.

17. **HYPOACTIVITY:**

- ☐ 1 None
- ☐ 2
- ☐ 3 Mild. Some body movements.
- ☐ 4
- ☐ 5 Moderate. Definite motor retardation.
- ☐ 6
- ☐ 7 Severe. Motionless throughout interview.

(DNDE)

Total of 1 - 17 _____

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CLINICAL GLOBAL IMPRESSION: EFFICACY INDEX

Using the worksheet below, enter the 2-digit efficacy index rating.

1. Efficacy index rating ___ ___

(DNDE)

EFFICACY INDEX WORKSHEET

Rate this item on the basis of DRUG EFFECT ONLY.

Select the terms that best describe the degrees of therapeutic effect and side effects and record the number from the box where the two items intersect in the blanks above.

THERAPEUTIC EFFECT	SIDE EFFECTS			
	None	Do not significantly interfere with patient's functioning	Significantly interferes with patient's functioning	Outweighs therapeutic effect
MARKED - Vast improvement. Complete or nearly complete remission of all symptoms.	**01**	**02**	**03**	**04**
MODERATE - Decided improvement. Partial remission of symptoms.	**05**	**06**	**07**	**08**
MINIMAL - Slight improvement which doesn't alter status of care of patient.	**09**	**10**	**11**	**12**
UNCHANGED OR WORSE	**13**	**14**	**15**	**16**
Not Assessed = **98**				

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CLINICAL GLOBAL IMPRESSION: SEVERITY

INFORMATION NOT OBTAINED ☐

Considering your total clinical experience with this particular population, how mentally ill is the patient at this time?

- ☐ 1 Normal, not at all ill
- ☐ 2 Borderline ill
- ☐ 3 Mildly ill
- ☐ 4 Moderately ill
- ☐ 5 Markedly ill
- ☐ 6 Severely ill
- ☐ 7 Among the most extremely ill patients

Evaluator's initials _____ _____ _____
First Middle Last

CLINICAL GLOBAL IMPRESSION: IMPROVEMENT

INFORMATION NOT OBTAINED ☐

Rate total improvement, whether or not in your judgement it is due entirely to drug treatment. Compared to the patient's condition at Visit 1, how much has he/she changed?

- ☐ 1 Very much improved
- ☐ 2 Much improved
- ☐ 3 Minimally improved
- ☐ 4 No change
- ☐ 5 Minimally worse
- ☐ 6 Much worse
- ☐ 7 Very much worse

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MONTGOMERY - ASBERG DEPRESSION RATING SCALE (MADRS)

INFORMATION NOT OBTAINED ☐

The rating should be based on a clinical interview moving from broadly phrased questions about symptoms to more detailed ones which allow a precise rating of severity. The rater must decide whether the rating lies on the defined scale steps (0, 2, 4, 6) or between them (1, 3, 5).

Check the box (number) that best characterizes the patient at this time

1. **APPARENT SADNESS**
   Representing despondency, gloom, and despair (more than just ordinary transient low spirits), reflected in speech, facial expression, and posture. Rate by depth and inability to brighten up.

   ☐ 0 No sadness.
   ☐ 1
   ☐ 2 Looks dispirited but does brighten up without difficulty.
   ☐ 3
   ☐ 4 Appears sad and unhappy most of the time.
   ☐ 5
   ☐ 6 Looks miserable all the time. Extremely despondent.

2. **REPORTED SADNESS**
   Represented by reports of depressed mood, regardless of whether it is reflected in appearance or not. Includes low spirits, despondency, or the feeling of being beyond help and without hope. Rate according to intensity, duration, and the extent to which the mood is reported to be influenced by events.

   ☐ 0 Occasional sadness in keeping with the circumstances.
   ☐ 1
   ☐ 2 Sad or low but brightens up without difficulty.
   ☐ 3
   ☐ 4 Pervasive feelings of sadness or gloominess. The mood is still influenced by external circumstances.
   ☐ 5
   ☐ 6 Continuous unvarying sadness, misery or despondency.

3. **INNER TENSION**
   Representing feelings of ill-defined discomfort, edginess, inner turmoil, mental tension mounting to either panic, dread, or anguish. Rate according to intensity, frequency, duration, and the extent of reassurance called for.

   ☐ 0 Placid. Only fleeting inner tension.
   ☐ 1
   ☐ 2 Occasional feelings of edginess and ill-defined discomfort.
   ☐ 3
   ☐ 4 Continuous feelings of inner tension or intermittent panic which the patient can only master with some difficulty.
   ☐ 5
   ☐ 6 Unrelenting dread or anguish. Overwhelming panic.

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MONTGOMERY - ASBERG DEPRESSION RATING SCALE (MADRS)

4. **REDUCED SLEEP**
Representing the experience of reduced duration or depth of sleep compared to the subject's own pattern when well.

- ☐ 0 Sleeps as usual.
- ☐ 1
- ☐ 2 Slight difficulty dropping off to sleep or slightly reduced, light or fitful sleep.
- ☐ 3
- ☐ 4 Sleep reduced or broken by at least two hours.
- ☐ 5
- ☐ 6 Less than two or three hours sleep.

5. **REDUCED APPETITE**
Representing the feeling of a loss of appetite compared with when well. Rate by loss of desire for food or the need to force oneself to eat.

- ☐ 0 Normal or increased appetite
- ☐ 1
- ☐ 2 Slightly reduced appetite.
- ☐ 3
- ☐ 4 No appetite. Food is tasteless.
- ☐ 5
- ☐ 6 Needs persuasion to eat at all.

6. **CONCENTRATION DIFFICULTIES**
Representing difficulties in collecting one's thoughts mounting to incapacitating lack of concentration.

- ☐ 0 No difficulties in concentrating.
- ☐ 1
- ☐ 2 Occasional difficulties in collecting one's thoughts.
- ☐ 3
- ☐ 4 Difficulties in concentrating and sustaining thought which reduces ability to read or hold a conversation.
- ☐ 5
- ☐ 6 Unable to read or converse without great difficulty.

7. **LASSITUDE**
Representing a difficulty getting started or slowness initiating and performing everyday activities.

- ☐ 0 Hardly any difficulty in getting started. No sluggishness.
- ☐ 1
- ☐ 2 Difficulties in starting activities
- ☐ 3
- ☐ 4 Difficulties in starting simple routine activities which are carried out with effort.
- ☐ 5
- ☐ 6 Complete lassitude. Unable to do anything without help.

8. **INABILITY TO FEEL**
Representing the subjective experience of reduced interest in the surroundings, or activities that normally give pleasure. The ability to react with adequate emotion to circumstances or people is reduced.

- ☐ 0 Normal interest in the surroundings and other people.
- ☐ 1
- ☐ 2 Reduced ability to enjoy usual interests.
- ☐ 3
- ☐ 4 Loss of interest in the surroundings. Loss of feelings for friends and acquaintances.
- ☐ 5
- ☐ 6 The experience of being emotionally paralyzed, inability to feel anger, grief, or pleasure and a complete or even painful failure to feel for close relatives and friends.

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MONTGOMERY - ASBERG DEPRESSION RATING SCALE (MADRS)

9. **PESSIMISTIC THOUGHTS**
Representing thoughts of guilt, inferiority, self-reproach, sinfulness, remorse, and ruin

- ☐ 0 No pessimistic thoughts.
- ☐ 1
- ☐ 2 Fluctuating ideas of failure, self-reproach, or self-depreciation.
- ☐ 3
- ☐ 4 Persistent self-accusations, or definite but still rational ideas of guilt, or sin. Increasingly pessimistic about the future.
- ☐ 5
- ☐ 6 Delusions of ruin, remorse, or unredeemable sin. Self-accusations which are absurd and unshakable.

10. **SUICIDAL THOUGHTS**
Representing the feeling that life is not worth living, that a natural death would be welcome, suicidal thoughts, and preparations for suicide. Suicidal attempts should not in themselves influence the rating.

- ☐ 0 Enjoys life or takes it as it comes.
- ☐ 1
- ☐ 2 Weary of life. Only fleeting suicidal thoughts.
- ☐ 3
- ☐ 4 Probably better off dead. Suicidal thoughts are common, and suicide is considered as a possible solution, but without specific plans or intention.
- ☐ 5
- ☐ 6 Explicit plans for suicide when there is an opportunity. Active preparations for suicide.

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COMMENTS : VISIT

NO COMMENTS ☐

Comments should address any clinical report form items that require further explanation. Repeating information from the clinical report form is discouraged.

Comment on all clinically significant lab values that are outside a clinically accepted reference range or clinically significant values that differ importantly from previous values.

If the patient is ending participation in the study at this visit, enter only comments that apply to this visit; then complete the Patient Summary and Study Summary Comments pages.

Print legibly and do not use abbreviations or symbols.

The information reported for this visit is accurate and complete.

_____ _____/_____/_____
Signature MM DD YY

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PATIENT AND VISIT IDENTIFICATION

Patient initials _____ _____ _____
First Middle Last

Visit date _____/_____/_____
MM DD YY

VITAL SIGNS : BLOOD PRESSURE AND HEART RATE

INFORMATION NOT OBTAINED ☐

Position
SI = Sitting

Position	Blood Pressure (mm Hg) Systolic/Diastolic	Heart Rate (bpm)
SI	/	

VITAL SIGNS: TEMPERATURE

INFORMATION NOT OBTAINED ☐

Temperature ___ ___ ___ . ___

Unit of measure (F) Fahrenheit

Method (E) Ear

REMINDER

On the Pre-existing Conditions and Study Adverse Events pages, record new events that occurred since the previous visit and re-evaluate any on-going conditions or events.

On the Concomitant Medication pages, record new medications the patient has taken since the previous visit, any changes to ongoing medications, and a stop date for any medication the patient is no longer taking.

Initials
Date Verified
Initials
Date Keyed
Date Received at Lilly
Reviewed
Inspected
Date

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STUDY DRUG : DATES OF MISSED DOSES

NO MISSED DOSES ☐

Record the date for any day on which the patient missed a full or partial dose of study drug.

	Dates of Missed Doses		
	MM	DD	YY
0.			
1.			
2.			
3.			
4.			
5.			
6.			
7.			
8.			
9.			

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Clinical Report Form
Fluoxetine Versus Placebo in Childhood/Adolescent Depression
B1Y-MC-HCJE

SIDE EFFECTS CHECKLIST

INFORMATION NOT OBTAINED ☐

Since your last visit, have you been bothered with or had any trouble with any of the items listed below? Check the box which best tells how much you were bothered.

	Not at all	Just a little	Pretty much	Very much	Don't know
1. Eating?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
2. Drinking?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
3. Dry mouth and lips?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
4. Wetness in mouth?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
5. Constipation?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
6. Diarrhea?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
7. Stomachaches?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
8. Muscle cramps?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
9. Being sick to your stomach?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
10. Wetting the bed?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
11. Urinating?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
12. Itchy or scratchy skin?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
13. Rashes?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
14. Cold or sniffles?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
15. Headache?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4

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Clinical Report Form
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B1Y-MC-HCJE

SIDE EFFECTS CHECKLIST

	Not at all	Just a little	Pretty much	Very much	Don't know
16. Dizziness?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
17. Playing sports?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
18. Shakiness?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
19. Pronouncing words?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
20. Doing things with your hands?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
21. Sitting still?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
22. Tiredness?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
23. Feeling sleepy?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
24. Trouble sleeping?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
25. Bad dreams?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
26. Getting along with parents?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
27. Getting along with kids?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
28. Crying?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
29. Getting mad?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
30. Not being happy?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
31. Being sad?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
32. Paying attention?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4

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CHILDRENS DEPRESSION RATING SCALE - REVISED

INFORMATION NOT OBTAINED ☐

CHECK THE NUMERIC CODE which best describes the patient.

1. **SCHOOLWORK**:

☐ 1 Performance consistent with ability
☐ 2
☐ 3 Decrease in school performance
☐ 4
☐ 5 Major interference in most subjects
☐ 6
☐ 7 No motivation to perform

2. **CAPACITY TO HAVE FUN**

☐ 1 Interest and activities realistically appropriate for age, personality, and social environment. Shows no appreciable change with present illness.
☐ 2
☐ 3 Describes some activities realistically available several times a week but not on a daily basis. Shows interest but not enthusiasm.
☐ 4
☐ 5 Is easily bored. Complains of "nothing to do." Participates in structured activities with a "going through the motions" attitude. May express interest primarily in activities that are (realistically) unavailable on a daily or weekly basis.
☐ 6
☐ 7 Has no initiative to become involved in any activities. Primarily passive. Watches others play or watches TV but shows little interest. Requires coaxing and/or pushing to get involved in activity. Shows no enthusiasm or real interest. Has difficulty naming activities.

3. **SOCIAL WITHDRAWAL**

☐ 1 Enjoys friendships with peers at school and home
☐ 2
☐ 3 May not actively seek out friendships but waits for others to initiate a relationship or may occasionally reject opportunities to play without a describable alternative
☐ 4
☐ 5 Frequently avoids or refuses opportunities for desirable interaction with others and/or sets up situations where rejection is inevitable.
☐ 6
☐ 7 Does not currently relate to other children. States he or she has "no friends" or actively rejects new or former friends.

4. **SLEEP**

☐ 1 No (or occasional) difficulty. (Goes to sleep within 1/2 hour or less.)
☐ 2
☐ 3 Frequently has mild difficulty with sleep
☐ 4
☐ 5 Moderate difficulty with sleep nearly every night.

5. **APPETITE OR EATING PATTERNS**

☐ 1 No problems or change in eating pattern
☐ 2
☐ 3 Mild change from usual eating habits within onset of current behavioral problem
☐ 4
☐ 5 Is not hungry most of the time or has excessive food intake since onset of current behavioral problems or marked increase in appetite

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B1Y-MC-HCJE

CHILDRENS DEPRESSION RATING SCALE - REVISED

CHECK THE NUMERIC CODE which best describes the patient.

6. **EXCESSIVE FATIGUE**

- ☐ 1 No unusual complaints of "feeling tired" during the day
- ☐ 2
- ☐ 3 Complaints of fatigue which seem somewhat excessive and not related to boredom
- ☐ 4
- ☐ 5 Daily complaints of feeling tired
- ☐ 6
- ☐ 7 Complains of feeling tired most of the day. May voluntarily take long naps without feeling refreshed. Interferes with play activities.

7. **PHYSICAL COMPLAINTS**:

- ☐ 1 Occasional complaints
- ☐ 2
- ☐ 3 Complaints appear mildly excessive
- ☐ 4
- ☐ 5 Complains daily. Some interference with the ability of the child to function
- ☐ 6
- ☐ 7 Preoccupied with aches and pains; interferes with play activities several times a week

8. **IRRITABILITY**

- ☐ 1 Rare
- ☐ 2 Occasional
- ☐ 3 Several times a week for short periods
- ☐ 4
- ☐ 5 Several times a week for longer periods
- ☐ 6
- ☐ 7 Constant

9. **GUILT**

- ☐ 1 Does not express any undue feeling of guilt. Appears appropriate to precipitating event.
- ☐ 2
- ☐ 3 Exaggerates guilt and/or shame out of proportion to the event described.
- ☐ 4
- ☐ 5 Feels guilty over things not under his or her control. Guilt is definitely pathological.
- ☐ 6
- ☐ 7 Severe delusions of guilt

10. **SELF-ESTEEM**

- ☐ 1 Describes self in primarily positive terms
- ☐ 2
- ☐ 3 Describes self with one important area where the child feels deficit
- ☐ 4
- ☐ 5 Describes self in preponderance of negative terms or gives bland answers to questions
- ☐ 6
- ☐ 7 Refers to self in derogatory terms. Reports that other children refer to him/her frequently by using derogatory nicknames and child puts self down

11. **DEPRESSED FEELINGS**

- ☐ 1 Occasional feelings of unhappiness which quickly disappear
- ☐ 2
- ☐ 3 Describes sustained periods of unhappiness which appear excessive for events described
- ☐ 4
- ☐ 5 Feels unhappy most of the time without a major precipitating cause
- ☐ 6
- ☐ 7 Feels unhappy all of the time. Accompanied by psychic pain (e.g., "I can't stand it").

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B1Y-MC-HCJE

CHILDRENS DEPRESSION RATING SCALE - REVISED

CHECK THE NUMERIC CODE which best describes the patient.

12. **MORBID IDEATION**

- ☐ 1 None
- ☐ 2
- ☐ 3 Has some morbid thought, all of which relate to a reality event but seem excessive.
- ☐ 4
- ☐ 5 Preoccupied with morbid thoughts several times a week. Morbid thoughts extend beyond external reality
- ☐ 6
- ☐ 7 Preoccupied with death themes or morbid thoughts that are elaborate, extensive or bizarre on a daily basis

13. **SUICIDAL IDEATION**

- ☐ 1 Understands the word "suicide" but does not apply term to self
- ☐ 2 Sharp denial of suicidal thoughts
- ☐ 3 Has thoughts about suicide, usually when angry.
- ☐ 4
- ☐ 5 Has recurrent thoughts of suicide
- ☐ 6
- ☐ 7 Has made suicide attempt within the last month or is actively suicidal

14. **WEEPING**:

- ☐ 1 Normal for age.
- ☐ 2 Suggestive statements that child cries, or feels like crying, more frequently than peers.
- ☐ 3 Child cries slightly more than peers.
- ☐ 4
- ☐ 5 Cries or feels like crying frequently (several times a week). Admits to crying without knowing reason why.
- ☐ 6
- ☐ 7 Cries nearly every day.

15. **DEPRESSED AFFECT:**

- ☐ 1 Definitely not depressed. Facial expression and voice animated during interview.
- ☐ 2 Mild suppression of affect. Some loss of spontaneity.
- ☐ 3 Overall loss of spontaneity. Looks distinctly unhappy during parts of the interview. May still be able to smile when discussing non-threatening areas.
- ☐ 4
- ☐ 5 Moderate restriction of affect throughout most of interview. Has longer and frequent periods of looking distinctly unhappy.
- ☐ 6
- ☐ 7 Severe. Looks sad, withdrawn. Minimal verbal interaction throughout interview. Cries or may appear tearful.

16. **TEMPO OF SPEECH:**

- ☐ 1 Normal
- ☐ 2 Slow
- ☐ 3 Slow: delays interview.
- ☐ 4
- ☐ 5 Severe. Low; marked interference with interview.

17. **HYPOACTIVITY:**

- ☐ 1 None
- ☐ 2
- ☐ 3 Mild. Some body movements.
- ☐ 4
- ☐ 5 Moderate. Definite motor retardation.
- ☐ 6
- ☐ 7 Severe. Motionless throughout interview.

(DNDE)

Total of 1 - 17 _____

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CLINICAL GLOBAL IMPRESSION: EFFICACY INDEX

Using the worksheet below, enter the 2-digit efficacy index rating.

1. Efficacy index rating ___ ___

(DNDE)

EFFICACY INDEX WORKSHEET

Rate this item on the basis of DRUG EFFECT ONLY.

Select the terms that best describe the degrees of therapeutic effect and side effects and record the number from the box where the two items intersect in the blanks above.

THERAPEUTIC EFFECT	SIDE EFFECTS			
	None	Do not significantly interfere with patient's functioning	Significantly interferes with patient's functioning	Outweighs therapeutic effect
MARKED - Vast improvement. Complete or nearly complete remission of all symptoms.	**01**	**02**	**03**	**04**
MODERATE - Decided improvement. Partial remission of symptoms.	**05**	**06**	**07**	**08**
MINIMAL - Slight improvement which doesn't alter status of care of patient.	**09**	**10**	**11**	**12**
UNCHANGED OR WORSE	**13**	**14**	**15**	**16**
Not Assessed = **98**				

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CLINICAL GLOBAL IMPRESSION: SEVERITY

INFORMATION NOT OBTAINED ☐

Considering your total clinical experience with this particular population, how mentally ill is the patient at this time?

- ☐ 1 Normal, not at all ill
- ☐ 2 Borderline ill
- ☐ 3 Mildly ill
- ☐ 4 Moderately ill
- ☐ 5 Markedly ill
- ☐ 6 Severely ill
- ☐ 7 Among the most extremely ill patients

Evaluator's initials _____ _____ _____
First Middle Last

CLINICAL GLOBAL IMPRESSION: IMPROVEMENT

INFORMATION NOT OBTAINED ☐

Rate total improvement, whether or not in your judgement it is due entirely to drug treatment. Compared to the patient's condition at Visit 1, how much has he/she changed?

- ☐ 1 Very much improved
- ☐ 2 Much improved
- ☐ 3 Minimally improved
- ☐ 4 No change
- ☐ 5 Minimally worse
- ☐ 6 Much worse
- ☐ 7 Very much worse

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MONTGOMERY - ASBERG DEPRESSION RATING SCALE (MADRS)

INFORMATION NOT OBTAINED ☐

The rating should be based on a clinical interview moving from broadly phrased questions about symptoms to more detailed ones which allow a precise rating of severity. The rater must decide whether the rating lies on the defined scale steps (0, 2, 4, 6) or between them (1, 3, 5).

Check the box (number) that best characterizes the patient at this time

1. **APPARENT SADNESS**
   Representing despondency, gloom, and despair (more than just ordinary transient low spirits), reflected in speech, facial expression, and posture. Rate by depth and inability to brighten up.

   ☐ 0 No sadness.
   ☐ 1
   ☐ 2 Looks dispirited but does brighten up without difficulty.
   ☐ 3
   ☐ 4 Appears sad and unhappy most of the time.
   ☐ 5
   ☐ 6 Looks miserable all the time. Extremely despondent.

2. **REPORTED SADNESS**
   Represented by reports of depressed mood, regardless of whether it is reflected in appearance or not. Includes low spirits, despondency, or the feeling of being beyond help and without hope. Rate according to intensity, duration, and the extent to which the mood is reported to be influenced by events.

   ☐ 0 Occasional sadness in keeping with the circumstances.
   ☐ 1
   ☐ 2 Sad or low but brightens up without difficulty.
   ☐ 3
   ☐ 4 Pervasive feelings of sadness or gloominess. The mood is still influenced by external circumstances.
   ☐ 5
   ☐ 6 Continuous unvarying sadness, misery or despondency.

3. **INNER TENSION**
   Representing feelings of ill-defined discomfort, edginess, inner turmoil, mental tension mounting to either panic, dread, or anguish. Rate according to intensity, frequency, duration, and the extent of reassurance called for.

   ☐ 0 Placid. Only fleeting inner tension.
   ☐ 1
   ☐ 2 Occasional feelings of edginess and ill-defined discomfort.
   ☐ 3
   ☐ 4 Continuous feelings of inner tension or intermittent panic which the patient can only master with some difficulty.
   ☐ 5
   ☐ 6 Unrelenting dread or anguish. Overwhelming panic.

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MONTGOMERY - ASBERG DEPRESSION RATING SCALE (MADRS)

4. **REDUCED SLEEP**
Representing the experience of reduced duration or depth of sleep compared to the subject's own pattern when well.

- ☐ 0 Sleeps as usual.
- ☐ 1
- ☐ 2 Slight difficulty dropping off to sleep or slightly reduced, light or fitful sleep.
- ☐ 3
- ☐ 4 Sleep reduced or broken by at least two hours.
- ☐ 5
- ☐ 6 Less than two or three hours sleep.

5. **REDUCED APPETITE**
Representing the feeling of a loss of appetite compared with when well. Rate by loss of desire for food or the need to force oneself to eat.

- ☐ 0 Normal or increased appetite
- ☐ 1
- ☐ 2 Slightly reduced appetite.
- ☐ 3
- ☐ 4 No appetite. Food is tasteless.
- ☐ 5
- ☐ 6 Needs persuasion to eat at all.

6. **CONCENTRATION DIFFICULTIES**
Representing difficulties in collecting one's thoughts mounting to incapacitating lack of concentration.

- ☐ 0 No difficulties in concentrating.
- ☐ 1
- ☐ 2 Occasional difficulties in collecting one's thoughts.
- ☐ 3
- ☐ 4 Difficulties in concentrating and sustaining thought which reduces ability to read or hold a conversation.
- ☐ 5
- ☐ 6 Unable to read or converse without great difficulty.

7. **LASSITUDE**
Representing a difficulty getting started or slowness initiating and performing everyday activities.

- ☐ 0 Hardly any difficulty in getting started. No sluggishness.
- ☐ 1
- ☐ 2 Difficulties in starting activities
- ☐ 3
- ☐ 4 Difficulties in starting simple routine activities which are carried out with effort.
- ☐ 5
- ☐ 6 Complete lassitude. Unable to do anything without help.

8. **INABILITY TO FEEL**
Representing the subjective experience of reduced interest in the surroundings, or activities that normally give pleasure. The ability to react with adequate emotion to circumstances or people is reduced.

- ☐ 0 Normal interest in the surroundings and other people.
- ☐ 1
- ☐ 2 Reduced ability to enjoy usual interests.
- ☐ 3
- ☐ 4 Loss of interest in the surroundings. Loss of feelings for friends and acquaintances.
- ☐ 5
- ☐ 6 The experience of being emotionally paralyzed, inability to feel anger, grief, or pleasure and a complete or even painful failure to feel for close relatives and friends.

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B1Y-MC-HCJE

MONTGOMERY - ASBERG DEPRESSION RATING SCALE (MADRS)

9. **PESSIMISTIC THOUGHTS**
Representing thoughts of guilt, inferiority, self-reproach, sinfulness, remorse, and ruin

- ☐ 0 No pessimistic thoughts.
- ☐ 1
- ☐ 2 Fluctuating ideas of failure, self-reproach, or self-depreciation.
- ☐ 3
- ☐ 4 Persistent self-accusations, or definite but still rational ideas of guilt, or sin. Increasingly pessimistic about the future.
- ☐ 5
- ☐ 6 Delusions of ruin, remorse, or unredeemable sin. Self-accusations which are absurd and unshakable.

10. **SUICIDAL THOUGHTS**
Representing the feeling that life is not worth living, that a natural death would be welcome, suicidal thoughts, and preparations for suicide. Suicidal attempts should not in themselves influence the rating.

- ☐ 0 Enjoys life or takes it as it comes.
- ☐ 1
- ☐ 2 Weary of life. Only fleeting suicidal thoughts.
- ☐ 3
- ☐ 4 Probably better off dead. Suicidal thoughts are common, and suicide is considered as a possible solution, but without specific plans or intention.
- ☐ 5
- ☐ 6 Explicit plans for suicide when there is an opportunity. Active preparations for suicide.

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B1Y-MC-HCJE

COMMENTS : VISIT

NO COMMENTS ☐

Comments should address any clinical report form items that require further explanation. Repeating information from the clinical report form is discouraged.

Comment on all clinically significant lab values that are outside a clinically accepted reference range or clinically significant values that differ importantly from previous values.

If the patient is ending participation in the study at this visit, enter only comments that apply to this visit; then complete the Patient Summary and Study Summary Comments pages.

Print legibly and do not use abbreviations or symbols.

The information reported for this visit is accurate and complete.

_____ _____/_____/_____
Signature MM DD YY

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Fluoxetine Versus Placebo in Childhood/Adolescent Depression
B1Y-MC-HCJE

CONCOMITANT MEDICATION Visit ___
Page 1 of 1

CONCOMITANT MEDICATION

NO CONCOMITANT MEDICATIONS ☐

Enter all medications, other than study drug, the patient is taking at **entry** and **during the study**.

Indication for Use (IFU)
Enter code from patient's Pre-existing Conditions and Study Adverse Events page. E__ = Pre-Existing Condition or Event (eg, E01) or X1 = Primary study condition X2 = Prophylaxis or non-therapeutic use

Initials
Date Verified
Initials
Date Keyed
Date Received at Lilly
Reviewed
Inspected
Date

	Brand or Trade Name (Use generic if brand or trade name unknown)	Dose	Unit	Fre-quency	Route	Start Date MM DD YY	Stop Date MM DD YY	IFU
0.								
1.								
2.								
3.								
4.								
5.								
6.								
7.								
8.								
9.								
10.								
11.								

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B1Y-MC-HCJE

CONCOMITANT MEDICATION Visit ____
Page 1 a of 1

CONCOMITANT MEDICATION

Continue listing all medications, other than study drug, the patient is taking at **entry** and **during the study**.

Indication for Use (IFU)
Enter code from patient's Pre-existing Conditions and Study Adverse Events page. E__ = Pre-Existing Condition or Event (eg, E01) or X1 = Primary study condition X2 = Prophylaxis or non-therapeutic use

	Brand or Trade Name (Use generic if brand or trade name unknown)	Dose	Unit	Fre-quency	Route	Start Date MM	Start Date DD	Start Date YY	Stop Date MM	Stop Date DD	Stop Date YY	IFU
12.												
13.												
14.												
15.												
16.												
17.												
18.												
19.												
20.												
21.												
22.												
23.												

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B1Y-MC-HCJE

CONCOMITANT MEDICATION Visit ____
Page 1 __ of 1

CONCOMITANT MEDICATION

Continue listing all medications, other than study drug, the patient is taking **during the study**.

Indication for Use (IFU)
Enter code from patient's Pre-existing Conditions and Study Adverse Events page. E__ = Pre-Existing Condition or Event (eg, E01) or X1 = Primary study condition X2 = Prophylaxis or non-therapeutic use

Brand or Trade Name (Use generic if brand or trade name unknown)	Dose	Unit	Fre-quency	Route	Start Date MM	Start Date DD	Start Date YY	Stop Date MM	Stop Date DD	Stop Date YY	IFU

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WORKSHEET (DNDE)
B1Y-MC-HCJE

Date: _____/_____/_____

ENTRY PROCEDURES AND CRITERIA FOR ENROLLMENT

Inclusion Criteria: The answers for Items 1-9 must be YES to qualify for study.

Yes	No	
☐	☐	1. Male and female outpatients.
☐	☐	2. Children (aged 8 to < 13 years) and adolescents (aged 13 to < 18 years) at the time of entry into the study.
☐	☐	3. A primary psychiatric diagnosis of nonpsychotic major depressive disorder (single or recurrent) as defined by the DSM-IV criteria.
☐	☐	4. Depressive symptoms of at least moderate severity as defined by a CDRS-R score of >40 and a CGI-Severity rating of moderate or greater.
☐	☐	5. Able to swallow whole medication without difficulty.
☐	☐	6. No clinically significant laboratory findings in hematology, chemistry, and urinalysis at study entry based on the judgment of the investigator.
☐	☐	7. ECG without clinically significant abnormalities. The clinical significance will be determined by the investigator and the physician interpreting the ECG.
☐	☐	8. Educational level and degree of understanding so that the patients and parents can communicate intelligibly with the investigator and study coordinator. Normal intelligence based on the judgment of the investigator.
☐	☐	9. Patients and parents judged to be reliable who agree to keep appointments for clinic visits and all tests and examinations required by the protocol.

Exclusion Criteria: The answers for Items 10-31 must be NO to qualify for study.

Yes	No	
☐	☐	10. Investigators and their immediate families are not permitted to be subjects or patients in Lilly-sponsored trials. Immediate family is defined as the investigator's spouse, parent, child, grandparent, or grandchild.
☐	☐	11. Persons who have previously completed or withdrawn from this study.
☐	☐	12. Females who are pregnant or breastfeeding or who are sexually active and are not using medically accepted means of contraception (IUD, birth control pills, barrier devices, or implanted progesterone rods stabilized for at least 3 months) .
☐	☐	13. Serious illness (including cardiac, hepatic, renal, respiratory, endocrinologic, neurologic, or hematologic disease) that is not stabilized so that hospitalized for treatment of that illness is likely within the next 2 months.
☐	☐	14. Patients with abnormal thyroid function.
☐	☐	15. Seizure disorder with a seizure occurring within the past 6 months, except for febrile seizures.

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WORKSHEET (DNDE)
B1Y-MC-HCJE

Exclusion Criteria: The answers for Items 10-31 must be NO to qualify for study.

Yes	No		
☐	☐	16.	Diagnosis of any of the following DSM-IV-defined disorders: bipolar I or II disorder, sleep-wake disorder, psychotic depression (lifetime), anorexia (lifetime), bulimia (lifetime), borderline personality disorder or substance abuse disorder (within the past 6 months).
☐	☐	17.	Patients with one or more first-degree relatives with bipolar I disorder.
☐	☐	18.	Organic brain diseases.
☐	☐	19.	Persons whose illness has previously failed to respond to adequate antidepressant treatment (at least 8 weeks treatment within the typical maximum adult therapeutic range).
☐	☐	20.	Serious suicidal risk.
☐	☐	21.	History of severe allergies, multiple adverse drug reactions, or known allergy to the study drug.
☐	☐	22.	Receipt of an investigational drug within 30 days prior to study entry.
☐	☐	23.	Receipt of any behavior-altering, centrally-acting, or excluded medication within 7 days prior to study entry.
☐	☐	24.	Documented hypersensitivity to fluoxetine.
☐	☐	25.	Prior adequate treatment with fluoxetine (12 weeks on a fixed dose of 20 mg or greater).
☐	☐	26.	Receipt of fluoxetine within 3 months prior to study entry. ***Note:*** Patients who have detectable levels of fluoxetine, norfluoxetine, or any other antidepressant in their initial blood draw will be discontinued.
☐	☐	27.	Regular use of other psychotropic or centrally-acting drugs, including lithium and the psychostimulants (i.e. drugs normally prescribed for depression, mania, anxiety, insomnia, attention deficit disorder, or psychosis) within 2 weeks prior to study entry that would need to be continued during the study. (The list of excluded medications is located in Appendix HCJE.3.)
☐	☐	28.	Use of neuroleptics during the 2 weeks prior to study entry or of depot neuroleptics within the 6 weeks prior to study entry.
☐	☐	29.	Use of a monoamine oxidase inhibitor (MAOI) within 2 weeks (14 days) prior to study entry or potential need to use an MAOI within 6 weeks of discontinuation of treatment.
☐	☐	30.	Use of tryptophan, St. John's Wort, or melatonin within 2 weeks prior to study entry.
☐	☐	31.	Potential need for the continuation or initiation of other treatments for depression, including cognitive behavioral therapy and behavioral therapy, except for supportive therapy on an individual or family basis.

DS1771
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February 12, 1998
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PATIENT AND VISIT IDENTIFICATION

Patient initials _____ _____ _____
First Middle Last

Visit date _____/_____/_____
MM DD YY

INFORMED CONSENT : PATIENT (CHILD)

Date patient (child) signed the consent document _____/_____/_____
MM DD YY

INFORMED CONSENT : PARENT/GUARDIAN

Date parent/guardian signed the consent document _____/_____/_____
MM DD YY

ID301, IC30101, IC30101

Visit 1

REMINDER

Record the patient's pre-existing conditions on the Pre-existing Conditions and Study Adverse Events pages.

Record all medications the patient is currently taking on the Concomitant Medication pages.

All other visits

REMINDER

On the Pre-existing Conditions and Study Adverse Events pages, record new events that occurred since the previous visit and re-evaluate any on-going conditions or events.

On the Concomitant Medication pages, record new medications the patient has taken since the previous visit, any changes to ongoing medications, and a stop date for any medication the patient is no longer taking.

PATIENT SUMMARY Visit ____
Page 1 of 1

PATIENT SUMMARY

Patient Initials _____ _____ _____
First Middle Last

CHECK ONE PRIMARY REASON FOR ENDING PARTICIPATION IN THE STUDY

☐ 1 Protocol completed

☐ 3 Adverse event E __ __
E__ Code

☐ 4 Death* E __ __ →
E__ Code

If # **4** is checked, enter date of death.

Date of Death _____/_____/_____
MM DD YY

☐ 5 Satisfactory response, patient perception
☐ 6 Satisfactory response, physician perception
☐ 7 Satisfactory response, patient and physician perception

☐ 8 Lack of efficacy, patient perception
☐ 9 Lack of efficacy, physician perception
☐ 10 Lack of efficacy, patient and physician perception

☐ 11 Unable to contact patient (lost to follow-up)
☐ 12 Patient moved
☐ 13 Personal conflict or other patient/parent decision _____
Specify

☐ 22 Physician decision _____
Specify

☐ 14 Protocol entry criteria not met _____ (Specify number from entry criteria checklist)
Specify

☐ 15 Protocol interim criteria not met

☐ 459 Relapse as defined by protocol

☐ 17 Clinical relapse
☐ 26 Nonresponder
☐ 59 Noncompliance

☐ 243 Protocol violation

☐ 18 Sponsor decision (study or patient discontinued by the Sponsor)

* Contact Lilly immediately in event of death. Obtain a copy of the autopsy report (if autopsy performed) or hospital discharge summary. Forward to Lilly as soon as possible. Explain circumstances of the death on the Study Summary Comments page.

SS31602

DEMOGRAPHICS

Date of birth _____/_____/__ __ __ __
MM DD Y Y Y Y

Sex ☐ F Female ☐ M Male

Origin ☐ CA Caucasian (European, Mediterranean, Middle Eastern)

☐ AF African Descent (Black)

☐ EA East/Southeast Asian (Burmese, Chinese, Japanese, Korean, Mongolian, Vietnamese)

☐ AS Western Asian (Pakistani, Indian Sub-continent)

☐ HP Hispanic (Mexican-American, Mexico, Central and South America)

☐ O Other (Mixed-racial parentage, American Indian, Eskimo)

DM30201

SIGNIFICANT HISTORICAL DIAGNOSES

NO SIGNIFICANT HISTORICAL DIAGNOSES ☐

List each clinically significant (at the discretion of the investigator) historical diagnosis that is **NO LONGER PRESENT** (no longer clinically active). If exact date is unknown, enter month and year. A year MUST be entered.

	Historical Diagnosis	Date Recovered MM	DD	YY
0.				
1.				
2.				
3.				
4.				
5.				
6.				
7.				
8.				
9.				
10.				
11.				
12.				
13.				
14.				
15.				
16.				
17.				

HX30101

PSYCHIATRIC HISTORY : MAJOR DEPRESSION

INFORMATION NOT OBTAINED ☐

Use whole numbers only.

1. What was the age of the patient at the first MDD episode? ____ years
2. What is the duration of the current MDD episode? ____ weeks
3. Has the patient had one or more previous episodes of MDD? ☐ 1 Yes ☐ 2 No

4. What was the number of previous episodes of MDD? ____ episodes
5. What was the duration of the last MDD episode? ____ weeks
6. What is the time interval between the start of the current MDD episode and remission of the last MDD episode? ____ weeks
7. If there have been 3 or more previous MDD episodes, was there a seasonal pattern for those episodes? ☐ 1 Yes ☐ 2 No ☐ 96 Not Applicable

DX318

FAMILY HISTORY : PSYCHIATRIC

INFORMATION NOT OBTAINED ☐

1. Is there a history of <depression> in the following *biological* family members:

Mother	☐ 1 Yes	☐ 2 No	☐ 97 Unknown	
Father	☐ 1 Yes	☐ 2 No	☐ 97 Unknown	
Siblings (brother, sister)	☐ 1 Yes	☐ 2 No	☐ 97 Unknown	☐ 96 Not Applicable

If yes, enter number of siblings with <depression> _____

2. Is there a history of <manic depression (bipolar)> in the following *biological* family members:

Mother	☐ 1 Yes	☐ 2 No	☐ 97 Unknown	
Father	☐ 1 Yes	☐ 2 No	☐ 97 Unknown	
Siblings (brother, sister)	☐ 1 Yes	☐ 2 No	☐ 97 Unknown	☐ 96 Not Applicable

If yes, enter number of siblings with <manic depression (bipolar) disorder> _____

3. Is there a history of <anxiety disorders (i.e., OCD, panic disorder, generalized)> in the following *biological* family members:

Mother	☐ 1 Yes	☐ 2 No	☐ 97 Unknown	
Father	☐ 1 Yes	☐ 2 No	☐ 97 Unknown	
Siblings (brother, sister)	☐ 1 Yes	☐ 2 No	☐ 97 Unknown	☐ 96 Not Applicable

If yes, enter number of siblings with <anxiety disorder> _____

version QS671

K-SADS : AFFECTIVE DISORDERS

INFORMATION NOT OBTAINED ☐

Check the appropriate boxes.

Depressive Disorders - Current	☐ 1 Yes	☐ 2 No
Depressive Disorders - Past	☐ 1 Yes	☐ 2 No
Mania - Current	☐ 1 Yes	☐ 2 No
. Mania -Past	☐ 1 Yes	☐ 2 No

Evaluator's initials _____ _____ _____
First Middle Last

New module #1

GLOBAL ASSESSMENT OF FUNCTIONING SCALE (GAF SCALE)

INFORMATION NOT OBTAINED ☐

Enter the number (between 1 and 90) that best represents the patient's:

1. **Current** level of functioning _____
2. **Highest** level of functioning in *past year* _____

Level of Functioning Definitions	
90 – 81	Absent or minimal symptoms, good functioning in all areas, interested and involved in a wide range of activities, socially effective, generally satisfied with life, no more than everyday problems or concerns.
80 – 71	If symptoms are present, they are transient and expectable reactions to psychosocial stressors; no more than slight impairment in social, occupational, or school functioning.
70 – 61	Some mild symptoms OR some difficulty in social, occupational, or school functioning, but generally functioning pretty well, has some meaningful interpersonal relationships.
60 – 51	Moderate symptoms OR any moderate difficulty in social, occupational, or school functioning.
50 – 41	Serious symptoms OR any serious impairment in social, occupational, or school functioning.
40 – 31	Some impairment in reality testing or communication OR major impairment in several areas, such as work or school, family relations, judgment, thinking, or mood.
30 – 21	Behavior is considered influenced by delusions or hallucinations OR serious impairment in communications or judgment OR inability to function in almost all areas.
20 – 11	Some danger of hurting self or other OR occasionally fails to maintain minimal personal hygiene OR gross impairment in communication.
10 – 1	Persistent danger of severely hurting self or others OR persistent inability to maintain minimum personal hygiene OR serious suicidal act with clear expectation of death.

DX309

PHYSICIAN CHECK LIST

INFORMATION NOT OBTAINED ☐

Answer the following questioning concerning the circumstances in the patient's life.

1. Attending school ☐1 Yes ☐2 No
2. Change to special classes/school ☐1 Yes ☐2 No
3. School difficulties ☐1 Yes ☐2 No
4. Other therapy ☐1 Yes ☐2 No
5. Vacation ☐1 Yes ☐2 No
6. Illness ☐1 Yes ☐2 No
7. Sexual activity ☐1 Yes ☐2 No
8. Change in family mental status ☐1 Yes ☐2 No
9. Change in family status (divorce, death, grandparent illentss, etc) ☐1 Yes ☐2 No
10. Family move ☐1 Yes ☐2 No
11. Death of friend or close family member ☐1 Yes ☐2 No
12. Sexual abuse ☐1 Yes ☐2 No
13. Physical abuse ☐1 Yes ☐2 No
14. Mental abuse ☐1 Yes ☐2 No
15. Other _____
    Specify

QSXXX _GL 2/12/98 (Core)

PSYCHIATRIC DIAGNOSTIC SURVEY

INFORMATION NOT OBTAINED ☐

DISORDER	LIFETIME				CURRENT (within past 1 month)		
	Absent	Sub-Threshold	Threshold	Unknown	Absent	Sub-Threshold	Threshold
A. Bipolar I Disorder							
1. Single manic episode	☐ 1	☐ 2	☐ 3	☐ 97	☐ 4	☐ 8	☐ 9
2. Recurrent manic episode	☐ 1	☐ 2	☐ 3	☐ 97	☐ 4	☐ 8	☐ 9
3. Single depressed episode	☐ 1	☐ 2	☐ 3	☐ 97	☐ 4	☐ 8	☐ 9
4. Recurrent depressed episode	☐ 1	☐ 2	☐ 3	☐ 97	☐ 4	☐ 8	☐ 9
5. Mixed episode	☐ 1	☐ 2	☐ 3	☐ 97	☐ 4	☐ 8	☐ 9
B. Bipolar II Disorder	☐ 1	☐ 2	☐ 3	☐ 97	☐ 4	☐ 8	☐ 9

C. Substance Use Disorder	Absent	Abuse	Dependence	Absent	Present
1. Alcohol	☐ 1	☐ 6	☐ 7	☐ 4	☐ 5
2. Sedative/hypnotic/ Anxiolytic	☐ 1	☐ 6	☐ 7	☐ 4	☐ 5
3. Cannabis	☐ 1	☐ 6	☐ 7	☐ 4	☐ 5
4. Stimulants (nonprescribed)	☐ 1	☐ 6	☐ 7	☐ 4	☐ 5
5. Opioid	☐ 1	☐ 6	☐ 7	☐ 4	☐ 5
6. Cocaine	☐ 1	☐ 6	☐ 7	☐ 4	☐ 5
7. Hallucinogen/PCP	☐ 1	☐ 6	☐ 7	☐ 4	☐ 5
8. Other	☐ 1	☐ 6	☐ 7	☐ 4	☐ 5

DX390

PSYCHIATRIC DIAGNOSTIC SURVEY

DISORDER	LIFETIME				CURRENT (within past 1 month)		
	Absent	Sub-Threshold	Threshold	Unknown	Absent	Sub-Threshold	Threshold
D. Attention Deficit Disorder	☐ 1	☐ 2	☐ 3	☐ 97	☐ 4	☐ 8	☐ 9
E. Oppositional Disorder	☐ 1	☐ 2	☐ 3	☐ 97	☐ 4	☐ 8	☐ 9
F. Conduct Disorder	☐ 1	☐ 2	☐ 3	☐ 97	☐ 4	☐ 8	☐ 9
G. Major Depressive Disorder	☐ 1	☐ 2	☐ 3	☐ 97	☐ 4	☐ 8	☐ 9
H. Mania	☐ 1	☐ 2	☐ 3	☐ 97	☐ 4	☐ 8	☐ 9
I. Dysthymic Disorder	☐ 1	☐ 2	☐ 3	☐ 97	☐ 4	☐ 8	☐ 9
J. Separation Anxiety Disorder	☐ 1	☐ 2	☐ 3	☐ 97	☐ 4	☐ 8	☐ 9
K. Overanxious Disorder	☐ 1	☐ 2	☐ 3	☐ 97	☐ 4	☐ 8	☐ 9
L. Simple Phobia	☐ 1	☐ 2	☐ 3	☐ 97	☐ 4	☐ 8	☐ 9
M. Obsessive Compulsive Disorder	☐ 1	☐ 2	☐ 3	☐ 97	☐ 4	☐ 8	☐ 9
N. Compulsions	☐ 1	☐ 2	☐ 3	☐ 97	☐ 4	☐ 8	☐ 9
O. Avoidant Disorder	☐ 1	☐ 2	☐ 3	☐ 97	☐ 4	☐ 8	☐ 9
P. Post-Traumatic Stress Disorder	☐ 1	☐ 2	☐ 3	☐ 97	☐ 4	☐ 8	☐ 9
Q. Anorexia Nervosa	☐ 1	☐ 2	☐ 3	☐ 97	☐ 4	☐ 8	☐ 9
R. Bulimia	☐ 1	☐ 2	☐ 3	☐ 97	☐ 4	☐ 8	☐ 9
S. Somatization	☐ 1	☐ 2	☐ 3	☐ 97	☐ 4	☐ 8	☐ 9
T. Enuresis	☐ 1	☐ 2	☐ 3	☐ 97	☐ 4	☐ 8	☐ 9
U. Encopresis	☐ 1	☐ 2	☐ 3	☐ 97	☐ 4	☐ 8	☐ 9
V. Gender Identity	☐ 1	☐ 2	☐ 3	☐ 97	☐ 4	☐ 8	☐ 9
W. Psychotic Symptoms	☐ 1	☐ 2	☐ 3	☐ 97	☐ 4	☐ 8	☐ 9

DX390

HABITS : SMOKING

Enter the average current daily use
0 = None
L = Less than one *(eg, cigar or pipe smoker who smokes only 1 or 2x a week)*
1, 2, 3, etc = Whole numbers ONLY

Number of cigarettes _____

Number of cigars _____

Number of pipesful _____

Enter the number of years (past or current) patient has smoked. If patient has never smoked, enter 0. _____ years

HABITS : SMOKELESS TOBACCO

INFORMATION NOT OBTAINED ☐

Does the patient currently use smokeless tobacco? ☐ 1 Yes ☐ 2 No

HABITS : ALCOHOL

INFORMATION NOT OBTAINED ☐

Enter the average current weekly consumption
0 = None
L = Less than one
1, 2, 3, etc = Whole numbers ONLY

Number of beers or wine coolers/spritzers _____

Number of glasses of wine _____

Number of drinks containing distilled spirits _____

HB31202, HB334, HB30902

HABITS : CAFFEINE

INFORMATION NOT OBTAINED ☐

Enter the average current daily consumption	
0	= None
L	= Less than one
1, 2, 3, etc	= Whole numbers ONLY

Number of cups of *caffeinated* coffee _____

Number of cups of *caffeinated* tea _____

Number of *caffeinated* colas _____

PROCEDURE : PHYSICAL EXAM

NOTE: A physical exam must be performed for entry into the study.

Was a physical exam performed? ☐1 Yes ☐2 No

WEIGHT

INFORMATION NOT OBTAINED ☐

Measure with shoes off. Round up or down to the nearest whole pound.

Weight ___ ___ ___ (lb)

HEIGHT

INFORMATION NOT OBTAINED ☐

Measure with shoes off. Round up or down to the nearest whole inch.

Height ___ ___ ___ (in)

HB31101, GM30102, PE30301, PE30201

VITAL SIGNS : BLOOD PRESSURE AND HEART RATE

INFORMATION NOT OBTAINED ☐

Position
SI = Sitting

Position	Blood Pressure (mm Hg) Systolic/Diastolic	Heart Rate (bpm)
SI	/	

VITAL SIGNS: TEMPERATURE

INFORMATION NOT OBTAINED ☐

Temperature ___ ___ ___ . ___

Unit of measure (F) Fahrenheit

Method (E) Ear

MENSTRUAL CYCLE

INFORMATION NOT OBTAINED ☐

1. Does the patient menstruate? ☐ 1 Yes ☐ 2 No ☐ 96 Not Applicable (males)

2. First day of last menstrual cycle _____/_____/_____ (MM DD YY)

3. Are cycles regular? ☐ 1 Yes ☐ 2 No

4. Number of days in cycle _____ (days)

VS301, VS303, MN306

CONTRACEPTION

INFORMATION NOT OBTAINED ☐

Contraception is ensured through:

- ☐13 Prepubertal status
- ☐9 Strict abstinence
- ☐7 Use of condom and spermicidal foam
- ☐4 Use of oral contraceptives
- ☐6 Use of contraceptive implant
- ☐5 Use of intra-uterine device (IUD)
- ☐11 Depo-Provera©
- ☐10 Solitary partner who is vasectomized
- ☐8 Homosexual lifestyle
- ☐1 Surgical sterilization
- ☐2 Radiation-induced sterilization
- ☐96 Not applicable (applies to male patients)

Note: If a female patient is not using one of the above methods of contraception, she cannot be entered into this phase of the study.

ELECTROCARDIOGRAM

INFORMATION NOT OBTAINED ☐

Electrocardiogram date _____/_____/_____
MM DD YY

Electrocardiogram result ☐12 Acceptable ☐13 Not Acceptable

Insert the ECG (original) in the envelope provided.

EM373, EG308

PREVIOUS DRUG THERAPY

NO PREVIOUS DRUG THERAPY ☐

Enter any previous medications and non-drug therapies (eg, electroconvulsive therapy, photo-therapy) for the treatment of any neuropsychiatric or behavior conditions that were discontinued within the last year.

Stop Code
59 = Noncompliance
79 = To enter this trial
52 = Inadequate response
3 = Adverse event
33 = Adequate response
99 = Other

	Brand or Trade Name (Enter generic if trade unknown)	Dose	Unit	Fre-quency	Route	Start Date MM DD YY	Stop Date MM DD YY	Stop Code
0.								
1.								
2.								
3.								
4.								
5.								
6.								
7.								
8.								
9.								
10.								

PT304

STUDY DRUG : DATES OF MISSED DOSES

NO MISSED DOSES ☐

Record the date for any day on which the patient missed a full or partial dose of study drug.

	Dates of Missed Doses		
	MM	DD	YY
0.			
1.			
2.			
3.			
4.			
5.			
6.			
7.			
8.			
9.			

NOTE: If the patient has missed 3 or more consecutive days of medication, the patient must be discontinued from the study.

NOTE: Visit 1 - 15 only

SD442

SIDE EFFECTS CHECKLIST

INFORMATION NOT OBTAINED ☐

{Since your last visit}, have you been bothered with or had any trouble with any of the items listed below? Check the box which best tells how much you were bothered.

	Not at all	Just a little	Pretty much	Very much	Don't know
1. Eating?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
2. Drinking?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
3. Dry mouth and lips?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
4. Wetness in mouth?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
5. Constipation?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
6. Diarrhea?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
7. Stomachaches?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
8. Muscle cramps?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
9. Being sick to your stomach?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
10. Wetting the bed?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
11. Urinating?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
12. Itchy or scratchy skin?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
13. Rashes?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
14. Cold or sniffles?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
15. Headache?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4

QSXXX GL_2/12/98 (CORE)

SIDE EFFECTS CHECKLIST

	Not at all	Just a little	Pretty much	Very much	Don't know
16. Dizziness?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
17. Playing sports?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
18. Shakiness?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
19. Pronouncing words?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
20. Doing things with your hands?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
21. Sitting still?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
22. Tiredness?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
23. Feeling sleepy?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
24. Trouble sleeping?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
25. Bad dreams?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
26. Getting along with parents?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
27. Getting along with kids?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
28. Crying?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
29. Getting mad?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
30. Not being happy?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
31. Being sad?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
32. Paying attention?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4

QSXXX GL_2/12/98 (CORE)

CLINICAL GLOBAL IMPRESSION: EFFICACY INDEX

Using the worksheet below, enter the 2-digit efficacy index rating.

1. Efficacy index rating ___ ___

(DNDE)

EFFICACY INDEX WORKSHEET

Rate this item on the basis of DRUG EFFECT ONLY.

Select the terms that best describe the degrees of therapeutic effect and side effects and record the number from the box where the two items intersect in the blanks above.

THERAPEUTIC EFFECT	SIDE EFFECTS			
	None	Do not significantly interfere with patient's functioning	Significantly interferes with patient's functioning	Outweighs therapeutic effect
MARKED - Vast improvement. Complete or nearly complete remission of all symptoms.	**01**	**02**	**03**	**04**
MODERATE - Decided improvement. Partial remission of symptoms.	**05**	**06**	**07**	**08**
MINIMAL - Slight improvement which doesn't alter status of care of patient.	**09**	**10**	**11**	**12**
UNCHANGED OR WORSE	**13**	**14**	**15**	**16**
Not Assessed = **98**				

Evaluator's initials _____ _____ _____
First Middle Last

EMXXX_GL 2/12/98 (CORE)

CHILDRENS DEPRESSION RATING SCALE - REVISED

INFORMATION NOT OBTAINED ☐

CHECK THE NUMERIC CODE which best describes the patient.

1. **SCHOOLWORK**:

☐ 1 Performance consistent with ability
☐ 2
☐ 3 Decrease in school performance
☐ 4
☐ 5 Major interference in most subjects
☐ 6
☐ 7 No motivation to perform

2. **CAPACITY TO HAVE FUN**

☐ 1 Interest and activities realistically appropriate for age, personality, and social environment. Shows no appreciable change with present illness.
☐ 2
☐ 3 Describes some activities realistically available several times a week but not on a daily basis. Shows interest but not enthusiasm.
☐ 4
☐ 5 Is easily bored. Complains of "nothing to do." Participates in structured activities with a "going through the motions" attitude. May express interest primarily in activities that are (realistically) unavailable on a daily or weekly basis.
☐ 6
☐ 7 Has no initiative to become involved in any activities. Primarily passive. Watches others play or watches TV but shows little interest. Requires coaxing and/or pushing to get involved in activity. Shows no enthusiasm or real interest. Has difficulty naming activities.

3. **SOCIAL WITHDRAWAL**

☐ 1 Enjoys friendships with peers at school and home
☐ 2
☐ 3 May not actively seek out friendships but waits for others to initiate a relationship or may occasionally reject opportunities to play without a describable alternative
☐ 4
☐ 5 Frequently avoids or refuses opportunities for desirable interaction with others and/or sets up situations where rejection is inevitable.
☐ 6
☐ 7 Does not currently relate to other children. States he or she has "no friends" or actively rejects new or former friends.

4. **SLEEP**

☐ 1 No (or occasional) difficulty. (Goes to sleep within 1/2 hour or less.)
☐ 2
☐ 3 Frequently has mild difficulty with sleep
☐ 4
☐ 5 Moderate difficulty with sleep nearly every night.

5. **APPETITE OR EATING PATTERNS**

☐ 1 No problems or change in eating pattern
☐ 2
☐ 3 Mild change from usual eating habits within onset of current behavioral problem
☐ 4
☐ 5 Is not hungry most of the time or has excessive food intake since onset of current behavioral problems or marked increase in appetite

QSXXX_GL 2/12/98 (CNS)

CHILDRENS DEPRESSION RATING SCALE - REVISED

CHECK THE NUMERIC CODE which best describes the patient.

6. **EXCESSIVE FATIGUE**

- ☐ 1 No unusual complaints of "feeling tired" during the day
- ☐ 2
- ☐ 3 Complaints of fatigue which seem somewhat excessive and not related to boredom
- ☐ 4
- ☐ 5 Daily complaints of feeling tired
- ☐ 6
- ☐ 7 Complains of feeling tired most of the day. May voluntarily take long naps without feeling refreshed. Interferes with play activities.

7. **PHYSICAL COMPLAINTS**:

- ☐ 1 Occasional complaints
- ☐ 2
- ☐ 3 Complaints appear mildly excessive
- ☐ 4
- ☐ 5 Complains daily. Some interference with the ability of the child to function
- ☐ 6
- ☐ 7 Preoccupied with aches and pains; interferes with play activities several times a week

8. **IRRITABILITY**

- ☐ 1 Rare
- ☐ 2 Occasional
- ☐ 3 Several times a week for short periods
- ☐ 4
- ☐ 5 Several times a week for longer periods
- ☐ 6
- ☐ 7 Constant

9. **GUILT**

- ☐ 1 Does not express any undue feeling of guilt. Appears appropriate to precipitating event.
- ☐ 2
- ☐ 3 Exaggerates guilt and/or shame out of proportion to the event described.
- ☐ 4
- ☐ 5 Feels guilty over things not under his or her control. Guilt is definitely pathological.
- ☐ 6
- ☐ 7 Severe delusions of guilt

10. **SELF-ESTEEM**

- ☐ 1 Describes self in primarily positive terms
- ☐ 2
- ☐ 3 Describes self with one important area where the child feels deficit
- ☐ 4
- ☐ 5 Describes self in preponderance of negative terms or gives bland answers to questions
- ☐ 6
- ☐ 7 Refers to self in derogatory terms. Reports that other children refer to him/her frequently by using derogatory nicknames and child puts self down

11. **DEPRESSED FEELINGS**

- ☐ 1 Occasional feelings of unhappiness which quickly disappear
- ☐ 2
- ☐ 3 Describes sustained periods of unhappiness which appear excessive for events described
- ☐ 4
- ☐ 5 Feels unhappy most of the time without a major precipitating cause
- ☐ 6
- ☐ 7 Feels unhappy all of the time. Accompanied by psychic pain (e.g., "I can't stand it").

QSXXX_GL 2/12/98 (CNS)

CHILDRENS DEPRESSION RATING SCALE - REVISED

CHECK THE NUMERIC CODE which best describes the patient.

12. **MORBID IDEATION**

- ☐ 1 None
- ☐ 2
- ☐ 3 Has some morbid thought, all of which relate to a reality event but seem excessive.
- ☐ 4
- ☐ 5 Preoccupied with morbid thoughts several times a week. Morbid thoughts extend beyond external reality
- ☐ 6
- ☐ 7 Preoccupied with death themes or morbid thoughts that are elaborate, extensive or bizarre on a daily basis

13. **SUICIDAL IDEATION**

- ☐ 1 Understands the word "suicide" but does not apply term to self
- ☐ 2 Sharp denial of suicidal thoughts
- ☐ 3 Has thoughts about suicide, usually when angry.
- ☐ 4
- ☐ 5 Has recurrent thoughts of suicide
- ☐ 6
- ☐ 7 Has made suicide attempt within the last month or is actively suicidal

14. **WEEPING**:

- ☐ 1 Normal for age.
- ☐ 2 Suggestive statements that child cries, or feels like crying, more frequently than peers.
- ☐ 3 Child cries slightly more than peers.
- ☐ 4
- ☐ 5 Cries or feels like crying frequently (several times a week). Admits to crying without knowing reason why.
- ☐ 6
- ☐ 7 Cries nearly every day.

15. **DEPRESSED AFFECT:**

- ☐ 1 Definitely not depressed. Facial expression and voice animated during interview.
- ☐ 2 Mild suppression of affect. Some loss of spontaneity.
- ☐ 3 Overall loss of spontaneity. Looks distinctly unhappy during parts of the interview. May still be able to smile when discussing non-threatening areas.
- ☐ 4
- ☐ 5 Moderate restriction of affect throughout most of interview. Has longer and frequent periods of looking distinctly unhappy.
- ☐ 6
- ☐ 7 Severe. Looks sad, withdrawn. Minimal verbal interaction throughout interview. Cries or may appear tearful.

16. **TEMPO OF SPEECH:**

- ☐ 1 Normal
- ☐ 2 Slow
- ☐ 3 Slow: delays interview.
- ☐ 4
- ☐ 5 Severe. Low; marked interference with interview.

17. **HYPOACTIVITY:**

- ☐ 1 None
- ☐ 2
- ☐ 3 Mild. Some body movements.
- ☐ 4
- ☐ 5 Moderate. Definite motor retardation.
- ☐ 6
- ☐ 7 Severe. Motionless throughout interview.

(DNDE)

Total of 1 - 17 _____

Evaluator's initials _____ _____ _____
First Middle Last

QSXXX_GL 2/12/98 (CNS)

CLINICAL GLOBAL IMPRESSION: SEVERITY

INFORMATION NOT OBTAINED ☐

Considering your total clinical experience with this particular population, how mentally ill is the patient at this time?

- ☐ 1 Normal, not at all ill
- ☐ 2 Borderline ill
- ☐ 3 Mildly ill
- ☐ 4 Moderately ill
- ☐ 5 Markedly ill
- ☐ 6 Severely ill
- ☐ 7 Among the most extremely ill patients

Evaluator's initials _____ _____ _____
First Middle Last

CLINICAL GLOBAL IMPRESSION: IMPROVEMENT

INFORMATION NOT OBTAINED ☐

Rate total improvement, whether or not in your judgement it is due entirely to drug treatment. Compared to the patient's condition at Visit 1, how much has he/she changed?

- ☐ 1 Very much improved
- ☐ 2 Much improved
- ☐ 3 Minimally improved
- ☐ 4 No change
- ☐ 5 Minimally worse
- ☐ 6 Much worse
- ☐ 7 Very much worse

Evaluator's initials _____ _____ _____
First Middle Last

new module #7, new module #8

MONTGOMERY - ASBERG DEPRESSION RATING SCALE (MADRS)

INFORMATION NOT OBTAINED ☐

The rating should be based on a clinical interview moving from broadly phrased questions about symptoms to more detailed ones which allow a precise rating of severity. The rater must decide whether the rating lies on the defined scale steps (0, 2, 4, 6) or between them (1, 3, 5).

Check the box (number) that best characterizes the patient at this time

1. **APPARENT SADNESS**
   Representing despondency, gloom, and despair (more than just ordinary transient low spirits), reflected in speech, facial expression, and posture. Rate by depth and inability to brighten up.

   ☐ 0 No sadness.
   ☐ 1
   ☐ 2 Looks dispirited but does brighten up without difficulty.
   ☐ 3
   ☐ 4 Appears sad and unhappy most of the time.
   ☐ 5
   ☐ 6 Looks miserable all the time. Extremely despondent.

2. **REPORTED SADNESS**
   Represented by reports of depressed mood, regardless of whether it is reflected in appearance or not. Includes low spirits, despondency, or the feeling of being beyond help and without hope. Rate according to intensity, duration, and the extent to which the mood is reported to be influenced by events.

   ☐ 0 Occasional sadness in keeping with the circumstances.
   ☐ 1
   ☐ 2 Sad or low but brightens up without difficulty.
   ☐ 3
   ☐ 4 Pervasive feelings of sadness or gloominess. The mood is still influenced by external circumstances.
   ☐ 5
   ☐ 6 Continuous unvarying sadness, misery or despondency.

3. **INNER TENSION**
   Representing feelings of ill-defined discomfort, edginess, inner turmoil, mental tension mounting to either panic, dread, or anguish. Rate according to intensity, frequency, duration, and the extent of reassurance called for.

   ☐ 0 Placid. Only fleeting inner tension.
   ☐ 1
   ☐ 2 Occasional feelings of edginess and ill-defined discomfort.
   ☐ 3
   ☐ 4 Continuous feelings of inner tension or intermittent panic which the patient can only master with some difficulty.
   ☐ 5
   ☐ 6 Unrelenting dread or anguish. Overwhelming panic.

EM310

MONTGOMERY - ASBERG DEPRESSION RATING SCALE (MADRS)

4. **REDUCED SLEEP**
Representing the experience of reduced duration or depth of sleep compared to the subject's own pattern when well.

- ☐ 0 Sleeps as usual.
- ☐ 1
- ☐ 2 Slight difficulty dropping off to sleep or slightly reduced, light or fitful sleep.
- ☐ 3
- ☐ 4 Sleep reduced or broken by at least two hours.
- ☐ 5
- ☐ 6 Less than two or three hours sleep.

5. **REDUCED APPETITE**
Representing the feeling of a loss of appetite compared with when well. Rate by loss of desire for food or the need to force oneself to eat.

- ☐ 0 Normal or increased appetite
- ☐ 1
- ☐ 2 Slightly reduced appetite.
- ☐ 3
- ☐ 4 No appetite. Food is tasteless.
- ☐ 5
- ☐ 6 Needs persuasion to eat at all.

6. **CONCENTRATION DIFFICULTIES**
Representing difficulties in collecting one's thoughts mounting to incapacitating lack of concentration.

- ☐ 0 No difficulties in concentrating.
- ☐ 1
- ☐ 2 Occasional difficulties in collecting one's thoughts.
- ☐ 3
- ☐ 4 Difficulties in concentrating and sustaining thought which reduces ability to read or hold a conversation.
- ☐ 5
- ☐ 6 Unable to read or converse without great difficulty.

7. **LASSITUDE**
Representing a difficulty getting started or slowness initiating and performing everyday activities.

- ☐ 0 Hardly any difficulty in getting started. No sluggishness.
- ☐ 1
- ☐ 2 Difficulties in starting activities
- ☐ 3
- ☐ 4 Difficulties in starting simple routine activities which are carried out with effort.
- ☐ 5
- ☐ 6 Complete lassitude. Unable to do anything without help.

8. **INABILITY TO FEEL**
Representing the subjective experience of reduced interest in the surroundings, or activities that normally give pleasure. The ability to react with adequate emotion to circumstances or people is reduced.

- ☐ 0 Normal interest in the surroundings and other people.
- ☐ 1
- ☐ 2 Reduced ability to enjoy usual interests.
- ☐ 3
- ☐ 4 Loss of interest in the surroundings. Loss of feelings for friends and acquaintances.
- ☐ 5
- ☐ 6 The experience of being emotionally paralyzed, inability to feel anger, grief, or pleasure and a complete or even painful failure to feel for close relatives and friends.

EM310

MONTGOMERY - ASBERG DEPRESSION RATING SCALE (MADRS)

9. **PESSIMISTIC THOUGHTS**
Representing thoughts of guilt, inferiority, self-reproach, sinfulness, remorse, and ruin

- ☐ 0 No pessimistic thoughts.
- ☐ 1
- ☐ 2 Fluctuating ideas of failure, self-reproach, or self-depreciation.
- ☐ 3
- ☐ 4 Persistent self-accusations, or definite but still rational ideas of guilt, or sin. Increasingly pessimistic about the future.
- ☐ 5
- ☐ 6 Delusions of ruin, remorse, or unredeemable sin. Self-accusations which are absurd and unshakable.

10. **SUICIDAL THOUGHTS**
Representing the feeling that life is not worth living, that a natural death would be welcome, suicidal thoughts, and preparations for suicide. Suicidal attempts should not in themselves influence the rating.

- ☐ 0 Enjoys life or takes it as it comes.
- ☐ 1
- ☐ 2 Weary of life. Only fleeting suicidal thoughts.
- ☐ 3
- ☐ 4 Probably better off dead. Suicidal thoughts are common, and suicide is considered as a possible solution, but without specific plans or intention.
- ☐ 5
- ☐ 6 Explicit plans for suicide when there is an opportunity. Active preparations for suicide.

Evaluator's initials _____ _____ _____
First Middle Last

EM310

CHILDREN'S DEPRESSION INDEX (CDI)

NOTE: Only complete if patient was 8 to 12 years old at Visit 1. If patient was not 8 to 12 years old, check the Information Not Obtained box.

INFORMATION NOT OBTAINED ☐

This lists the feelings and ideas in groups. From each group of three sentences, pick one sentence that describes you **best** for the past two weeks. After you pick a sentence from the first group, go on to the next group. There is no right answer or wrong answer. Just pick the sentence that best describes the way you have been recently. Put an "X" in the box next to your answer.
Remember: pick out the sentences that describe you best **in the past two weeks**.

Item 1

- ☐ 0 I am sad once in a while.
- ☐ 1 I am sad many times.
- ☐ 2 I am sad all the time.

Item 2

- ☐ 2 Nothing will ever work out for me.
- ☐ 1 I am not sure if things will work out for me.
- ☐ 0 Things will work out for me O.K.

Item 3

- ☐ 0 I do most things O.K.
- ☐ 1 I do many things wrong.
- ☐ 2 I do everything wrong.

Item 4

- ☐ 0 I have fun in many things.
- ☐ 1 I have fun in some things.
- ☐ 2 Nothing is fun at all.

Item 5

- ☐ 2 I am bad all the time.
- ☐ 1 I am bad many times.
- ☐ 0 I am bad once in a while.

Item 6

- ☐ 0 I think about bad things happening to me once in a while.
- ☐ 1 I worry that bad things will happen to me.
- ☐ 2 I am sure that terrible things will happen to me.

Item 7

- ☐ 2 I hate myself.
- ☐ 1 I do not like myself.
- ☐ 0 I like myself.

Item 8

- ☐ 2 All bad things are my fault.
- ☐ 1 Many bad things are my fault.
- ☐ 0 Bad things are not usually my fault.

Item 9

- ☐ 0 I do not think about killing myself.
- ☐ 1 I think about killing myself but I would not do it.
- ☐ 2 I want to kill myself.

Item 10

- ☐ 2 I feel like crying every day.
- ☐ 1 I feel like crying many days.
- ☐ 0 I feel like crying once in a while.

Item 11

- ☐ 2 Things bother me all the time.
- ☐ 1 Things bother me many times.
- ☐ 0 Things bother me once in a while.

Item 12

- ☐ 0 I like being with people.
- ☐ 1 I do not like being with people many times.
- ☐ 2 I do not want to be with people at all.

QSXXX_GL 2/12/98 (CNS)

CHILDREN'S DEPRESSION INDEX (CDI)

Item 13

- ☐ 2 I cannot make up my mind about things.
- ☐ 1 It is hard to make up my mind about things.
- ☐ 0 I make up my mind about things easily.

Item 14

- ☐ 0 I look O.K.
- ☐ 1 There are some bad things about my looks.
- ☐ 2 I look ugly.

Item 15

- ☐ 2 I have to push myself all the time to do my schoolwork.
- ☐ 1 I have to push myself many times to do my schoolwork.
- ☐ 0 Doing schoolwork is not a big problem.

Item 16

- ☐ 2 I have trouble sleeping every night.
- ☐ 1 I have trouble sleeping many nights.
- ☐ 0 I sleep pretty well.

Item 17

- ☐ 0 I am tired once in a while.
- ☐ 1 I am tired many days.
- ☐ 2 I am tired all the time.

Item 18

- ☐ 2 Most days I do not feel like eating.
- ☐ 1 Many days I do not feel like eating.
- ☐ 0 I eat pretty well.

Item 19

- ☐ 0 I do not worry about aches and pains.
- ☐ 1 I worry about aches and pains many times.
- ☐ 2 I worry about aches and pains all the time.

Item 20

- ☐ 0 I do not feel alone.
- ☐ 1 I feel alone many times.
- ☐ 2 I feel alone all the time.

Item 21

- ☐ 2 I never have fun at school.
- ☐ 1 I have fun at school only once in a while.
- ☐ 0 I have fun at school many times.

Item 22

- ☐ 0 I have plenty of friends.
- ☐ 1 I have some friends but I wish I had more.
- ☐ 2 I do not have any friends.

Item 23

- ☐ 0 My schoolwork is alright.
- ☐ 1 My schoolwork is not as good as before.
- ☐ 2 I do very badly in subjects I used to be good in.

Item 24

- ☐ 2 I can never be as good as other kids.
- ☐ 1 I can be as good as other kids if I want to.
- ☐ 0 I am just as good as other kids.

QSXXX_GL 2/12/98 (CNS)

CHILDREN'S DEPRESSION INDEX (CDI)

Item 25

☐ 2 Nobody really loves me.
☐ 1 I am not sure if anybody loves me.
☐ 0 I am sure that somebody loves me.

Item 26

☐ 0 I usually do what I am told.
☐ 1 I do not do what I am told most times.
☐ 2 I never do what I am told.

Item 27

☐ 0 I get along with people.
☐ 1 I get into fights many times.
☐ 2 I get into fights all the time.

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QSXXX_GL 2/12/98 (CNS)

BECK DEPRESSION INVENTORY

NOTE: Only complete if patient was 13 to 17 years old at Visit 1. If patient was not 13 to 17 years old, check the Information Not Obtained box.

INFORMATION NOT OBTAINED ☐

This questionnaire consists of 21 groups of statements. After reading each group of statements carefully circle the number (0, 1, 2, 3) next to the one statement in each group which best describes the way you have been feeling **the past week, including today**. If several statements within a group seem to apply equally well, circle each one. Be sure to read all the statements in each group before making your choice.

1

0 I do not feel sad.
1 I feel sad.
2 I am sad all the time and I can't snap out of it.
3 I am so sad or unhappy that I can't stand it.

2

0 I am not particularly discouraged about the future.
1 I feel discouraged about the future.
2 I feel I have nothing to look forward to.
3 I feel that the future is hopeless and that things cannot improve.

3

0 I do not feel like a failure.
1 I feel I have failed more than the average person.
2 As I look back on my life, all I can see is a lot of failures.
3 I feel I am a complete failure as a person.

4

0 I get as much satisfaction out of things as I used to.
1 I don't enjoy things the way I used to.
2 I don't get real satisfaction out of anything anymore.
3 I am dissatisfied or bored with everything.

5

0 I don't feel particularly guilty.
1 I feel guilty a good part of the time.
2 I feel quite guilty most of the time.
3 I feel guilty all of the time.

6

0 I don't feel I am being punished.
1 I feel I may be punished.
2 I expect to be punished.
3 I feel I am being punished.

7

0 I don't feel disappointed in myself.
1 I am disappointed in myself.
2 I am disgusted with myself.
3 I hate myself.

8

0 I don't feel I am any worse than anybody else.
1 I am critical of myself for my weaknesses or mistakes.
2 I blame myself all the time for my faults.
3 I blame myself for everything bad that happens.

9

0 I don't have any thoughts of killing myself.
1 I have thoughts of killing myself, but I would not carry them out.
2 I would like to kill myself.
3 I would kill myself if I had the chance.

10

0 I don't cry any more than usual.
1 I cry more now than I used to.
2 I cry all the time now.
3 I used to be able to cry, but now I can't cry even though I want to.

11

0 I am no more irritated now than I ever am.
1 I get annoyed or irritated more easily than I used to.
2 I feel irritated all the time now.
3 I don't get irritated at all by the things that used to irritate me.

12

0 I have not lost interest in other people.
1 I am less interested in other people than I used to be.
2 I have lost most of my interest in other people.
3 I have lost all of my interest in other people.

QS366

BECK DEPRESSION INVENTORY

13

0 I make decisions about as well as I ever could.
1 I put off making decisions more than I used to.
2 I have greater difficulty in making decisions than before.
3 I can't make decisions at all anymore.

14

0 I don't feel I look any worse than I used to.
1 I am worried that I am looking old or unattractive.
2 I feel that there are permanent changes in my appearance that make me look unattractive.
3 I believe that I look ugly.

15

0 I can work about as well as before.
1 It takes an extra effort to get started at doing something.
2 I have to push myself very hard to do anything.
3 I can't do any work at all.

16

0 I can sleep as well as usual.
1 I don't sleep as well as I used to.
2 I wake up 1-2 hours earlier than usual and find it hard to get back to sleep.
3 I wake up several hours earlier than I used to and cannot get back to sleep.

17

0 I don't get more tired than usual.
1 I get tired more easily than I used to.
2 I get tired from doing almost anything.
3 I am too tired to do anything.

18

0 My appetite is no worse than usual.
1 My appetite is not as good as it used to be.
2 My appetite is much worse now.
3 I have no appetite at all anymore.

19

0 I haven't lost much weight, if any, lately.
1 I have lost more than 5 pounds.
2 I have lost more than 10 pounds.
3 I have lost more than 15 pounds.

19a

I am purposely trying to lose weight by eating less.
1 Yes
2 No

20

0 I am no more worried about my health than usual.
1 I am worried about physical problems such as aches and pains; or upset stomach or constipation.
2 I am very worried about physical problems and it's hard to think of much else.
3 I am so worried about my physical problems that I cannot think about anything else.

21

0 I have not noticed any recent change in my interest in sex.
1 I am less interested in sex than I used to be.
2 I am much less interested in sex now.
3 I have lost interest in sex completely.

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QS366

HAMILTON ANXIETY SCALE

INFORMATION NOT OBTAINED ☐

For each of the items below, **CHECK ONE BOX** that best describes the patient.

1. **ANXIOUS MOOD:** Worries, anticipation of the worst, fearful anticipation, irritability

   ☐ 0 Not present
   ☐ 1 Mild
   ☐ 2 Moderate
   ☐ 3 Severe
   ☐ 4 Very severe

2. **TENSION**: Feelings of tension, fatigability, startle response, moved to tears easily, trembling, feeling of restlessness, inability to relax

   ☐ 0 Not present
   ☐ 1 Mild
   ☐ 2 Moderate
   ☐ 3 Severe
   ☐ 4 Very severe

3. **FEARS**: Of dark, of strangers, of being alone, of animals, of traffic, of crowds

   ☐ 0 Not present
   ☐ 1 Mild
   ☐ 2 Moderate
   ☐ 3 Severe
   ☐ 4 Very severe

4. **INSOMNIA**: Difficulty in falling asleep, broken sleep, unsatisfying sleep and fatigue on waking, dreams, nightmares, night terrors

   ☐ 0 Not present
   ☐ 1 Mild
   ☐ 2 Moderate
   ☐ 3 Severe
   ☐ 4 Very severe

5. **INTELLECTUAL (COGNITIVE)**: Difficulty in concentration, poor memory

   ☐ 0 Not present
   ☐ 1 Mild
   ☐ 2 Moderate
   ☐ 3 Severe
   ☐ 4 Very severe

6. **DEPRESSED MOOD**: Loss of interest, lack of pleasure in hobbies, depression, early waking, diurnal swing

   ☐ 0 Not present
   ☐ 1 Mild
   ☐ 2 Moderate
   ☐ 3 Severe
   ☐ 4 Very severe

7. **SOMATIC (MUSCULAR)**: Pains and aches, twitchings, stiffness, myoclonic jerks, grinding of teeth, unsteady voice, increased muscular tone

   ☐ 0 Not present
   ☐ 1 Mild
   ☐ 2 Moderate
   ☐ 3 Severe
   ☐ 4 Very severe

8. **SOMATIC (SENSORY)**: Tinnitus, blurring of vision, hot and cold flushes, feeling of weakness, pricking sensation

   ☐ 0 Not present
   ☐ 1 Mild
   ☐ 2 Moderate
   ☐ 3 Severe
   ☐ 4 Very severe

QS307

HAMILTON ANXIETY SCALE

9. **CARDIOVASCULAR SYMPTOMS:** Tachycardia, palpitations, pain in chest, throbbing of vessels, fainting feelings, missing beat

   ☐ 0 Not present
   ☐ 1 Mild
   ☐ 2 Moderate
   ☐ 3 Severe
   ☐ 4 Very severe

10. **RESPIRATORY SYMPTOMS:** Pressure or constriction in chest, choking feelings, sighing, dyspnea

   ☐ 0 Not present
   ☐ 1 Mild
   ☐ 2 Moderate
   ☐ 3 Severe
   ☐ 4 Very severe

11. **GASTROINTESTINAL SYMPTOMS:** Difficulty in swallowing, wind, abdominal pain, burning sensations, abdominal fullness, nausea, vomiting, borborygmi, looseness of bowels, loss of weight, constipation

   ☐ 0 Not present
   ☐ 1 Mild
   ☐ 2 Moderate
   ☐ 3 Severe
   ☐ 4 Very severe

12. **GENITOURINARY SYMPTOMS:** Frequency of micturition, urgency of micturition, amenorrhea, menorrhagia, development of frigidity, premature ejaculation, loss of libido, impotence

   ☐ 0 Not present
   ☐ 1 Mild
   ☐ 2 Moderate
   ☐ 3 Severe
   ☐ 4 Very severe

13. **AUTONOMIC SYMPTOMS:** Dry mouth, flushing, pallor, tendency to sweat, giddiness, tension headache, raising of hair

   ☐ 0 Not present
   ☐ 1 Mild
   ☐ 2 Moderate
   ☐ 3 Severe
   ☐ 4 Very severe

14. **BEHAVIOR AT INTERVIEW:** Fidgeting, restlessness or pacing, tremor of hands, furrowed brow, strained face, sighing or rapid respiration, facial pallor, swallowing, belching, brisk tendon jerks, dilated pupils, exophthalmos

   ☐ 0 Not present
   ☐ 1 Mild
   ☐ 2 Moderate
   ☐ 3 Severe
   ☐ 4 Very severe

Evaluator's Initials _____ _____ _____
First Middle Last

QS307

COMMENTS : VISIT

NO COMMENTS ☐

Comments should address any clinical report form items that require further explanation. Repeating information from the clinical report form is discouraged.

Comment on all clinically significant lab values that are outside a clinically accepted reference range or clinically significant values that differ importantly from previous values.

If the patient is ending participation in the study at this visit, enter only comments that apply to this visit; then complete the Patient Summary and Study Summary Comments pages.

Print legibly and do not use abbreviations or symbols.

The information reported for this visit is accurate and complete.

_____ Signature

_____/_____/_____ MM DD YY

CM30501

COMMENTS : STUDY SUMMARY

NO COMMENTS ☐

Repeating information from the clinical report form is discouraged. If the patient is ending participation in the study for any reason other than protocol complete (Reason 1 on Patient Summary page) give a brief description of the circumstances.

Enter comments below. Print legibly and do not use abbreviations or symbols.

All information reported for this patient is accurate and complete.

_____ _____/_____/_____
Signature of INVESTIGATOR who is a PHYSICIAN MM DD YY

CM30502

ADVERSE EVENTS Visit ____
Page 1 of 1

PRE-EXISTING CONDITIONS AND STUDY ADVERSE EVENTS

NO CONDITIONS OR EVENTS ☐

- List all pre-existing conditions or symptoms present at entry to study.
- List all clinically relevant abnormalities found on the physical exam or ECG.
- List all events that occur during study.

*** If Event is serious, notify Lilly immediately.**

Serious Outcome Codes	
1 = Fatal	5 = Congenital anomaly
2 = Life-threatening	6 = Cancer
3 = Permanently disabling	7 = Overdose
4 = Hospitalization	8 = Other reason

Severity Codes
1 = Mild
2 = Moderate
3 = Severe

Evaluate when:
- event stops or at the end of patient's participation in study
- or at any time event becomes serious

CODE	Description of Condition/Event	Onset Date MM DD YY / Stop Date MM DD YY	Severity of Condition/Event: Record the onset visit number and *maximum severity* at that visit. **Then** record the *maximum severity* in each subsequent visit **ONLY** if there is a change in severity.	Study Disease Related?	Possibly Related to Study Drug?	Serious* At Any Time During Trial?
E01			Visit Number / Severity	☐1 Yes ☐2 No ☐97 Un-known	☐1 Yes ☐2 No	☐N No If **Yes**, Serious Code(s) ____
E02			Visit Number / Severity	☐1 Yes ☐2 No ☐97 Un-known	☐1 Yes ☐2 No	☐N No If **Yes**, Serious Code(s) ____
E03			Visit Number / Severity	☐1 Yes ☐2 No ☐97 Un-known	☐1 Yes ☐2 No	☐N No If **Yes**, Serious Code(s) ____
E04			Visit Number / Severity	☐1 Yes ☐2 No ☐97 Un-known	☐1 Yes ☐2 No	☐N No If **Yes**, Serious Code(s) ____
E05			Visit Number / Severity	☐1 Yes ☐2 No ☐97 Un-known	☐1 Yes ☐2 No	☐N No If **Yes**, Serious Code(s) ____
E06			Visit Number / Severity	☐1 Yes ☐2 No ☐97 Un-known	☐1 Yes ☐2 No	☐N No If **Yes**, Serious Code(s) ____
E07			Visit Number / Severity	☐1 Yes ☐2 No ☐97 Un-known	☐1 Yes ☐2 No	☐N No If **Yes**, Serious Code(s) ____

RE31401

ADVERSE EVENTS Visit ____
Page 1 a of 1

PRE-EXISTING CONDITIONS AND STUDY ADVERSE EVENTS

- List all pre-existing conditions or symptoms present at entry to study.
- List all clinically relevant abnormalities found on the physical exam or ECG.
- List all events that occur during study.

*** If Event is serious, notify Lilly immediately.**

Serious Outcome Codes	
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1 = Mild
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Evaluate when:
- event stops or at the end of patient's participation in study
- or at any time event becomes serious

CODE	Description of Condition/Event	Onset Date MM DD YY / Stop Date MM DD YY	Severity of Condition/Event: Record the onset visit number and *maximum severity* at that visit. **Then** record the *maximum severity* in each subsequent visit **ONLY** if there is a change in severity.	Study Disease Related?	Possibly Related to Study Drug?	Serious* At Any Time During Trial?
E01			Visit Number / Severity	☐1 Yes ☐2 No ☐97 Un-known	☐1 Yes ☐2 No	☐N No If **Yes**, Serious Code(s) ____
E02			Visit Number / Severity	☐1 Yes ☐2 No ☐97 Un-known	☐1 Yes ☐2 No	☐N No If **Yes**, Serious Code(s) ____
E03			Visit Number / Severity	☐1 Yes ☐2 No ☐97 Un-known	☐1 Yes ☐2 No	☐N No If **Yes**, Serious Code(s) ____
E04			Visit Number / Severity	☐1 Yes ☐2 No ☐97 Un-known	☐1 Yes ☐2 No	☐N No If **Yes**, Serious Code(s) ____
E05			Visit Number / Severity	☐1 Yes ☐2 No ☐97 Un-known	☐1 Yes ☐2 No	☐N No If **Yes**, Serious Code(s) ____
E06			Visit Number / Severity	☐1 Yes ☐2 No ☐97 Un-known	☐1 Yes ☐2 No	☐N No If **Yes**, Serious Code(s) ____
E07			Visit Number / Severity	☐1 Yes ☐2 No ☐97 Un-known	☐1 Yes ☐2 No	☐N No If **Yes**, Serious Code(s) ____

RE31401

ADVERSE EVENTS Visit ____
Page 1 __ of 1

PRE-EXISTING CONDITIONS AND STUDY ADVERSE EVENTS

- List all pre-existing conditions or symptoms present at entry to study.
- List all clinically relevant abnormalities found on the physical exam or ECG.
- List all events that occur during study.

*** If Event is serious, notify Lilly immediately.**

Serious Outcome Codes	
1 = Fatal	5 = Congenital anomaly
2 = Life-threatening	6 = Cancer
3 = Permanently disabling	7 = Overdose
4 = Hospitalization	8 = Other reason

Severity Codes
1 = Mild
2 = Moderate
3 = Severe

Evaluate when:
- event stops or at the end of patient's participation in study
- or at any time event becomes serious

CODE	Description of Condition/Event	Onset Date MM DD YY / Stop Date MM DD YY	Severity of Condition/Event: Record the onset visit number and *maximum severity* at that visit. **Then** record the *maximum severity* in each subsequent visit **ONLY** if there is a change in severity.	Study Disease Related?	Possibly Related to Study Drug?	Serious* At Any Time During Trial?
E01			Visit Number / Severity	☐1 Yes ☐2 No ☐97 Un-known	☐1 Yes ☐2 No	☐N No If **Yes**, Serious Code(s) ____
E02			Visit Number / Severity	☐1 Yes ☐2 No ☐97 Un-known	☐1 Yes ☐2 No	☐N No If **Yes**, Serious Code(s) ____
E03			Visit Number / Severity	☐1 Yes ☐2 No ☐97 Un-known	☐1 Yes ☐2 No	☐N No If **Yes**, Serious Code(s) ____
E04			Visit Number / Severity	☐1 Yes ☐2 No ☐97 Un-known	☐1 Yes ☐2 No	☐N No If **Yes**, Serious Code(s) ____
E05			Visit Number / Severity	☐1 Yes ☐2 No ☐97 Un-known	☐1 Yes ☐2 No	☐N No If **Yes**, Serious Code(s) ____
E06			Visit Number / Severity	☐1 Yes ☐2 No ☐97 Un-known	☐1 Yes ☐2 No	☐N No If **Yes**, Serious Code(s) ____
E07			Visit Number / Severity	☐1 Yes ☐2 No ☐97 Un-known	☐1 Yes ☐2 No	☐N No If **Yes**, Serious Code(s) ____

RE31401

CONCOMITANT MEDICATION Visit ___
Page 1 of 1

CONCOMITANT MEDICATION

NO CONCOMITANT MEDICATIONS ☐

Enter all medications, other than study drug, the patient is taking at **entry** and **during the study**.

Indication for Use (IFU)
Enter code from patient's Pre-existing Conditions and Study Adverse Events page. E__ = Pre-Existing Condition or Event (eg, E01) or X1 = Primary study condition X2 = Prophylaxis or non-therapeutic use

	Brand or Trade Name (Use generic if brand or trade name unknown)	Dose	Unit	Fre-quency	Route	Start Date MM	Start Date DD	Start Date YY	Stop Date MM	Stop Date DD	Stop Date YY	IFU
0.												
1.												
2.												
3.												
4.												
5.												
6.												
7.												
8.												
9.												
10.												
11.												

CC307

CONCOMITANT MEDICATION Visit ____
Page 1 a of 1

CONCOMITANT MEDICATION

Continue listing all medications, other than study drug, the patient is taking at **entry** and **during the study**.

Indication for Use (IFU)
Enter code from patient's Pre-existing Conditions and Study Adverse Events page. E__ = Pre-Existing Condition or Event (eg, E01) or X1 = Primary study condition X2 = Prophylaxis or non-therapeutic use

	Brand or Trade Name (Use generic if brand or trade name unknown)	Dose	Unit	Fre-quency	Route	Start Date MM	Start Date DD	Start Date YY	Stop Date MM	Stop Date DD	Stop Date YY	IFU
12.												
13.												
14.												
15.												
16.												
17.												
18.												
19.												
20.												
21.												
22.												
23.												

CC307

CONCOMITANT MEDICATION Visit ____
Page 1 __ of 1

CONCOMITANT MEDICATION

Continue listing all medications, other than study drug, the patient is taking **during the study**.

Indication for Use (IFU)
Enter code from patient's Pre-existing Conditions and Study Adverse Events page. E__ = Pre-Existing Condition or Event (eg, E01) or X1 = Primary study condition X2 = Prophylaxis or non-therapeutic use

Brand or Trade Name (Use generic if brand or trade name unknown)	Dose	Unit	Fre-quency	Route	Start Date MM	Start Date DD	Start Date YY	Stop Date MM	Stop Date DD	Stop Date YY	IFU

CC307

Clinical Report Form
Fluoxetine Versus Placebo in Childhood/Adolescent Depression
B1Y-MC-HCJE

PATIENT SUMMARY

Initials | Date Verified | Initials | Date Keyed | Date Received at Lilly | Reviewed | Inspected | Date

Patient Initials _____ _____ _____
First Middle Last

CHECK ONE PRIMARY REASON FOR ENDING PARTICIPATION IN THE STUDY

☐1 Protocol completed

☐3 Adverse event E __ __
E__ Code

☐4 Death* E __ __ →
E__ Code

If # **4** is checked, enter date of death.
Date of Death _____/_____/_____
MM DD YY

☐5 Satisfactory response, patient perception
☐6 Satisfactory response, physician perception
☐7 Satisfactory response, patient and physician perception

☐8 Lack of efficacy, patient perception
☐9 Lack of efficacy, physician perception
☐10 Lack of efficacy, patient and physician perception

☐11 Unable to contact patient (lost to follow-up)
☐12 Patient moved
☐13 Personal conflict or other patient/parent decision _____
Specify

☐22 Physician decision _____
Specify

☐14 Protocol entry criteria not met _____ (Specify number from entry criteria checklist)
Specify

☐15 Protocol interim criteria not met

☐459 Relapse as defined by protocol

☐17 Clinical relapse
☐26 Nonresponder
☐59 Noncompliance

☐243 Protocol violation

☐18 Sponsor decision (study or patient discontinued by the Sponsor)

* Contact Lilly immediately in event of death. Obtain a copy of the autopsy report (if autopsy performed) or hospital discharge summary. Forward to Lilly as soon as possible. Explain circumstances of the death on the Study Summary Comments page.

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Fluoxetine Versus Placebo in Childhood/Adolescent Depression
B1Y-MC-HCJE

K-SADS : AFFECTIVE DISORDERS

INFORMATION NOT OBTAINED ☐

Check the appropriate boxes.

Depressive Disorders - Current	☐ 1 Yes	☐ 2 No
Depressive Disorders - Past	☐ 1 Yes	☐ 2 No
Mania - Current	☐ 1 Yes	☐ 2 No
Mania -Past	☐ 1 Yes	☐ 2 No

Evaluator's initials _____ _____ _____
First Middle Last

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Fluoxetine Versus Placebo in Childhood/Adolescent Depression
B1Y-MC-HCJE

PATIENT SUMMARY Visit ____
Page 3 of 12

GLOBAL ASSESSMENT OF FUNCTIONING SCALE (GAF SCALE)

INFORMATION NOT OBTAINED ☐

Enter the number (between 1 and 90) that best represents the patient's:

1. **Current** level of functioning _____
2. **Highest** level of functioning in *past year* _____

Level of Functioning Definitions	
90 – 81	Absent or minimal symptoms, good functioning in all areas, interested and involved in a wide range of activities, socially effective, generally satisfied with life, no more than everyday problems or concerns.
80 – 71	If symptoms are present, they are transient and expectable reactions to psychosocial stressors; no more than slight impairment in social, occupational, or school functioning.
70 – 61	Some mild symptoms OR some difficulty in social, occupational, or school functioning, but generally functioning pretty well, has some meaningful interpersonal relationships.
60 – 51	Moderate symptoms OR any moderate difficulty in social, occupational, or school functioning.
50 – 41	Serious symptoms OR any serious impairment in social, occupational, or school functioning.
40 – 31	Some impairment in reality testing or communication OR major impairment in several areas, such as work or school, family relations, judgment, thinking, or mood.
30 – 21	Behavior is considered influenced by delusions or hallucinations OR serious impairment in communications or judgment OR inability to function in almost all areas.
20 – 11	Some danger of hurting self or other OR occasionally fails to maintain minimal personal hygiene OR gross impairment in communication.
10 – 1	Persistent danger of severely hurting self or others OR persistent inability to maintain minimum personal hygiene OR serious suicidal act with clear expectation of death.

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Fluoxetine Versus Placebo in Childhood/Adolescent Depression
B1Y-MC-HCJE

PROCEDURE : PHYSICAL EXAM

Was a physical exam performed? ☐1 Yes ☐2 No

WEIGHT

INFORMATION NOT OBTAINED ☐

Measure with shoes off. Round up or down to the nearest whole pound.

Weight ___ ___ ___ (lb)

HEIGHT

INFORMATION NOT OBTAINED ☐

Measure with shoes off. Round up or down to the nearest whole inch.

Height ___ ___ ___ (in)

ELECTROCARDIOGRAM

INFORMATION NOT OBTAINED ☐

Electrocardiogram date _____/_____/_____
MM DD YY

Electrocardiogram result ☐12 Acceptable ☐13 Not Acceptable

Insert the ECG (original) in the envelope provided.

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Fluoxetine Versus Placebo in Childhood/Adolescent Depression
B1Y-MC-HCJE

PATIENT SUMMARY Visit ____
Page 5 of 12

CHILDREN'S DEPRESSION INDEX (CDI)

NOTE: Only complete if patient was 8 to 12 years old at Visit 1. If patient was not 8 to 12 years old, check the Information Not Obtained box.

INFORMATION NOT OBTAINED ☐

This lists the feelings and ideas in groups. From each group of three sentences, pick one sentence that describes you **best** for the past two weeks. After you pick a sentence from the first group, go on to the next group. There is no right answer or wrong answer. Just pick the sentence that best describes the way you have been recently. Put an "X" in the box next to your answer.
Remember: pick out the sentences that describe you best **in the past two weeks**.

Item 1

- ☐ 0 I am sad once in a while.
- ☐ 1 I am sad many times.
- ☐ 2 I am sad all the time.

Item 2

- ☐ 2 Nothing will ever work out for me.
- ☐ 1 I am not sure if things will work out for me.
- ☐ 0 Things will work out for me O.K.

Item 3

- ☐ 0 I do most things O.K.
- ☐ 1 I do many things wrong.
- ☐ 2 I do everything wrong.

Item 4

- ☐ 0 I have fun in many things.
- ☐ 1 I have fun in some things.
- ☐ 2 Nothing is fun at all.

Item 5

- ☐ 2 I am bad all the time.
- ☐ 1 I am bad many times.
- ☐ 0 I am bad once in a while.

Item 6

- ☐ 0 I think about bad things happening to me once in a while.
- ☐ 1 I worry that bad things will happen to me.
- ☐ 2 I am sure that terrible things will happen to me.

Item 7

- ☐ 2 I hate myself.
- ☐ 1 I do not like myself.
- ☐ 0 I like myself.

Item 8

- ☐ 2 All bad things are my fault.
- ☐ 1 Many bad things are my fault.
- ☐ 0 Bad things are not usually my fault.

Item 9

- ☐ 0 I do not think about killing myself.
- ☐ 1 I think about killing myself but I would not do it.
- ☐ 2 I want to kill myself.

Item 10

- ☐ 2 I feel like crying every day.
- ☐ 1 I feel like crying many days.
- ☐ 0 I feel like crying once in a while.

Item 11

- ☐ 2 Things bother me all the time.
- ☐ 1 Things bother me many times.
- ☐ 0 Things bother me once in a while.

Item 12

- ☐ 0 I like being with people.
- ☐ 1 I do not like being with people many times.
- ☐ 2 I do not want to be with people at all.

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Clinical Report Form
Fluoxetine Versus Placebo in Childhood/Adolescent Depression
B1Y-MC-HCJE

PATIENT SUMMARY Visit ____
Page 6 of 12

CHILDREN'S DEPRESSION INDEX (CDI)

Item 13

- ☐ 2 I cannot make up my mind about things.
- ☐ 1 It is hard to make up my mind about things.
- ☐ 0 I make up my mind about things easily.

Item 14

- ☐ 0 I look O.K.
- ☐ 1 There are some bad things about my looks.
- ☐ 2 I look ugly.

Item 15

- ☐ 2 I have to push myself all the time to do my schoolwork.
- ☐ 1 I have to push myself many times to do my schoolwork.
- ☐ 0 Doing schoolwork is not a big problem.

Item 16

- ☐ 2 I have trouble sleeping every night.
- ☐ 1 I have trouble sleeping many nights.
- ☐ 0 I sleep pretty well.

Item 17

- ☐ 0 I am tired once in a while.
- ☐ 1 I am tired many days.
- ☐ 2 I am tired all the time.

Item 18

- ☐ 2 Most days I do not feel like eating.
- ☐ 1 Many days I do not feel like eating.
- ☐ 0 I eat pretty well.

Item 19

- ☐ 0 I do not worry about aches and pains.
- ☐ 1 I worry about aches and pains many times.
- ☐ 2 I worry about aches and pains all the time.

Item 20

- ☐ 0 I do not feel alone.
- ☐ 1 I feel alone many times.
- ☐ 2 I feel alone all the time.

Item 21

- ☐ 2 I never have fun at school.
- ☐ 1 I have fun at school only once in a while.
- ☐ 0 I have fun at school many times.

Item 22

- ☐ 0 I have plenty of friends.
- ☐ 1 I have some friends but I wish I had more.
- ☐ 2 I do not have any friends.

Item 23

- ☐ 0 My schoolwork is alright.
- ☐ 1 My schoolwork is not as good as before.
- ☐ 2 I do very badly in subjects I used to be good in.

Item 24

- ☐ 2 I can never be as good as other kids.
- ☐ 1 I can be as good as other kids if I want to.
- ☐ 0 I am just as good as other kids.

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Clinical Report Form
Fluoxetine Versus Placebo in Childhood/Adolescent Depression
B1Y-MC-HCJE

PATIENT SUMMARY Visit ____
Page 7 of 12

CHILDREN'S DEPRESSION INDEX (CDI)

Item 25

- ☐ 2 Nobody really loves me.
- ☐ 1 I am not sure if anybody loves me.
- ☐ 0 I am sure that somebody loves me.

Item 26

- ☐ 0 I usually do what I am told.
- ☐ 1 I do not do what I am told most times.
- ☐ 2 I never do what I am told.

Item 27

- ☐ 0 I get along with people.
- ☐ 1 I get into fights many times.
- ☐ 2 I get into fights all the time.

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B1Y-MC-HCJE

BECK DEPRESSION INVENTORY

NOTE: Only complete if patient was 13 to 17 years old at Visit 1. If patient was not 13 to 17 years old, check the Information Not Obtained box.

INFORMATION NOT OBTAINED ☐

This questionnaire consists of 21 groups of statements. After reading each group of statements carefully circle the number (0, 1, 2, 3) next to the one statement in each group which best describes the way you have been feeling **the past week, including today**. If several statements within a group seem to apply equally well, circle each one. Be sure to read all the statements in each group before making your choice.

1

0 I do not feel sad.
1 I feel sad.
2 I am sad all the time and I can't snap out of it.
3 I am so sad or unhappy that I can't stand it.

2

0 I am not particularly discouraged about the future.
1 I feel discouraged about the future.
2 I feel I have nothing to look forward to.
3 I feel that the future is hopeless and that things cannot improve.

3

0 I do not feel like a failure.
1 I feel I have failed more than the average person.
2 As I look back on my life, all I can see is a lot of failures.
3 I feel I am a complete failure as a person.

4

0 I get as much satisfaction out of things as I used to.
1 I don't enjoy things the way I used to.
2 I don't get real satisfaction out of anything anymore.
3 I am dissatisfied or bored with everything.

5

0 I don't feel particularly guilty.
1 I feel guilty a good part of the time.
2 I feel quite guilty most of the time.
3 I feel guilty all of the time.

6

0 I don't feel I am being punished.
1 I feel I may be punished.
2 I expect to be punished.
3 I feel I am being punished.

7

0 I don't feel disappointed in myself.
1 I am disappointed in myself.
2 I am disgusted with myself.
3 I hate myself.

8

0 I don't feel I am any worse than anybody else.
1 I am critical of myself for my weaknesses or mistakes.
2 I blame myself all the time for my faults.
3 I blame myself for everything bad that happens.

9

0 I don't have any thoughts of killing myself.
1 I have thoughts of killing myself, but I would not carry them out.
2 I would like to kill myself.
3 I would kill myself if I had the chance.

10

0 I don't cry any more than usual.
1 I cry more now than I used to.
2 I cry all the time now.
3 I used to be able to cry, but now I can't cry even though I want to.

11

0 I am no more irritated now than I ever am.
1 I get annoyed or irritated more easily than I used to.
2 I feel irritated all the time now.
3 I don't get irritated at all by the things that used to irritate me.

12

0 I have not lost interest in other people.
1 I am less interested in other people than I used to be.
2 I have lost most of my interest in other people.
3 I have lost all of my interest in other people.

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Clinical Report Form
Fluoxetine Versus Placebo in Childhood/Adolescent Depression
B1Y-MC-HCJE

PATIENT SUMMARY Visit ____
Page 9 of 12

BECK DEPRESSION INVENTORY

13

0 I make decisions about as well as I ever could.
1 I put off making decisions more than I used to.
2 I have greater difficulty in making decisions than before.
3 I can't make decisions at all anymore.

14

0 I don't feel I look any worse than I used to.
1 I am worried that I am looking old or unattractive.
2 I feel that there are permanent changes in my appearance that make me look unattractive.
3 I believe that I look ugly.

15

0 I can work about as well as before.
1 It takes an extra effort to get started at doing something.
2 I have to push myself very hard to do anything.
3 I can't do any work at all.

16

0 I can sleep as well as usual.
1 I don't sleep as well as I used to.
2 I wake up 1-2 hours earlier than usual and find it hard to get back to sleep.
3 I wake up several hours earlier than I used to and cannot get back to sleep.

17

0 I don't get more tired than usual.
1 I get tired more easily than I used to.
2 I get tired from doing almost anything.
3 I am too tired to do anything.

18

0 My appetite is no worse than usual.
1 My appetite is not as good as it used to be.
2 My appetite is much worse now.
3 I have no appetite at all anymore.

19

0 I haven't lost much weight, if any, lately.
1 I have lost more than 5 pounds.
2 I have lost more than 10 pounds.
3 I have lost more than 15 pounds.

19a

I am purposely trying to lose weight by eating less.
1 Yes
2 No

20

0 I am no more worried about my health than usual.
1 I am worried about physical problems such as aches and pains; or upset stomach or constipation.
2 I am very worried about physical problems and it's hard to think of much else.
3 I am so worried about my physical problems that I cannot think about anything else.

21

0 I have not noticed any recent change in my interest in sex.
1 I am less interested in sex than I used to be.
2 I am much less interested in sex now.
3 I have lost interest in sex completely.

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Clinical Report Form
Fluoxetine Versus Placebo in Childhood/Adolescent Depression
B1Y-MC-HCJE

PATIENT SUMMARY Visit ____
Page 10 of 12

HAMILTON ANXIETY SCALE

INFORMATION NOT OBTAINED ☐

For each of the items below, **CHECK ONE BOX** that best describes the patient.

1. **ANXIOUS MOOD:** Worries, anticipation of the worst, fearful anticipation, irritability

   ☐ 0 Not present
   ☐ 1 Mild
   ☐ 2 Moderate
   ☐ 3 Severe
   ☐ 4 Very severe

2. **TENSION**: Feelings of tension, fatigability, startle response, moved to tears easily, trembling, feeling of restlessness, inability to relax

   ☐ 0 Not present
   ☐ 1 Mild
   ☐ 2 Moderate
   ☐ 3 Severe
   ☐ 4 Very severe

3. **FEARS**: Of dark, of strangers, of being alone, of animals, of traffic, of crowds

   ☐ 0 Not present
   ☐ 1 Mild
   ☐ 2 Moderate
   ☐ 3 Severe
   ☐ 4 Very severe

4. **INSOMNIA**: Difficulty in falling asleep, broken sleep, unsatisfying sleep and fatigue on waking, dreams, nightmares, night terrors

   ☐ 0 Not present
   ☐ 1 Mild
   ☐ 2 Moderate
   ☐ 3 Severe
   ☐ 4 Very severe

5. **INTELLECTUAL (COGNITIVE)**: Difficulty in concentration, poor memory

   ☐ 0 Not present
   ☐ 1 Mild
   ☐ 2 Moderate
   ☐ 3 Severe
   ☐ 4 Very severe

6. **DEPRESSED MOOD**: Loss of interest, lack of pleasure in hobbies, depression, early waking, diurnal swing

   ☐ 0 Not present
   ☐ 1 Mild
   ☐ 2 Moderate
   ☐ 3 Severe
   ☐ 4 Very severe

7. **SOMATIC (MUSCULAR)**: Pains and aches, twitchings, stiffness, myoclonic jerks, grinding of teeth, unsteady voice, increased muscular tone

   ☐ 0 Not present
   ☐ 1 Mild
   ☐ 2 Moderate
   ☐ 3 Severe
   ☐ 4 Very severe

8. **SOMATIC (SENSORY)**: Tinnitus, blurring of vision, hot and cold flushes, feeling of weakness, pricking sensation

   ☐ 0 Not present
   ☐ 1 Mild
   ☐ 2 Moderate
   ☐ 3 Severe
   ☐ 4 Very severe

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Clinical Report Form
Fluoxetine Versus Placebo in Childhood/Adolescent Depression
B1Y-MC-HCJE

PATIENT SUMMARY Visit ____
Page 11 of 12

HAMILTON ANXIETY SCALE

9. **CARDIOVASCULAR SYMPTOMS:** Tachycardia, palpitations, pain in chest, throbbing of vessels, fainting feelings, missing beat

- ☐ 0 Not present
- ☐ 1 Mild
- ☐ 2 Moderate
- ☐ 3 Severe
- ☐ 4 Very severe

10. **RESPIRATORY SYMPTOMS:** Pressure or constriction in chest, choking feelings, sighing, dyspnea

- ☐ 0 Not present
- ☐ 1 Mild
- ☐ 2 Moderate
- ☐ 3 Severe
- ☐ 4 Very severe

11. **GASTROINTESTINAL SYMPTOMS:** Difficulty in swallowing, wind, abdominal pain, burning sensations, abdominal fullness, nausea, vomiting, borborygmi, looseness of bowels, loss of weight, constipation

- ☐ 0 Not present
- ☐ 1 Mild
- ☐ 2 Moderate
- ☐ 3 Severe
- ☐ 4 Very severe

12. **GENITOURINARY SYMPTOMS:** Frequency of micturition, urgency of micturition, amenorrhea, menorrhagia, development of frigidity, premature ejaculation, loss of libido, impotence

- ☐ 0 Not present
- ☐ 1 Mild
- ☐ 2 Moderate
- ☐ 3 Severe
- ☐ 4 Very severe

13. **AUTONOMIC SYMPTOMS:** Dry mouth, flushing, pallor, tendency to sweat, giddiness, tension headache, raising of hair

- ☐ 0 Not present
- ☐ 1 Mild
- ☐ 2 Moderate
- ☐ 3 Severe
- ☐ 4 Very severe

14. **BEHAVIOR AT INTERVIEW:** Fidgeting, restlessness or pacing, tremor of hands, furrowed brow, strained face, sighing or rapid respiration, facial pallor, swallowing, belching, brisk tendon jerks, dilated pupils, exophthalmos

- ☐ 0 Not present
- ☐ 1 Mild
- ☐ 2 Moderate
- ☐ 3 Severe
- ☐ 4 Very severe

Evaluator's Initials _____ _____ _____
First Middle Last

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Fluoxetine Versus Placebo in Childhood/Adolescent Depression
B1Y-MC-HCJE

COMMENTS : STUDY SUMMARY

NO COMMENTS ☐

Repeating information from the clinical report form is discouraged. If the patient is ending participation in the study for any reason other than protocol complete (Reason 1 on Patient Summary page) give a brief description of the circumstances.

Enter comments below. Print legibly and do not use abbreviations or symbols.

All information reported for this patient is accurate and complete.

_____ _____/_____/_____
Signature of INVESTIGATOR who is a PHYSICIAN MM DD YY

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REMINDER TO PHOTOCOPY

Remember to photocopy all

- **Pre-existing Conditions and Study Adverse Events** pages

  DO NOT assess and record the **relationship to study drug** for an event until the event stops or at the patient's final visit (ie, this question does not have to be completed on the photocopy).

  DO NOT record "NO" for the **Serious During Trial?** question for an event until the event stops or at the patient's final visit (ie, this question does not have to be completed on the photocopy).

- **Concomitant Medication** pages

(both are located in separate sections) and send them in with this visit packet of clinical report forms.

After photocopying . . .

Remember to record the **visit number** in the top right corner of all photocopied pages.

Lilly

CUSTOMER QUESTIONNAIRE

In our effort to continuously improve our clinical report forms (CRFs), we are asking for your feedback and suggestions for change in the CRFs and instructions you have been using for the following study:

Protocol: **B1Y-MC-HJCE** Study Title: Fluoxetine versus Placebo in Childhood/Adolescent Depression

This feedback questionnaire should be completed *midway through your study*, after the CRFs have been given an adequate period of usage.

1. Overall, compared to the CRFs of other pharmaceutical companies, Lilly's CRFs rank . . .

Much Better	Somewhat Better	Same	Somewhat Worse	Much Worse	Not Applicable
☐ 5	☐ 4	☐ 3	☐ 2	☐ 1	☐ 0

a. Lilly's CRFs are worse because too much data is collected ☐ 1 Yes ☐ 2 No

b. Lilly's CRFs are worse because of the layout and design ☐ 1 Yes ☐ 2 No

Specify _____

_____

2. The instructions that accompanied the CRF modules were . . .

Very Helpful	Somewhat Helpful	Neutral	Fair	Of No Value	Not Applicable
☐ 5	☐ 4	☐ 3	☐ 2	☐ 1	☐ 0

If "Fair" or "Of No Value" was checked, how could the instructions be improved? _____

_____

_____

3. The way the CRFs were printed and packaged were . . .

Very Good	Good	Neutral	Fair	Bad
☐ 5	☐ 4	☐ 3	☐ 2	☐ 1

If "Fair" or "Bad" was checked, how could the printing or packaging be improved? _____

_____

_____

(Please turn over)

4. The CRF training you received at the study start-up meeting was . . .

Very Helpful	Somewhat Helpful	Neutral	Fair	Of No Value	Not Applicable (did not receive any training)
☐ 5	☐ 4	☐ 3	☐ 2	☐ 1	☐ 0

If "Fair" or "Of No Value" was checked, how could the training be improved? _____

_____

_____

5. What did you like **BEST** about Lilly's CRFs?_____

_____

_____

6. What did you like **LEAST** about Lilly's CRFs? Why? (When referring to a specific module, please give module title and Page #)

_____

_____

_____

7. What suggestions do you have for improvement?_____

_____

_____

_____

_____

_____

_____

We appreciate your time and efforts in completing this survey. Your feedback is very important to us. There may be something you mentioned in your responses that we would like to speak with you about. If so, may we telephone you?

Optional:

Printed name: _____ Telephone: _____

Please fold the survey and return it to Lilly in the enclosed postage-paid envelope. Thank you for your time!

Sincerely,
ELI LILLY AND COMPANY

Clinical Report Form
Fluoxetine Versus Placebo in Childhood/Adolescent Depression
B1Y-MC-HCJE

Unscheduled Visit ____ ___ (numeric) (alpha)
Page 1 of 9

PATIENT AND VISIT IDENTIFICATION

Patient initials _____ _____ _____
First Middle Last

Visit date _____/_____/_____
MM DD YY

VITAL SIGNS : BLOOD PRESSURE AND HEART RATE

INFORMATION NOT OBTAINED ☐

Position
SI = Sitting

Position	Blood Pressure (mm Hg) Systolic/Diastolic	Heart Rate (bpm)
SI	/	

VITAL SIGNS: TEMPERATURE

INFORMATION NOT OBTAINED ☐

Temperature ___ ___ ___ . ___

Unit of measure (F) Fahrenheit

Method (E) Ear

REMINDER

On the Pre-existing Conditions and Study Adverse Events pages, record new events that occurred since the previous visit and re-evaluate any on-going conditions or events.

On the Concomitant Medication pages, record new medications the patient has taken since the previous visit, any changes to ongoing medications, and a stop date for any medication the patient is no longer taking.

Initials
Date Verified
Initials
Date Keyed
Date Received at Lilly
Reviewed
Inspected
Date

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B1Y-MC-HCJE

Unscheduled Visit ____ ___ (numeric) (alpha)
Page 2 of 9

CHILDRENS DEPRESSION RATING SCALE - REVISED

INFORMATION NOT OBTAINED ☐

CHECK THE NUMERIC CODE which best describes the patient.

1. **SCHOOLWORK**:

☐ 1 Performance consistent with ability
☐ 2
☐ 3 Decrease in school performance
☐ 4
☐ 5 Major interference in most subjects
☐ 6
☐ 7 No motivation to perform

2. **CAPACITY TO HAVE FUN**

☐ 1 Interest and activities realistically appropriate for age, personality, and social environment. Shows no appreciable change with present illness.
☐ 2
☐ 3 Describes some activities realistically available several times a week but not on a daily basis. Shows interest but not enthusiasm.
☐ 4
☐ 5 Is easily bored. Complains of "nothing to do." Participates in structured activities with a "going through the motions" attitude. May express interest primarily in activities that are (realistically) unavailable on a daily or weekly basis.
☐ 6
☐ 7 Has no initiative to become involved in any activities. Primarily passive. Watches others play or watches TV but shows little interest. Requires coaxing and/or pushing to get involved in activity. Shows no enthusiasm or real interest. Has difficulty naming activities.

3. **SOCIAL WITHDRAWAL**

☐ 1 Enjoys friendships with peers at school and home
☐ 2
☐ 3 May not actively seek out friendships but waits for others to initiate a relationship or may occasionally reject opportunities to play without a describable alternative
☐ 4
☐ 5 Frequently avoids or refuses opportunities for desirable interaction with others and/or sets up situations where rejection is inevitable.
☐ 6
☐ 7 Does not currently relate to other children. States he or she has "no friends" or actively rejects new or former friends.

4. **SLEEP**

☐ 1 No (or occasional) difficulty. (Goes to sleep within 1/2 hour or less.)
☐ 2
☐ 3 Frequently has mild difficulty with sleep
☐ 4
☐ 5 Moderate difficulty with sleep nearly every night.

5. **APPETITE OR EATING PATTERNS**

☐ 1 No problems or change in eating pattern
☐ 2
☐ 3 Mild change from usual eating habits within onset of current behavioral problem
☐ 4
☐ 5 Is not hungry most of the time or has excessive food intake since onset of current behavioral problems or marked increase in appetite

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Clinical Report Form
Fluoxetine Versus Placebo in Childhood/Adolescent Depression
B1Y-MC-HCJE

Unscheduled Visit ____ ___ (numeric) (alpha)

CHILDRENS DEPRESSION RATING SCALE - REVISED

CHECK THE NUMERIC CODE which best describes the patient.

6. **EXCESSIVE FATIGUE**

- ☐ 1 No unusual complaints of "feeling tired" during the day
- ☐ 2
- ☐ 3 Complaints of fatigue which seem somewhat excessive and not related to boredom
- ☐ 4
- ☐ 5 Daily complaints of feeling tired
- ☐ 6
- ☐ 7 Complains of feeling tired most of the day. May voluntarily take long naps without feeling refreshed. Interferes with play activities.

7. **PHYSICAL COMPLAINTS**:

- ☐ 1 Occasional complaints
- ☐ 2
- ☐ 3 Complaints appear mildly excessive
- ☐ 4
- ☐ 5 Complains daily. Some interference with the ability of the child to function
- ☐ 6
- ☐ 7 Preoccupied with aches and pains; interferes with play activities several times a week

8. **IRRITABILITY**

- ☐ 1 Rare
- ☐ 2 Occasional
- ☐ 3 Several times a week for short periods
- ☐ 4
- ☐ 5 Several times a week for longer periods
- ☐ 6
- ☐ 7 Constant

9. **GUILT**

- ☐ 1 Does not express any undue feeling of guilt. Appears appropriate to precipitating event.
- ☐ 2
- ☐ 3 Exaggerates guilt and/or shame out of proportion to the event described.
- ☐ 4
- ☐ 5 Feels guilty over things not under his or her control. Guilt is definitely pathological.
- ☐ 6
- ☐ 7 Severe delusions of guilt

10. **SELF-ESTEEM**

- ☐ 1 Describes self in primarily positive terms
- ☐ 2
- ☐ 3 Describes self with one important area where the child feels deficit
- ☐ 4
- ☐ 5 Describes self in preponderance of negative terms or gives bland answers to questions
- ☐ 6
- ☐ 7 Refers to self in derogatory terms. Reports that other children refer to him/her frequently by using derogatory nicknames and child puts self down

11. **DEPRESSED FEELINGS**

- ☐ 1 Occasional feelings of unhappiness which quickly disappear
- ☐ 2
- ☐ 3 Describes sustained periods of unhappiness which appear excessive for events described
- ☐ 4
- ☐ 5 Feels unhappy most of the time without a major precipitating cause
- ☐ 6
- ☐ 7 Feels unhappy all of the time. Accompanied by psychic pain (e.g., "I can't stand it").

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Fluoxetine Versus Placebo in Childhood/Adolescent Depression
B1Y-MC-HCJE

Unscheduled Visit _____ ___ (numeric) (alpha)
Page 4 of 9

CHILDRENS DEPRESSION RATING SCALE - REVISED

CHECK THE NUMERIC CODE which best describes the patient.

12. **MORBID IDEATION**

- ☐ 1 None
- ☐ 2
- ☐ 3 Has some morbid thought, all of which relate to a reality event but seem excessive.
- ☐ 4
- ☐ 5 Preoccupied with morbid thoughts several times a week. Morbid thoughts extend beyond external reality
- ☐ 6
- ☐ 7 Preoccupied with death themes or morbid thoughts that are elaborate, extensive or bizarre on a daily basis

13. **SUICIDAL IDEATION**

- ☐ 1 Understands the word "suicide" but does not apply term to self
- ☐ 2 Sharp denial of suicidal thoughts
- ☐ 3 Has thoughts about suicide, usually when angry.
- ☐ 4
- ☐ 5 Has recurrent thoughts of suicide
- ☐ 6
- ☐ 7 Has made suicide attempt within the last month or is actively suicidal

14. **WEEPING**:

- ☐ 1 Normal for age.
- ☐ 2 Suggestive statements that child cries, or feels like crying, more frequently than peers.
- ☐ 3 Child cries slightly more than peers.
- ☐ 4
- ☐ 5 Cries or feels like crying frequently (several times a week). Admits to crying without knowing reason why.
- ☐ 6
- ☐ 7 Cries nearly every day.

15. **DEPRESSED AFFECT:**

- ☐ 1 Definitely not depressed. Facial expression and voice animated during interview.
- ☐ 2 Mild suppression of affect. Some loss of spontaneity.
- ☐ 3 Overall loss of spontaneity. Looks distinctly unhappy during parts of the interview. May still be able to smile when discussing non-threatening areas.
- ☐ 4
- ☐ 5 Moderate restriction of affect throughout most of interview. Has longer and frequent periods of looking distinctly unhappy.
- ☐ 6
- ☐ 7 Severe. Looks sad, withdrawn. Minimal verbal interaction throughout interview. Cries or may appear tearful.

16. **TEMPO OF SPEECH:**

- ☐ 1 Normal
- ☐ 2 Slow
- ☐ 3 Slow: delays interview.
- ☐ 4
- ☐ 5 Severe. Low; marked interference with interview.

17. **HYPOACTIVITY:**

- ☐ 1 None
- ☐ 2
- ☐ 3 Mild. Some body movements.
- ☐ 4
- ☐ 5 Moderate. Definite motor retardation.
- ☐ 6
- ☐ 7 Severe. Motionless throughout interview.

(DNDE)
Total of 1 - 17 _____

Evaluator's initials _____ _____ _____
First Middle Last

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Fluoxetine Versus Placebo in Childhood/Adolescent Depression
B1Y-MC-HCJE

Unscheduled Visit ____ ___ (numeric) (alpha)
Page 5 of 9

CLINICAL GLOBAL IMPRESSION: SEVERITY

INFORMATION NOT OBTAINED ☐

Considering your total clinical experience with this particular population, how mentally ill is the patient at this time?

- ☐ 1 Normal, not at all ill
- ☐ 2 Borderline ill
- ☐ 3 Mildly ill
- ☐ 4 Moderately ill
- ☐ 5 Markedly ill
- ☐ 6 Severely ill
- ☐ 7 Among the most extremely ill patients

Evaluator's initials _____ _____ _____
First Middle Last

CLINICAL GLOBAL IMPRESSION: IMPROVEMENT

INFORMATION NOT OBTAINED ☐

Rate total improvement, whether or not in your judgement it is due entirely to drug treatment. Compared to the patient's condition at Visit 1, how much has he/she changed?

- ☐ 1 Very much improved
- ☐ 2 Much improved
- ☐ 3 Minimally improved
- ☐ 4 No change
- ☐ 5 Minimally worse
- ☐ 6 Much worse
- ☐ 7 Very much worse

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Fluoxetine Versus Placebo in Childhood/Adolescent Depression
B1Y-MC-HCJE

Unscheduled Visit ____ ___ (numeric) (alpha)
Page 6 of 9

MONTGOMERY - ASBERG DEPRESSION RATING SCALE (MADRS)

INFORMATION NOT OBTAINED ☐

The rating should be based on a clinical interview moving from broadly phrased questions about symptoms to more detailed ones which allow a precise rating of severity. The rater must decide whether the rating lies on the defined scale steps (0, 2, 4, 6) or between them (1, 3, 5).

Check the box (number) that best characterizes the patient at this time

1. **APPARENT SADNESS**
   Representing despondency, gloom, and despair (more than just ordinary transient low spirits), reflected in speech, facial expression, and posture. Rate by depth and inability to brighten up.

   ☐ 0 No sadness.
   ☐ 1
   ☐ 2 Looks dispirited but does brighten up without difficulty.
   ☐ 3
   ☐ 4 Appears sad and unhappy most of the time.
   ☐ 5
   ☐ 6 Looks miserable all the time. Extremely despondent.

2. **REPORTED SADNESS**
   Represented by reports of depressed mood, regardless of whether it is reflected in appearance or not. Includes low spirits, despondency, or the feeling of being beyond help and without hope. Rate according to intensity, duration, and the extent to which the mood is reported to be influenced by events.

   ☐ 0 Occasional sadness in keeping with the circumstances.
   ☐ 1
   ☐ 2 Sad or low but brightens up without difficulty.
   ☐ 3
   ☐ 4 Pervasive feelings of sadness or gloominess. The mood is still influenced by external circumstances.
   ☐ 5
   ☐ 6 Continuous unvarying sadness, misery or despondency.

3. **INNER TENSION**
   Representing feelings of ill-defined discomfort, edginess, inner turmoil, mental tension mounting to either panic, dread, or anguish. Rate according to intensity, frequency, duration, and the extent of reassurance called for.

   ☐ 0 Placid. Only fleeting inner tension.
   ☐ 1
   ☐ 2 Occasional feelings of edginess and ill-defined discomfort.
   ☐ 3
   ☐ 4 Continuous feelings of inner tension or intermittent panic which the patient can only master with some difficulty.
   ☐ 5
   ☐ 6 Unrelenting dread or anguish. Overwhelming panic.

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Fluoxetine Versus Placebo in Childhood/Adolescent Depression
B1Y-MC-HCJE

Unscheduled Visit ____ ___ (numeric) (alpha)
Page 7 of 9

MONTGOMERY - ASBERG DEPRESSION RATING SCALE (MADRS)

4. **REDUCED SLEEP**
Representing the experience of reduced duration or depth of sleep compared to the subject's own pattern when well.

- ☐ 0 Sleeps as usual.
- ☐ 1
- ☐ 2 Slight difficulty dropping off to sleep or slightly reduced, light or fitful sleep.
- ☐ 3
- ☐ 4 Sleep reduced or broken by at least two hours.
- ☐ 5
- ☐ 6 Less than two or three hours sleep.

5. **REDUCED APPETITE**
Representing the feeling of a loss of appetite compared with when well. Rate by loss of desire for food or the need to force oneself to eat.

- ☐ 0 Normal or increased appetite
- ☐ 1
- ☐ 2 Slightly reduced appetite.
- ☐ 3
- ☐ 4 No appetite. Food is tasteless.
- ☐ 5
- ☐ 6 Needs persuasion to eat at all.

6. **CONCENTRATION DIFFICULTIES**
Representing difficulties in collecting one's thoughts mounting to incapacitating lack of concentration.

- ☐ 0 No difficulties in concentrating.
- ☐ 1
- ☐ 2 Occasional difficulties in collecting one's thoughts.
- ☐ 3
- ☐ 4 Difficulties in concentrating and sustaining thought which reduces ability to read or hold a conversation.
- ☐ 5
- ☐ 6 Unable to read or converse without great difficulty.

7. **LASSITUDE**
Representing a difficulty getting started or slowness initiating and performing everyday activities.

- ☐ 0 Hardly any difficulty in getting started. No sluggishness.
- ☐ 1
- ☐ 2 Difficulties in starting activities
- ☐ 3
- ☐ 4 Difficulties in starting simple routine activities which are carried out with effort.
- ☐ 5
- ☐ 6 Complete lassitude. Unable to do anything without help.

8. **INABILITY TO FEEL**
Representing the subjective experience of reduced interest in the surroundings, or activities that normally give pleasure. The ability to react with adequate emotion to circumstances or people is reduced.

- ☐ 0 Normal interest in the surroundings and other people.
- ☐ 1
- ☐ 2 Reduced ability to enjoy usual interests.
- ☐ 3
- ☐ 4 Loss of interest in the surroundings. Loss of feelings for friends and acquaintances.
- ☐ 5
- ☐ 6 The experience of being emotionally paralyzed, inability to feel anger, grief, or pleasure and a complete or even painful failure to feel for close relatives and friends.

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Clinical Report Form
Fluoxetine Versus Placebo in Childhood/Adolescent Depression
B1Y-MC-HCJE

Unscheduled Visit _____ ___ (numeric) (alpha)
Page 8 of 9

MONTGOMERY - ASBERG DEPRESSION RATING SCALE (MADRS)

9. **PESSIMISTIC THOUGHTS**
Representing thoughts of guilt, inferiority, self-reproach, sinfulness, remorse, and ruin

- ☐ 0 No pessimistic thoughts.
- ☐ 1
- ☐ 2 Fluctuating ideas of failure, self-reproach, or self-depreciation.
- ☐ 3
- ☐ 4 Persistent self-accusations, or definite but still rational ideas of guilt, or sin. Increasingly pessimistic about the future.
- ☐ 5
- ☐ 6 Delusions of ruin, remorse, or unredeemable sin. Self-accusations which are absurd and unshakable.

10. **SUICIDAL THOUGHTS**
Representing the feeling that life is not worth living, that a natural death would be welcome, suicidal thoughts, and preparations for suicide. Suicidal attempts should not in themselves influence the rating.

- ☐ 0 Enjoys life or takes it as it comes.
- ☐ 1
- ☐ 2 Weary of life. Only fleeting suicidal thoughts.
- ☐ 3
- ☐ 4 Probably better off dead. Suicidal thoughts are common, and suicide is considered as a possible solution, but without specific plans or intention.
- ☐ 5
- ☐ 6 Explicit plans for suicide when there is an opportunity. Active preparations for suicide.

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Fluoxetine Versus Placebo in Childhood/Adolescent Depression
B1Y-MC-HCJE

Unscheduled Visit _____ ___ (numeric) (alpha)
Page 9 of 9

COMMENTS : VISIT

NO COMMENTS ☐

Comments should address any clinical report form items that require further explanation. Repeating information from the clinical report form is discouraged.

Comment on all clinically significant lab values that are outside a clinically accepted reference range or clinically significant values that differ importantly from previous values.

If the patient is ending participation in the study at this visit, enter only comments that apply to this visit; then complete the Patient Summary and Study Summary Comments pages.

Print legibly and do not use abbreviations or symbols.

The information reported for this visit is accurate and complete.

_____ _____/_____/_____
Signature MM DD YY

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16.1.3.
List of Investigators and Other Key Individuals

B1Y-MC-HCJE Investigators and Other Key Individuals

Site Number	Principal Investigator's Name and Address	Subinvestigators and Other Key Individuals
001	[redacted]	[redacted]
002	[redacted]	[redacted]
003	[redacted]	[redacted]

B1Y-MC-HCJE Investigators and Other Key Individuals (continued)

Site Number	Principal Investigator's Name and Address	Subinvestigators and Other Key Individuals
004	[redacted]	[redacted]
005	[redacted]	[redacted]
006	[redacted]	[redacted]
008	[redacted]	[redacted]

B1Y-MC-HCJE Investigators and Other Key Individuals (continued)

Site Number	Principal Investigator's Name and Address	Subinvestigators and Other Key Individuals
009	[redacted]	[redacted]
010	[redacted]	[redacted]
011	[redacted]	[redacted]
012	[redacted]	[redacted]

B1Y-MC-HCJE Investigators and Other Key Individuals (continued)

Site Number	Principal Investigator's Name and Address	Subinvestigators and Other Key Individuals
013	[redacted]	[redacted]
015	[redacted]	[redacted]
016	[redacted]	[redacted]
165	[redacted]	

B1Y-MC-HCJE Investigators and Other Key Individuals (continued)

Site Number	Principal Investigator's Name and Address	Subinvestigators and Other Key Individuals
017	[redacted]	[redacted]
018	[redacted]	[redacted]
019	[redacted]	[redacted]
021	[redacted]	[redacted]

B1Y-MC-HCJE Investigators and Other Key Individuals (concluded)

Site Number	Principal Investigator's Name and Address	Subinvestigators and Other Key Individuals
022	[redacted]	[redacted]

16.1.4.
Signature of Investigator or Sponsor's Responsible Medical Officer

Principal or Coordinating Investigator(s) Signature(s) or Sponsor's Responsible Medical Officer

Study Title: Fluoxetine versus Placebo in Childhood/Adolescent Depression

Study Author(s): [redacted]

I have read this report and confirm that to the best of my knowledge it accurately describes the conduct and results of the study.

[redacted] 2 August 02

Investigator [redacted] Date
or Sponsor's Responsible Medical Officer

Affiliation: Eli Lilly and Company

16.1.5.
Randomization Scheme and Codes

Randomization Codes
All Randomized Patients
B1Y-MC-HCJE

Protocol: B1Y-MC-HCJE

Inv	Pat	Therapy Group
1	103	Placebo
	104	Flx20
	107	Placebo
	110	Flx20
	112	Placebo
	113	Placebo
	114	Flx20
	118	Flx20
	119	Placebo
	124	Flx20
	126	Flx20
	127	Flx20
	131	Placebo
	133	Flx20
	135	Placebo
	137	Flx20
	139	Flx20
	140	Placebo
	141	Flx20
	142	Flx20

RMP.B1YP.JCLLIB2(MIL1JEKL)
RMP.B1Y0.HCJEREP(MIL1JEKL)
XMIL0001

Randomization Codes
All Randomized Patients
B1Y-MC-HCJE

Protocol: B1Y-MC-HCJE

Inv	Pat	Therapy Group
1	143	Placebo
	149	Placebo
	150	Flx20
	151	Flx20
	153	Placebo
2	201	Placebo
	202	Flx20
	203	Placebo
	204	Flx20
	205	Placebo
	206	Placebo
	208	Flx20
	209	Placebo
	210	Placebo
3	301	Placebo
	302	Flx20
	303	Placebo
	305	Flx20
	306	Placebo
	307	Flx20

RMP.B1YP.JCLLIB2(MIL1JEKL)
RMP.B1Y0.HCJEREP(MIL1JEKL)
XMIL0001

Randomization Codes
All Randomized Patients
B1Y-MC-HCJE

Protocol: B1Y-MC-HCJE

Inv	Pat	Therapy Group
3	309	Placebo
	312	Placebo
	313	Flx20
	315	Placebo
	318	Flx20
	319	Flx20
	323	Placebo
	326	Flx20
	330	Placebo
	332	Flx20
	334	Flx20
	335	Placebo
	336	Placebo
	339	Placebo
	343	Placebo
	346	Flx20
	350	Placebo
	352	Placebo
	353	Flx20
	354	Flx20

RMP.B1YP.JCLLIB2(MIL1JEKL)
RMP.B1Y0.HCJEREP(MIL1JEKL)
XMIL0001

Randomization Codes
All Randomized Patients
B1Y-MC-HCJE

Protocol: B1Y-MC-HCJE

Inv	Pat	Therapy Group
3	355	Flx20
	356	Placebo
4	401	Flx20
	403	Placebo
	404	Flx20
	407	Placebo
	408	Flx20
	412	Placebo
	413	Flx20
	415	Flx20
	416	Flx20
	417	Placebo
	419	Flx20
	422	Flx20
	424	Flx20
	425	Placebo
	427	Placebo
	432	Placebo
	433	Flx20
	441	Flx20

RMP.B1YP.JCLLIB2(MIL1JEKL)
RMP.B1Y0.HCJEREP(MIL1JEKL)
XMIL0001

Randomization Codes
All Randomized Patients
B1Y-MC-HCJE

Protocol: B1Y-MC-HCJE

Inv	Pat	Therapy Group
6	601	Placebo
8	804	Placebo
	806	Placebo
	807	Placebo
	808	Placebo
	809	Placebo
	810	Flx20
	811	Flx20
	812	Flx20
	813	Flx20
	814	Flx20
	815	Flx20
9	901	Flx20
	905	Placebo
	906	Flx20
	911	Placebo
	912	Placebo
	913	Flx20
	915	Flx20
	916	Placebo

RMP.B1YP.JCLLIB2(MIL1JEKL)
RMP.B1Y0.HCJEREP(MIL1JEKL)
XMIL0001

Randomization Codes
All Randomized Patients
B1Y-MC-HCJE

Protocol: B1Y-MC-HCJE

Inv	Pat	Therapy Group
9	919	Placebo
	920	Flx20
11	1101	Flx20
	1102	Placebo
	1105	Placebo
	1107	Placebo
	1109	Flx20
	1118	Flx20
	1120	Placebo
	1121	Placebo
	1122	Placebo
	1126	Placebo
	1129	Flx20
	1131	Flx20
	1134	Placebo
	1135	Placebo
	1137	Flx20
	1138	Placebo
	1139	Placebo
	1141	Flx20

RMP.B1YP.JCLLIB2(MIL1JEKL)
RMP.B1Y0.HCJEREP(MIL1JEKL)
XMIL0001

Randomization Codes
All Randomized Patients
B1Y-MC-HCJE

Protocol: B1Y-MC-HCJE

Inv	Pat	Therapy Group
11	1143	Placebo
	1144	Placebo
	1152	Flx20
	1153	Flx20
	1156	Flx20
12	1201	Placebo
	1202	Flx20
	1203	Flx20
	1204	Flx20
	1205	Flx20
	1206	Placebo
	1207	Placebo
	1208	Flx20
	1209	Flx20
	1211	Flx20
	1212	Placebo
	1213	Flx20
	1215	Flx20
	1216	Placebo
	1217	Flx20

RMP.B1YP.JCLLIB2(MIL1JEKL)
RMP.B1Y0.HCJEREP(MIL1JEKL)
XMIL0001

Randomization Codes
All Randomized Patients
B1Y-MC-HCJE

Protocol: B1Y-MC-HCJE

Inv	Pat	Therapy Group
12	1220	Flx20
	1221	Placebo
	1222	Placebo
	1223	Placebo
	1225	Flx20
13	1301	Placebo
	1303	Placebo
	1304	Placebo
	1305	Flx20
	1307	Placebo
	1308	Placebo
	1309	Placebo
	1310	Placebo
	1311	Placebo
15	1501	Placebo
	1503	Flx20
	1504	Placebo
	1506	Placebo
	1510	Flx20
	1513	Placebo

RMP.B1YP.JCLLIB2(MIL1JEKL)
RMP.B1Y0.HCJEREP(MIL1JEKL)
XMIL0001

Randomization Codes
All Randomized Patients
B1Y-MC-HCJE

Protocol: B1Y-MC-HCJE

Inv	Pat	Therapy Group
15	1514	Flx20
	1515	Flx20
	1516	Flx20
16	1601	Flx20
	1602	Flx20
	1603	Flx20
	1604	Flx20
	1605	Flx20
	1606	Flx20
	1608	Placebo
	1609	Flx20
	1612	Flx20
	1651	Placebo
	1652	Flx20
	1653	Placebo
	1654	Flx20
	1655	Placebo
	1656	Placebo
	1657	Placebo
	1658	Flx20

RMP.B1YP.JCLLIB2(MIL1JEKL)
RMP.B1Y0.HCJEREP(MIL1JEKL)
XMIL0001

Randomization Codes
All Randomized Patients
B1Y-MC-HCJE

Protocol: B1Y-MC-HCJE

Inv	Pat	Therapy Group
16	1659	Flx20
	1667	Flx20
	1669	Placebo
17	1701	Flx20
	1702	Flx20
	1705	Placebo
	1707	Placebo
19	1901	Placebo
	1903	Placebo
	1904	Flx20
	1905	Flx20
	1906	Flx20
	1907	Placebo
	1913	Placebo
	1914	Placebo
	1915	Flx20
	1918	Placebo
	1919	Flx20
	1921	Flx20
	1924	Flx20

RMP.B1YP.JCLLIB2(MIL1JEKL)
RMP.B1Y0.HCJEREP(MIL1JEKL)
XMIL0001

Randomization Codes
All Randomized Patients
B1Y-MC-HCJE

Protocol: B1Y-MC-HCJE

Inv	Pat	Therapy Group
19	1925	Placebo
	1927	Placebo
22	2201	Placebo
	2202	Flx20
	2203	Placebo
	2204	Flx20
	2205	Flx20
	2206	Placebo
	2207	Placebo
	2208	Flx20
	2210	Placebo
	2212	Placebo
	2213	Placebo
	2214	Flx20
	2216	Flx20
	2217	Placebo
	2218	Placebo
	2220	Flx20
	2221	Placebo

RMP.B1YP.JCLLIB2(MIL1JEKL)
RMP.B1Y0.HCJEREP(MIL1JEKL)
XMIL0001

16.1.6.
Documentation of Statistical Methods

B1Y-MC-HCJE STATISTICAL ANALYSIS PLAN

General Considerations

The total number of randomized patients to be included in this study is approximately 220 patients or 110 patients per arm. The distribution of patients across investigators is expected to be approximately equal. Investigators who enroll no patients into one or more treatment groups will be pooled together for the purpose of statistical analyses when assessing treatment-by-investigator interactions.

All tests of hypotheses will be considered statistically significant if the two-sided p-value is less than 0.05. All total and subtotal scores from rating scales will be derived from individual items. If any of the individual items are missing, the total or subtotal will be treated as missing.

Additional exploratory analyses of the data will be conducted as deemed appropriate.

Data to be Analyzed

Analyses will be done on an intent-to-treat basis unless otherwise specified. An intent-to-treat analysis is an analysis of data by the groups to which patients are assigned by random allocation, even if the patient does not take the assigned treatment, does not receive the correct treatment, or otherwise does not follow the protocol. Patients who have their dose reduced to 10 mg during the study will be included in all analyses as if they remained on 20 mg. (A summary of the number of patients who do have their dose reduced to 10 mg will be provided.)

All patients with a randomization (Visit 4) and at least one postrandomization visit will be included in the analyses of efficacy from Study Periods III through V. All randomly assigned patients will be included in the analyses of safety data from Study Periods III through V. All patients with a Study Period VI baseline visit (Visit S: visit at which rerandomized treatment will begin, both investigators and patients are blinded to the actual timing of the switch to new treatment) and at least one visit beyond baseline will be included in the analyses of efficacy from Study Period VI. All patients remaining in the Study Period VI at Visit S will be included in the analyses of safety from Study Period VI.

Patient Disposition

The reasons for discontinuation during this study will be summarized across all study periods. Reasons for discontinuation will be compared between treatment groups using Pearson's chi-square test for Study Periods III through IV and Study Periods III through V.

Patient Characteristics

Patient characteristics of age, age category (children and adolescents), gender, origin, height and weight will be compared between treatment groups. Means will be compared between the treatment groups using ANOVA with treatment in the model. Percentages will be compared using Pearson's chi-square test. Since randomization will be stratified by gender and age category (children/adolescents), no differences between age and gender are expected. Should there be a difference in any characteristic on random assignment to the treatment period, analysis of covariance will be performed for the primary efficacy measure to check the robustness of the results, but will be considered as a secondary analysis.

Psychiatric History

Psychiatric history and family history will be summarized for each treatment group for all randomized patients. Percentages will be compared between treatment groups using Pearson's chi-square test and means will be compared between groups using an ANOVA with treatment in the model.

Previous Treatment Current Episode

The use of previous treatments for the current episode of illness will be compared between treatment groups using Pearson's chi-square test.

Concomitant Medications

Concomitant medication use will be compared between treatment groups using Pearson's chi-square test.

Compliance

The percentage of compliant patients for each treatment group will be summarized by visit.

Baseline Psychiatric Evaluation

Baseline scores (Visit 4) for the CDRS-R total, CGI-Severity, MADRS, CDI, BDI, and HAMA total scales will be compared between treatment groups using ANOVA with treatment in the model.

Habits

The percentage of patients who smoke, use tobacco, drink alcohol, and use caffeine will be compared between treatment groups using Pearson's chi-square test.

Efficacy Analyses

The primary efficacy measure will be the CDRS-R. Secondary efficacy measures include the CGI-Severity, CGI-Improvement, MADRS, CDI, BDI, HAMA, GAF, and K-SADS.

Acute Treatment (Study Periods III-V)

CDRS-R response rates will be compared between fluoxetine 20 mg and placebo as the primary analysis for the acute treatment periods. A CDRS-R responder for this analysis will be defined as a patient whose CDRS-R total score decreased at least 30% from baseline (Visit 4) to the endpoint of Study Period IV (last of Visits 6-Visit 10). As a secondary analysis, CDRS-R response rates will be compared between fluoxetine 20 to 60 mg and placebo (endpoint defined as the last of Visits 6-15).

The above analyses include only patients treated at least one week with 20 mg (2 weeks total). Change in the CDRS-R score from baseline (Visit 4) to Study Periods III through IV endpoint (last measurement from Visits 5 through 10) and from baseline to Study Periods III through V endpoint (last measurement from Visits 5 through Visit 15) will be compared between fluoxetine and placebo as secondary efficacy analyses.

Change in CDRS-R scores from baseline (Visit 4) to each subsequent visit (Visits 5 through Visit 15) will be compared between treatment groups as additional secondary analyses on the CDRS-R score. The by-visit analyses will be performed 1) by including only patients active in the study at the visit of interest and 2) by including all patients with at least one postrandomization measure using a last-observation-carried-forward approach. A repeated measures analysis on the CDRS-R score will also be performed as a secondary analysis.

A CDRS-R remitter will be defined as a patient who has an endpoint CDRS-R score ≤28. CDRS-R remission rates (using both the Study Period IV endpoint and Study Periods IV through V endpoint) will be compared between treatment groups and will include only those patients treated at least 1 week with 20 mg (2 weeks total).

Analyses on change from baseline (Visit 4) to Study Periods III through IV endpoint (last measurement from Visits 5 through 10) and Study Periods III through V endpoint (last of measurement from Visit 5 through Visit 15) will be performed for the following secondary efficacy measures:

- CDRS-R Mood Subtotal – sum of Items 8, 11, 14, 15
- CDRS-R Somatic Subtotal – sum of Items 4, 5, 6, 7, 16, 17
- CDRS-R Subjective Subtotal – sum of Items 9, 10, 12, 13
- CDRS-R Behavior Subtotal – sum of Items 1, 2, 3
- CGI-Severity

- MADRS Total
- CDI Total
- BDI Total
- HAMA Total
- GAF

CGI-Improvement endpoint scores will be compared between treatment groups for both the Study Periods III through IV endpoint (last measurement from Visits 5 through 10) and the Study Periods III through V endpoint (last of measurement from Visit 5 through Visit 15). Since this scale inherently measures total improvement in direct comparison to the patient's condition at enrollment, endpoint is analyzed instead of change scores. CGI-defined response rates will also be compared between treatment groups. A CGI responder will be defined as a patient whose endpoint CGI-improvement score was 1 or 2. All patients with at least one postrandomization measure will be included in the analysis.

The percentage of patients with a diagnosis of depression using the K-SADS will be compared between treatment groups at Study Periods III through IV endpoint (last measurement from Visits 5 through 10) and Study Periods III through V endpoint (last of measurement from Visit 5 through Visit 15).

To address the clinical question of whether nonresponders to fluoxetine 20 mg for 8 weeks would respond if the dosage was increased to 40-60 mg or maintained at 20 mg for a longer period of time, CDRS-R response rates will be compared between the nonresponders randomized to fluoxetine 20 mg and the nonresponders randomized to fluoxetine 40-60 mg (using Visit 4 as baseline). In addition, mean change in the CDRS-R, CGI-Severity, CDI, and BDI from the Study Period V baseline (Visit 10) to the Study Period V endpoint (last of Visits 11 through Visit 15) and endpoint CGI-Improvement will be compared.

Fisher's exact test will be used to compare percentages. An ANOVA (Type III sums of squares) with the term treatment in the model will be used when comparing change scores or endpoint scores between treatments. Logistic regression and ANOVA models with treatment, investigator, and the treatment-by-investigator interaction will also be used to compare percentages and mean scores, respectively, but will be considered secondary. If the treatment-by-investigator interaction effect is not statistically significant at the 0.10 level, the interaction effect will be excluded from the model and the analysis will be based on the reduced model.

For the repeated measures analysis of variance, the dependent variable will be the baseline and postbaseline CDRS-R total scores. The independent factors will consist of treatment, investigator, treatment-by-investigator interaction, visit, and treatment-by visit interaction. If the treatment-by-investigator interaction is not statistically significant at

level 0.10, this interaction effect will be excluded from the model. All main effects and interaction tests will be made using the approximate F test reported by SAS PROC MIXED. An unstructured covariance matrix will be used.

Relapse Prevention Phase (Study Period VI)

Time to relapse during the relapse prevention phase will be compared between fluoxetine (10-60 mg) and placebo. A relapser will be defined as a patient whose CDRS-R score increased to over 40 at any one time during the relapse prevention phase in the presence of a history of 2 weeks of clinical deterioration as determined by patient report, parent report, or clinical history. If the physician feels patients have experienced relapse sufficient enough to discontinue the patient from the study but have not met criteria for relapse, the patient will also be considered a relapser for the primary analysis of relapse. As a secondary analysis of relapse, only those patients meeting the protocol-defined criteria will be considered a relapser. Time to relapse will be analyzed using Kaplan-Meier survival curves (log-rank test).

Change in CDRS-R, CGI-Severity, MADRS, CDI, BDI, HAMA, and GAF scores from baseline (Visit S) to each visit during the relapse prevention therapy phase (Visits S through 26), and CGI-Improvement scores will be summarized between fluoxetine and placebo by 1) including only patients active in the study at the visit of interest and 2) by including all patients with at least one measure beyond Visit 17 using a last-observation-carried-forward approach. The percentage of patients with a diagnosis of depression using the K-SADS will also be summarized at Study Period VI endpoint (last measurement from Visits S through 26).

Safety Analyses

Acute Treatment (Study Periods III-IV)

Length of exposure will be summarized by treatment group. Exposure will be defined as the last dose date minus the first dose date.

Adverse events will be analyzed by comparing the incidence of treatment-emergent adverse events between treatment groups during Study Period III through IV and again for Study Period III through V using Study Periods I and II as baseline for the spontaneously collected adverse events. Treatment-emergent solicited adverse events will be compared between treatments using Study Period II as baseline for events collected by the Side Effect Checklist. (The Side Effect Checklist is not collected during Study Period I.) An event is considered treatment-emergent if it first occurs or worsens from baseline.

To compare the impact of titration to 40-60 mg, the incidence of treatment-emergent and treatment-emergent solicited adverse events during Study Period V will be compared between the nonresponders randomized to fluoxetine 20 mg and the nonresponders

randomized to fluoxetine 40-60 mg. As a supplemental analysis to assess longer-term events, the incidence of treatment-emergent and treatment-emergent solicited adverse events during Study Period V will be compared between treatments (fluoxetine arms pooled versus placebo). Study Periods I through IV will be used as baseline for these analyses.

Change from baseline (last measurement from Visits 1 through 4) to Study Period III through V endpoint (last measurement from Visits 5 through Visit 15) in vital signs, continuous laboratory analytes, and ECG values (heart rate, RR interval, PR interval, QRS interval, QT interval, and QTc interval) will be compared between treatment groups. Note that since laboratory analytes and ECGs will not be collected routinely at Visits 2 through Visit 14, baseline values will be those collected at Visit 1 and endpoint values will be those collected at Visit 15 or the visit of discontinuation if discontinued prior to Visit 15 for most, if not all patients. The incidence of treatment-emergent extreme values (using [redacted] Reference Ranges or FDA specified reference ranges) during Study Period III through V will also be compared between treatments for continuous laboratory analytes. Specifically, percentages of patients whose values changed from normal or low during Study Period I and II to high at any time during Study Period III through V will be compared between treatment groups among patients with normal or low values during Study Period I and II. Similarly, percentages of patients whose values changed from normal or high during Study Period I and II to low at any time during Study Period III through V will be compared between treatment groups for categorical laboratory analytes. For non-numeric laboratory analytes, the percentages of patients whose values changed from normal during Study Periods I and II to abnormal at anytime during Study Period III through V will be compared between treatment groups among patients with normal values during Study Period I and II. The proportion of patients with normal and abnormal ECGs at baseline (last from Visits 1 through 4) and endpoint (last from Visits 5 through 15) will also be presented.

As supplemental analyses for longer-term data, vital signs, laboratories, and ECG values will be analyzed for patient in Study Period V (fluoxetine arms pooled versus placebo). Change from baseline (last measurement from Visits 1 through 10) to Study Period V endpoint (last measurement from Visits 11 through Visit 15) in vital signs, continuous laboratory analytes, and ECG values will be compared between treatment groups. The incidence of treatment-emergent extreme values (using [redacted] Reference Ranges) during Study Period V will also be compared between treatments for continuous laboratory analytes. Specifically, percentages of patients whose values changed from normal or low during Study Period I through IV to high at any time during Study Period V will be compared between treatment groups among patients with normal or low values during Study Period I through IV. Similarly, percentages of patients whose values changed from normal or high during Study Period I through IV to low at any time during Study Period V will be compared between treatment groups for categorical laboratory analytes. For non-numeric laboratory analytes, the percentages of patients whose values changed from normal during Study Periods I through IV to abnormal at anytime during

Study Period V will be compared between treatment groups among patients with normal values during Study Period I through IV. The proportion of patients with normal and abnormal ECGs at baseline (last from Visits 1 through 4) and endpoint (last from Visits 11 through 15) will also be presented.

Fisher's exact test will be used to compare percentages. An ANOVA (Type III sums of squares) with the term treatment in the model will be used when comparing change scores or endpoint scores between treatments.

Relapse Prevention Phase (Study Period VI)

Adverse events will be analyzed by comparing the incidence of treatment-emergent adverse events between treatment groups during Study Period VI (after Visit S) using Study Periods I through V (and up through Visit S) as baseline for the spontaneously collected adverse events. Treatment-emergent solicited adverse events during Study Period VI (after Visit S) will be compared between treatments using Study Period II through V (and up through Visit S) as baseline for events collected by the Side Effect Checklist. (The Side Effect Checklist is not collected during Study Period I.) Fisher's exact test will be used to compare the percentages.

Subgroup Analyses

Efficacy analyses of the CDRS-R total score (response and mean change from baseline to endpoint), CGI-Improvement response rates, treatment-emergent adverse events, and treatment-emergent solicited adverse events will be performed for children and adolescents separately, males and females separately, and for children with a family history of depression. To test for a treatment-by-subgroup interaction on mean change, an ANOVA with treatment, subgroup, and the treatment-by-subgroup interaction in the model may also be performed. For response and possibly specific adverse events of interest, a Breslow-Day test for the homogeneity of odds ratios across subgroups may also be performed. Tests of interaction and homogeneity of odds ratios will be tested at the 0.10 significance level.

Interim Analyses

One interim analysis is planned. The interim analysis will take place after all patients complete Study Period V (Visit 15). The interim analysis will be conducted in order to obtain and communicate the results from the acute treatment phase in a more timely manner. The results from the acute treatment unblinded at the treatment level may be presented outside the company including to regulatory agencies. Additional interim analyses may take place after all patients complete Study Period IV (Visit 10) and/or after all patients complete Visit 13 (2 weeks with doses up to 60 mg). These interim analyses will only take place if results are needed for decision-making purposes prior to the expected completion of the study. The study will not be stopped if evidence of efficacy is observed, thus adjustment of p-values is not required. To minimize the bias for the

relapse prevention therapy phase, no one at the study site will be unblinded at the patient level.

Planned interim analyses, and any unplanned interim analyses, will be conducted under the auspices of the data monitoring board assigned to this study. Only the data monitoring board is authorized to review completely unblinded interim efficacy and safety analyses and, if necessary, to disseminate those results. The data monitoring board will disseminate interim results in a manner that will minimize bias. Study sites will not receive information about interim results unless they need to know for the safety of their patients.

Pharmacokinetic/Pharmacodynamic Analyses

A formal pharmacokinetic analysis of the plasma concentration data is not planned because each patient will only provide a maximum of 4 blood samples. Baseline fluoxetine serum concentrations will be assayed. Fluoxetine, norfluoxetine, and other antidepressants and their metabolites must be nondetectable by urine screen at baseline for inclusion into the study. Steady-state serum concentrations of fluoxetine and norfluoxetine will be collected. The steady-state plasma concentration data will be used to characterize the degree of exposure to fluoxetine and norfluoxetine and to account for similarities and differences in steady-state concentrations compared to adult patients given the same dosage. Pharmacokinetic data will be presented using descriptive and graphical analyses.

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16.1.7.
Publications Based on the Study

There have been no publications based on this study, as of 4 August 2000.

16.1.8.
Important Publications Referenced in the Report

Depressive Symptoms by Self-Report in Adolescence: Phase I of the Development of a Questionnaire for Depression by Self-Report

Graham J. Emslie, MD; Warren A. Weinberg, MD; A. John Rush, MD; Richard M. Adams, MD; Jeanne W. Rintelmann, BA

Abstract

As the first step in validating a criteria-based, self-report depression questionnaire specifically for children and adolescents and to determine the prevalence of self-reported depressive symptoms, we studied 3,294 high school students of mixed ethnic background in a large urban school district. They completed the Weinberg Screening Affective Scale. The 21-item Beck Depression Inventory was also completed to allow comparison with a previous study. The prevalence of clinically significant depressive symptoms suggesting depression by self-report ranged from 18% on the Beck Depression Inventory to 13% on the Weinberg Screening Affective Scale. Hispanic females had the highest scores, while white males had the lowest. Being behind in school, female, and nonwhite predicted more self-reported depressive symptoms. (*J Child Neurol* 1989;3:114-121).

Adolescent depression and suicide are major mental health problems. Depression with or without learning disabilities is a common cause of school failure in normally intelligent young people.[1-3] In addition, school failure and school dropout are significant problems.[4] Depression is an identifiable condition that meets established systematic criteria. Recognition that affective illness is a cause of poor school performance requires systematic evaluation utilizing established criteria for depression, eg, *Diagnostic and Statistical Manual of Mental Disorders*, ed 3 (*DSM-III*),[5] Feighner et al,[6] Research Diagnostic Centers (RDC),[7] Weinberg et al[1] and Poznanski et al.[8] The Weinberg and Poznanski groups' criteria were developed specifically for school-aged populations. Useful adjuncts to clinical interviews are self-report measures.[9-11] However most self-report instruments are scored using cutoff scores and do not take into account the need for the presence of a cluster of symptoms to make a diagnosis of depression. There are no validated criteria-based questionnaires for depression specific to children and adolescents.

This study was undertaken as the first step in ongoing research into the Weinberg Screening Affective Scale,[12] a self-report questionnaire based on established criteria for depression in children and adolescents. Additionally the Beck Depression Inventory[13] was used to allow comparison with a previous study of a different population of high school students.[14] This paper will present preliminary data on (1) prevalence of self-reported depressive symptoms in a large sample of urban adolescents of mixed ethnic background by both instruments, (2) the demographic characteristics of adolescents self-reporting depressive symptoms, (3) the relationship between the two self-report measures of depressive

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From the Departments of Psychiatry (Dr Emslie, Dr Rush, and Ms Rintelmann) and Neurology (Dr Weinberg), University of Texas Southwestern Medical Center at Dallas and Dallas Independent School District Health Services (Dr Adams), Dallas, TX.

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Address correspondence to Dr Emslie, Department of Psychiatry, University of Texas Southwestern Medical Center at Dallas, 5323 Harry Hines Boulevard, Dallas, TX 75235.

symptoms in adolescents, and (4) whether different depressive symptoms differentiated depressed from nondepressed adolescents in various ethnic groups.

Kaplan et al[14] reported on 385 high school students and found that 8.6% scored in the moderate to severe range (16 or higher) on the Beck Depression Inventory. This population was 71% white and 22% black. They found no significant gender differences in scores when age and social class were controlled. Kandel and Davies[15] administered a 6-item self-report inventory to 4,204 adolescents ages 13 to 19 years. In this study, there were no age or socioeconomic status differences, but females scored higher than males. In a study by Schoenbach et al[16] of 624 junior high students completing the Center for Epidemiological Studies Depression Scale (CES-D), overall persistent symptoms were reported more often by blacks than by whites, with black males being predominant in the high-scoring group.

Little information is available on mental health problems specific to Hispanic adolescents. Langner et al[17] studied 1,034 children aged 6 to 18 years selected from a cross-section of Manhattan households, 29% of which were Spanish speaking. Hispanic and black groups evidenced more behavioral difficulties than whites. In a study by Canino et al[18] comparing referred black and Hispanic children and adolescents in Manhattan with regard to 22 common mental health symptoms, Hispanics reported significantly more depression, sadness, and anxiety symptoms. Hoppe and Martin[19] compared patterns of suicide among Hispanics and non-Hispanics in Texas over a 20-year period (1960 to 1980). In the 15- to 24-year age group, an increase in suicide rates in both male and female Hispanics were noted. However, this increase was less than that for non-Hispanics.

Methods

We studied 3,294 high school students in a large metropolitan school district who were beginning the mental health section of their Health Education class. Health Education is a required course for one semester and is usually taken in the 10th grade, with about half the students taking it each semester. In the summer prior to the fall semester, we met with all the health education teachers in the district. The project was explained and the specific instructions to students for teachers was reviewed. Each high school principal sent a letter to the parents of adolescents enrolled in Health Education to explain the study and to request return notification if they did not want their child to participate. During the third week of the school year, the precoded questionnaires were sent in packets to each Health Education teacher for each class and then picked up 1 week later. Twenty-three of the 25 high schools in the district participated.

The timing of the study was chosen so that results would not be influenced by reports of grades, ie, it was done 1 to 2 weeks before the first marking period. The study was performed at the beginning of the mental health section of the Health Education classes so that the results would not be influenced by having spent several weeks talking about mental health issues. All students present in class on the day the questionnaire was handed out were given a form. Specific instructions were read by the teacher to the students, and the students were told their participation was voluntary.

The sample constituted 89% of those students enrolled in Health Education classes by school records. Of those students participating, 98% completed more than 90% of the questions on both forms. The sample was representative of the total high school population with regard to sex (50.7% male) and race: 1,825 or 55.4% were black, 783 or 23.8% were white, 599 or 18.2% were Hispanic, and 86 or 2.6% were "other," including Asian, American Indian, and Oriental. The mean age for the sample was 15.7 years (SD, 1.1; range, 13 to 20 years), with the median and modal grade being the 10th grade.

Measures

The two self-report measures of depressive symptoms used were: the 21-item Beck Depression Inventory[13] and the Weinberg Screening Affective Scale.[1,12]

The Beck Depression Inventory is a widely used, well-studied clinical and research measure of depressive symptoms. It has been utilized in adult and adolescent populations. It consists of 21 questions with four choices of answers giving scores of 0 to 3 for each item and a possible total score of 0 to 63. Cutoff scores used in previous studies that included adolescents for total Beck Depression Inventory score are 0 to 9, nondepressed; 10 to 15, mild depression; 16 to 23, moderate depression; 24+, severe depression. A total Beck Depression Inventory score of 16+ has been validated to be a cutoff score for major depressive disorder in adults,[20] college students,[21] and adolescents.[22]

In addition, the above cutoff scores were used to allow direct comparison with a similar study in a different adolescent population.[14] Recently, the use of the Beck Depression Inventory was reviewed by Kendall et al.[23] They clarified the use of the Beck Depression Inventory for syndromal assessment.

Those with Beck Depression Inventory scores of 16 or greater, when interviewed, comprise the following: those who do not meet criteria for depression, termed "dysphoric"; those meeting criteria for depression; and those with other predominant medical or psychiatric disorders, ie, a secondary depression.

The Weinberg Screening Affective Scale[1,11,12] consists of 55 statements that require yes or no responses and a 4th-grade reading level. Fifty of the 55 questions directly relate to the Weinberg Criteria for Depression[1] and the Bellevue Index of Depression.[24,25] The Weinberg Screening Affective Scale was used to assess whether by self-report the child or adolescent fulfilled an established set of criteria for the diagnosis of depressive syndrome. The Weinberg Criteria were developed specifically for school-age children and contain 10 major symptom categories.

Two categories are deemed essential (depressed mood and self-deprecatory ideation). The eight remaining categories are agitation, sleep disturbance, change in school performance, decreased socialization, change in attitude towards school, somatic complaints, decreased energy, and change in appetite or weight. For each symptom category, specific definitions and behaviors are delineated. The total number of items for the 10 categories is 40. Subsequently, the original 40 items (symptoms and behaviors) were developed by Petti into the Bellevue Index of Depression and were validated in hospitalized child psychiatry patients.[24] The Weinberg Criteria for Depression initially required the presence of the two essential categories (depressed mood and self-deprecatory ideation) plus two of the eight additional symptom categories. Petti found that 20 positive responses of the original 40 items by interview were diagnostic for depression.

Comparisons of the original criteria and other criteria for depression have been made.[8,26] In clinical populations, a requirement of two essential symptom categories plus four of the eight additional categories correlated better with major depression as defined by *DSM-III* in children and adolescents than did the previous method of requiring only two of the eight additional symptom categories.[27]

The Weinberg Screening Affective Scale is a self-report form that asks questions parallel to the Bellevue Index of Depression and Weinberg Criteria. There are more than 40 questions because some individual symptoms or behaviors previously published are asked with more than one question. The Weinberg Screening Affective Scale form consists of four to eight questions in each of the 10 major symptom categories. For this study, the Weinberg Screening Affective Scale was scored both as a total score and as a self-report criterion measure. A subject was scored as depressed if they met a diagnostic criteria of two essential symptoms (depressed mood and self-deprecatory ideation) plus at least four of the eight additional symptom categories. For a given symptom category to be scored positive, at least two of the self-report questions relevant to that symptom had to be answered in the affirmative, and the subject had to respond "yes" to the statement, "My answers are how I have been feeling most of the time."

Results

According to the Beck Depression Inventory, 597/3,294 (18.1%) of the students scored in the moderate to severe range (score of 16+), while 743/3,294 (22.6%) scored in the mild depressive range (10 to 15) (see Table 1). Significantly more females (368/1,624 or 22.7%) than males (229/1,670 or 13.7%) fell into the moderate to severe range ($\chi^2 = 43.8$, $P < .001$). Within the three major ethnic groups, Hispanic females had the highest proportion in the moderate to severe range (96/308 or 31.2%), while white males had the lowest representation (36/418 or 8.6%); ($\chi^2 = 59.1$, $P = .001$). The group comprising Asian, American Indian, and Oriental students was too small for meaningful comparisons.

Table 2 shows the results with the Weinberg Screening Affective Scale. Criteria for depressive syndrome by self-report as defined above were met by 440/3,294 (13.4%) of subjects. Hispanic females again evidenced the highest percentage with depression (69/308 or 22.4%), while white males had the lowest percentage (33/418 or 7.9%). Although proportionally more Hispanic females reported themselves as depressed than black females (22.4% *v* 17.5%), this was not significantly different ($\chi^2 = 0.3$, $P = .56$).

In combining males and females (Table 3), blacks and Hispanics had significantly more depression on both the Beck Depression Inventory and the Weinberg Screening Affective Scale than whites ($P < .01$).

To ascertain whether demographic factors differentiated depressed from nondepressed subjects, a stepwise discriminant function analysis was conducted. Variables included age, sex, race, and being behind in school (age minus grade). The factors that differentiated those who were depressed on the Beck Depression Inventory from the rest were, in order: behind in school, female, and nonwhite. These same three variables also discriminated the Weinberg Screening Affective Scale positive and negative

TABLE 1
Gender Differences of Levels of Depressive Symptoms on Beck Depression Inventory by Ethnic Group

	Beck Depression Inventory Scores*				
Race	≤ 9, % (n = 1,954)	10–15, % (n = 743)	≥ 16, % (n = 597)	χ^2	P
Black (N = 1,826)					
Female	49.9	28.4	21.7†		
Male	64.7	21.8	13.6	42.5	< .001
White (N = 783)					
Female	62.7	21.4	15.9†		
Male	76.8	14.6	8.6	19.12	< .00007
Hispanic (N = 599)					
Female	44.8	24.0	31.2†		
Male	63.2	17.9	18.9	21.08	< .00002
Other (N = 86)					
Female	43.6	15.4	41.0		
Male	40.4	29.8	29.8	3.18	< .204
Total (N = 3,294)					
Female	51.7	25.7	22.7†		
Male	66.8	19.5	13.7	81.87	< .001

* ≤ 9 = not depressed; 10–15 = mild depression, ≥ 16 = moderate to severe depression.
† Significantly more depression in females than males in designated ethnic group ($P < .05$).

TABLE 2
Gender Differences of Depression on Weinberg Screening Affective Scale by Ethnic Group

Race	% Depressed	χ^2	P
Black (N = 1,826)			
Female (n = 912)	17.5*	18.19	.00001
Male (n = 914)	10.5		
White (N = 783)			
Female (n = 365)	9.6*	.51	.476
Male (n = 418)	7.9		
Hispanic (N = 599)			
Female (n = 308)	22.4*	10.51	.001
Male (n = 291)	12.0		
Other (N = 86)			
Female (n = 47)	18.0	.35	.556
Male (n = 39)	10.6		
Total (N = 3,294)			
Female (n = 1,624)	16.7*	30.12	.001
Male (n = 1,670)	10.1		

* Significantly more depression in females than males in designated ethnic groups ($P < .05$).

TABLE 3
Prevalence of Depression by Ethnic Group

Race	BDI, %	WSAS, %
Black (n = 1,826)	17.6	14.0
White (n = 783)	12.0	8.7
Hispanic (n = 599)	25.2	17.4
Other (n = 86)	34.9	14.0

BDI = Beck Depression Inventory; WSAS = Weinberg Screening Affective Scale.

groups. However, for both analyses, only 2% of the variance was accounted for by those three variables.

Figure 1 demonstrates there was a large number of subjects who were positive only on one of the measures. However, the group that was positive for depression on both measures had the highest scores on both measures (Table 4). The mean total Beck Depression Inventory score for the group positive only on that scale was 22.3 (SD = 6.4) compared to the Beck Depression Inventory total score in the group positive on both measures of 26.2 (SD = 7.8) ($t = 6.6$, $df = 595$, $P < .001$). The mean total Weinberg

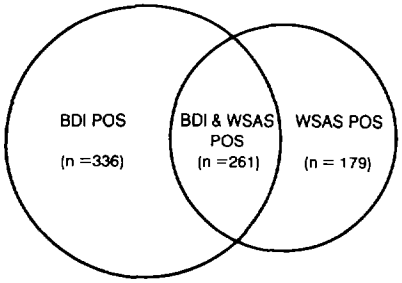

FIGURE 1
Number of students meeting criteria for depression by Beck Depression Inventory (BDI) and/or Weinberg Screening Affective Scale (WSAS). Of 776 students, 336 were positive (POS) for depression on BDI only, 179 were positive for depression on WSAS only, and 261 had positive scores on both tests.

Screening Affective Scale score in the group positive only on that scale was 21.8 (SD = 4.3) compared to 25.7 (SD = 5.7) in the group positive on both scales (t = 8.2, df = 438, $P < .001$).

Finally, we were interested to know if different symptoms would differentiate depressed from nondepressed adolescents in different ethnic groups. Table 5 lists the top 10 Beck Depression Inventory symptoms for whites using a stepwise discriminant function analysis that predicted those subjects whose Beck Depression Inventory scores were ≥ 16. Similarly, Table 6 lists the Weinberg Screening Affective Scale symptoms that differentiated depressed from nondepressed in a similar analysis.

On the Beck Depression Inventory, while statements relating to self-dislike, for example "I am disgusted with myself," was the first symptom in whites and Hispanics, it was not significantly discriminatory in blacks. Unattractiveness was less meaningful in Hispanics than in both whites and blacks. Withdrawal and crying discriminated depressed from nondepressed blacks and Hispanics but not whites. Self-accusation was ranked fairly high in Hispanics but not in the other two major groups. The top 10 symptoms in blacks, whites and Hispanics accounted for 63%, 65%, and 69% of the variance, respectively, and little more was gained by additional symptoms

On the Weinberg Screening Affective Scale, the statement "I am lonely too much of the time" discriminated depressed and nondepressed whites but not blacks or Hispanics. The statements "My friends don't like me anymore," "It seems like some part of my body always hurts me," and "This is not a good world," discriminated depressed and nondepressed blacks but not whites or Hispanics. "I have many bad moods," and "School makes me feel sick," discriminated depressed and nondepressed Hispanics but not whites and blacks. The first 10 symptoms on the Weinberg Screening Affective Scale in blacks, whites and Hispanics accounted for 44%, 47%, and 53% of variance, respectively. The total variance accounted for by all variables included were 51%, 51%, and 58%, respectively.

In the Weinberg Screening Affective Scale, if there is a pattern distinctive of each group, it would appear that whites were more likely to endorse self-punitive symptoms (eg, "I am lonely too much of the time," "I cause trouble for everybody"), while blacks tended to report complaints more related to a negative view of their immediate interpersonal world (eg, "School makes me nervous," "This is not a good world"). Hispanics had a mixture of negative views of themselves and their interpersonal relationships. All three groups reported 2 to 3 somatic symptoms, though they were different for each ethnic group. By Beck Depression Inventory and Weinberg Screening Affective Scale, all three groups were very likely to endorse school difficulties, sad mood, feelings of failure, indecision, and guilt or self-dislike.

Discussion

The prevalence of depression by self-report in adolescents from a large metropolitan school district of mixed ethnic background ranged from 13% to

TABLE 4
Severity of Depression Scores in Students Meeting Criteria for Depression*

	BDI = Positive (n = 336)	WSAS = Postive (n = 179)	Both Positive (n = 261)
BDI total score	22.3 ± 6.4	9.2 ± 4.1	26.2 ± 7.8
WSAS total score	15.2 ± 5.6	21.8 ± 4.3	25.7 ± 5.7

BDI = Beck Depression Inventory; WSAS = Weinberg Screening Affective Scale.
* Mean ± SD

TABLE 5
Rank Order of Beck Depression Inventory Items Predicting Score ≥ 16 by Ethnic Group

Symptoms	White	Black	Hispanic
G. Self-dislike	1	—	1
A. Sadness	2	7	5
M. Indecisive	3	1	2
N. Unattractive	4	2	14
P. Insomnia	5	13	16
D. Dissatisfaction	6	14	15
K. Anorexia	7	9	3
F. Punishment	8	3	12
C. Failure	9	8	7
O. Work Effort	10	12	11
L. Withdrawal	—	—	8
I. Crying	13	—	6
E. Guilt	—	—	—
I. Suicidal	—	—	—
H. Self Accusation	—	—	4
B. Pessimism	—	—	9
K. Irritability	—	—	10

18%. Hispanic females showed the highest scores, while white males the lowest. Being behind in school and female and nonwhite status predicted more depression by self-report. For the total group, these figures are somewhat higher than previously reported for adolescents.[14] By Beck Depression Inventory, whites in our sample were closer to the previous study, which was predominantly white (12% *v* 8.6%). The school district studied is predominantly lower socioeconomic status, which may be a factor in the higher rates, in addition to or separate from ethnic background. In this school district, student dropout is a significant problem, particularly in Hispanics. Clearly, those students who are behind in school had higher depression scores. Whether depression leads to falling behind in school or vice versa is unclear. In such a population, social disadvantage may lead to feelings of hopelessness and helplessness. Specific factors leading to minority student dropout bears further study.

In contrast to the previous study in adolescents

TABLE 6
Rank Order of Weinberg Screening Affective Scale Predicting Depressed Versus Nondepressed by Ethnic Group

Questions	White	Black	Hispanic
16. I feel lonely too much of the time	1	—	—
45. I cause trouble for everybody	2	—	16
24. I don't want to go to school anymore	3	6	2
37. I have too many aches and pains in my muscles	4	23	—
53. I can't have fun anymore	5	27	1
3. I can't do my homework anymore	6	25	—
41. It's hard to fall asleep and that bothers me	7	10	—
20. I am not as good as other people	8	14	20
6. Sometimes I wish I were dead	9	29	—
18. Nothing is ever done the way I like it	10	30	—
42. My friends don't like me anymore	—	1	—
49. School makes me nervous	16	2	—
27. It seems like some part of my body always hurts me	—	3	—
10. I can't do my school work anymore, it's too hard	20	4	17
47. Everybody picks on me	11	5	—
32. I'm too hard to get along with	12	7	—
14. This is not a good world	—	8	—
21. It seems like I'm always in trouble for fighting and that is not fair	—	9	10
13. I have too many bad moods	—	—	3
5. I can't do anything right	18	22	4
31. My friends don't want to be with me anymore	—	15	5
34. I daydream too much in school	—	28	6
12. School makes me feel sick	—	—	7
22. I have gained too much weight	17	24	8
43. When I wake up at night, it is hard to go back to sleep	—	—	9

using the Beck Depression Inventory,[14] our sample showed more depressive symptoms in females. Although we were unable to control for socioeconomic status, another factor might be that this sample was predominantly an older adolescent age group, when most males and females are postpubertal. Age is probably not a factor in this study because the design limits the age range studied, predominantly to one grade level.

As to whether self-reported measures are actually indicative of major depressive disorder is dependent on the ability to study the same population with structured interviews. It is expected that a number of subjects would meet criteria for "caseness" of major depressive disorder as in the study by Kashani et al,[28] while others would have symptoms but without clear disorder. Studies assessing the actual prevalence of depression in adolescents using interview and specific criteria for caseness and diagnosis are limited. Kashani and colleagues[28] interviewed a representative sample of 150 adolescents attending public school in Missouri and found that seven (4.7%) had major depressive disorder and five (3.3%) had dysthymic disorder by *DSM-III* criteria. Depressive symptoms sufficient for meeting criteria for major depressive disorder and dysthymic disorder were present in another 33 (22%) adolescents but these were not considered cases because (1) insufficient duration of symptoms, (2) treatment was not necessary, or (3) the depressive symptoms resulted in minimal dysfunction. Finally, 28 (19%) reported dysphoric mood for at least 2 weeks but did not meet criteria for depression. This left 77 (51%) not reporting any dysphoric mood.

While there is no evidence to date that the rate of actual depressive disorder is different between ethnic groups, this is the first study to report significant self-reported depressive symptomatology differences between ethnic groups in adolescents. While the diagnosis of depression cannot be made based only on self-report measures, there is substantial evidence that higher scores correlate with dysfunction, both current and future.[29-33]

The two self-report measures used identified different populations, with overlap between the groups. However, the group that was positive by both measures seemed significantly more depressed than either group alone. If one assumes that clinical depression is most likely in adolescents who are positive on both measures, then 261/3,294 (7.9%) may be judged likely to be clinically depressed, which is similar to prevalence rates obtained by interview.[28]

With regard to differences in depressive symptoms reported by different ethnic groups, black adolescents' tendency to externalize their depression by blaming their environment and others often leads to their depression manifesting in conduct problems. The depressed Hispanic adolescents seem to internalize their depression, blame themselves, feel hopeless, withdraw, and drop out. Since all conceptualizations of depressive symptoms and criteria have been determined in whites, it is important to examine the different presentations of depression in different ethnic groups.

Depression as a disease, having the same psychological and vegetative symptoms across ethnic groups, may manifest differently in various ethnic groups. It is important to consider depression as a primary disease entity in adolescents doing poorly in school, at home, or with free time, independent of their ethnic group. These two self-report measures can be useful in screening for depression and as adjuncts to clinical evaluation.

In summary, this study presents preliminary data on an instrument designed specifically for children and adolescents to recognize depression by self-report using established criteria. This initial study is intended as a first step in developing such an instrument. The next phase of validating this instrument includes interviewing a random sample of a screened population and is currently in progress.

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A RATING SCALE FOR DEPRESSION

BY

MAX HAMILTON

From the Department of Psychiatry, University of Leeds

The appearance of yet another rating scale for measuring symptoms of mental disorder may seem unnecessary, since there are so many already in existence and many of them have been extensively used. Unfortunately, it cannot be said that perfection has been achieved, and indeed, there is considerable room for improvement.

Types of Rating Scale

The value of this one, and its limitations, can best be considered against its background, so it is useful to consider the limitations of the various rating scales extant. They can be classified into four groups, the first of which has been devised for use on normal subjects. Patients suffering from mental disorders score very highly on some of the variables and these high scores serve as a measure of their illness. Such scales can be very useful, but have two defects: many symptoms are not found in normal persons; and less obviously, but more important, there is a qualitative difference between symptoms of mental illness and normal variations of behaviour. The difference between the two is not a philosophical problem but a biological one. There is always a loss of function in illness, with impaired efficiency.

Self-rating scales are popular because they are easy to administer. Aside from the notorious unreliability of self-assessment, such scales are of little use for semiliterate patients and are no use for seriously ill patients who are unable to deal with them.

Many rating scales for behaviour have been devised for assessing the social adjustment of patients and their behaviour in the hospital ward. They are very useful for their purpose but give little or no information about symptoms.

Finally, a number of scales have been devised specifically for rating symptoms of mental illness. They cover the whole range of symptoms, but such all-inclusiveness has its disadvantages. In the first place, it is extremely difficult to differentiate some symptoms, *e.g.*, apathy, retardation, stupor. These three look alike, but they are quite different and appear in different settings. Other symptoms are difficult to define, except in terms of their settings, *e.g.*, mild agitation and derealization. A more serious difficulty lies in the fallacy of naming. For example, the term "delusions" covers schizophrenic, depressive, hypochrondriacal, and paranoid delusions. They are all quite different and should be clearly distinguished. Another difficulty may be summarized by saying that the weights given to symptoms should not be linear. Thus, in schizophrenia, the amount of anxiety is of no importance, whereas in anxiety states it is fundamental. Again, a schizophrenic patient who has delusions is not necessarily worse than one who has not, but a depressive patient who has, is much worse. Finally, although rating scales are not used for making a diagnosis, they should have some relation to it. Thus the schizophrenic patients should have a high score on schizophrenia and comparatively small scores on other syndromes. In practice, this does not occur.

The present scale has been devised for use only on patients already diagnosed as suffering from affective disorder of depressive type. It is used for quantifying the results of an interview, and its value depends entirely on the skill of the interviewer in eliciting the necessary information. The interviewer may, and should, use all information available to help him with his interview and in making the final assessment. The scale has undergone a number of changes since it was first tried out, and although there is room for further improvement, it will be found efficient and simple in use. It has been found to be of great practical value in assessing results of treatment.

Description of the Rating Scale

The scale contains 17 variables (see Appendix I). Some are defined in terms of a series of categories of increasing intensity, while others are defined by a number of equal-valued terms (see Appendix II). The form on which ratings are recorded also includes four additional variables: Diurnal variation, derealization, paranoid symptoms, obsessional symp-

toms. These are excluded from the scale because the first is not a measure of depression or of its intensity, but defines the type of depression. The other three occur so infrequently that there is no point in including them.

The variables are measured either on five-point or three-point scales, the latter being used where quantification of the variable is either difficult or impossible. No distinction is made between intensity and frequency of symptom, the rater having to give due weight to both of them in making his judgment.

Various problems are to be found with specific symptoms. Thus considerable difficulty is found with the depressive triad: depressive mood, guilt, and suicidal tendencies. These are so closely linked in description and judgment as to be very difficult to separate. It is very important to avoid the halo effect by automatically giving all of them high or low scores, as the case may be.

Depressed Mood.—This tends to have a narrow range of scores, for no diagnosed patients will score zero and few will score 1 or 4. The most useful indicator for depressed mood is the tendency to weep, but it must always be considered against the cultural background, and patients may also "go beyond weeping".

Suicide.—An attempt at suicide scores 4, but such an attempt may sometimes occur suddenly against a background of very little suicidal tendency; in such cases it should be scored as 3. There will be great difficulty sometimes in differentiating between a real attempt at suicide and a demonstrative attempt; the rater must use his judgment.

Work and Loss of Interest.—Difficulties at work and loss of interest in hobbies and social activities are both included. The patient who has given up work solely because of his illness is rated 4.

Retardation.—A grade 4 patient is completely mute, and is therefore unsuitable for rating on the scale. Grade 3 patients need much care and patience to rate, but it can be done.

Agitation.—This is defined as restlessness associated with anxiety. Unfortunately, a five-point scale was found impracticable, and therefore this variable is rated on a three-point scale. The mildest degrees of agitation cause considerable difficulty.

Gastro-intestinal Symptoms.—These occur in connexion with both anxiety and depression. Considerable clinical experience is required to evaluate them satisfactorily. The definitions given have been found very useful in practice.

General Somatic Symptoms.—In depressions these are characteristically vague and ill defined, and it is extremely difficult to get a satisfactory description of them from the patient.

Hypochondriasis.—This is easy to rate when it is obviously present, but difficulties arise with mild hypochondriacal preoccupations. Phobias of specific disease can cause difficulties. A phobia of venereal disease or of cancer will sometimes be rated under "guilt" by the nature of the symptom, but other cases may give rise to much doubt and judgment requires care. Fortunately, phobias are not common, but the whole subject of hypochondriasis could well repay clinical investigation.

Insight.—This must always be considered in relation to the patient's thinking and background of knowledge. It is important to distinguish between a patient who has no insight and one who is reluctant to admit that he is "mental".

Loss of Weight.—Ideally this would be measured in pounds or kilograms, but few patients know their normal weight and keep a check on it. It was therefore necessary to use a three-point scale.

After recovery from depression, some patients sometimes show a brief hypomanic reaction, during which the exuberantly cheerful patient will deny that he has any symptoms whatever, though he is obviously not to be regarded as normal. In such cases, the rating scale is inapplicable and should be delayed until the patient has fully recovered.

Scoring

It is particularly useful to have two raters independently scoring a patient at the same interview, since this gives data for calculating the inter-physician reliability. The score for the patient is obtained by summing the scores of the two physicians. This is, of course, the best way of learning how to use the scale, Where only one rater uses the scale, the scores should be doubled so as to make them comparable. With sufficient experience, a skilled rater can learn to give half-points.

Results

For two raters, the correlation between summed scores for the first 10 patients was 0·84. Adding successively 10 patients at a time, the correlation changed to 0·84, 0·88, 0·89, 0·89, 0·90, 0·90. The last correlation is therefore total for 70 patients.

Product-moment correlations were calculated for the 17 variables on the first 49 male patients (Table I). The correlation matrix was then factor-analysed by extracting the latent roots and vectors (Table II). As the intercorrelations are in general low because of the intense selection of patients, the latent roots (variances extracted by factors) diminish

TABLE I

CORRELATION MATRIX OF THE SCALE FOR DEPRESSION

	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)	(10	(11)	(12	(13)	(14	(15)	(16)
1 Depressed mood	1·0	0·491	0·373	0·082	0·236	0·140	0·362	0·590	−0·055	−0·198	−0·224	−0·032	0·014	0·370	−0·024	0·341
2 Guilt		1·0	0·522	−0·049	−0·048	0·121	0·358	0·370	0·027	−0·167	−0·151	0·071	−0·063	0·426	0·113	0·419
3 Suicide			1·0	0·043	0·098	−0·073	0·016	0·335	−0·068	−0·216	−0·065	−0·087	−0·115	0·304	−0·042	0·201
4 Insomnia, initial				1·0	0·199	0·309	0·130	−0·115	0·191	−0·001	−0·036	0·438	0·169	−0·044	0·152	0·179
5 ,, middle					1·0	0·054	0·035	0·200	0·126	0·003	0·095	0·308	0·278	0·111	0·067	0·146
6 ,, delayed						1·0	0·17	0·126	0·022	−0·180	−0·162	0·376	−0·038	0·142	0·171	0·012
7 Work and interests							1·0	0·230	0·183	0·017	−0·045	0·285	0·094	−0·058	−0·020	0·313
8 Retardation								1·0	−0·305	−0·365	−0·356	0·067	0·127	0·269	−0·208	0·232
9 Agitation									1·0	0·274	0·329	0·199	−0·107	0·045	0·001	0·217
0 Anxiety, psychic										1·0	0·370	−0·146	−0·058	−0·026	0·043	−0·159
1 ,, somatic											1·0	−0·082	0·060	0·033	−0·014	−0·310
2 Somatic, gastro-intestinal												1·0	0·248	−0·115	0·135	0·074
3 Somatic general													1·0	0·048	0·137	−0·024
4 ,, genital														1·0	0·199	0·254
5 Hypochondriasis															1·0	0·275
6 Insight																1·0
7 Loss of weight																

TABLE II

FACTOR SATURATIONS AND LATENT ROOTS

Condition	Factor 1	Factor 2	Factor 3	Factor 4
(1) Depressed mood	0·763	−0·172	0·103	0·151
(2) Guilt	0·728	−0·156	0·341	−0·138
(3) Suicide	0·531	−0·311	0·283	0·122
(4) Insomnia, initial	0·207	0·614	−0·208	−0·025
(5) ,, middle	0·284	0·363	−0·081	0·639
(6) ,, delayed	0·338	0·371	−0·304	−0·340
(7) Work and interests	0·458	0·275	0·043	−0·134
(8) Retardation	0·683	−0·371	−0·253	0·224
(9) Agitation	−0·034	0·539	0·503	−0·032
(10) Anxiety, psychic	−0·373	0·326	0·557	0·072
(11) ,, somatic	−0·403	0·250	0·480	0·421
(12) Somatic, gastro-intestinal	0·282	0·674	−0·395	−0·010
(13) ,, general	0·087	0·245	−0·356	0·628
(14) Genital	0·474	−0·139	0·397	0·225
(15) Hypochondriasis	0·157	0·367	0·117	−0·144
(16) Insight	0·603	0·107	0·204	−0·173
(17) Loss of weight	0·353	0·439	0·214	−0·192
Latent root	3·4358	2·3439	1·7496	1·3658

slowly. Out of the total variance of 17, the first six roots take up 3·44, 2·34, 1·75, 1·37, 1·28, 1·07, 0·99. The first four factors were used for calculating factor measurements for the patients, in the form of T-scores.

For the interest of those factorists who have a taste for factors rotated to give simple structure, the first three factors were rotated by an orthogonal rotation matrix (Table III) to give the results shown in Table IV. The fourth factor was left as it is, as it already has a fair number of near-zero saturations. The final saturations give a good approximation to simple structure and still retain the advantage of orthogonality.

TABLE III

ORTHOGONAL ROTATION MATRIX

Factor	Matrix		
F_1	0·7377	0·4932	−0·4610
F_2	−0·4182	0·8699	0·2614
F_3	0·5300	0	0·8480

TABLE IV

SATURATIONS OF ROTATED FACTORS

Condition	Factor 1	Factor 2	Factor 3	Factor 4
(3) Suicide	0·672	−0·009	−0·086	0·122
(14) Genital	0·618	0·113	0·081	0·225
(2) Guilt	0·783	0·224	−0·087	−0·138
(8) Retardation	0·525	0·014	−0·626	0·224
(1) Depressed mood	0·690	0·227	−0·309	0·151
(12) Somatic, gastro-intestinal	−0·283	0·725	−0·288	−0·010
(16) Loss of insight	0·508	0·401	−0·077	−0·173
(4) Insomnia, initial	−0·214	0·637	−0·111	−0·025
(5) ,, middle	0·015	0·456	−0·105	0·639
(7) Work and interests	0·245	0·466	−0·102	−0·134
(15) Hypochondriasis	0·024	0·397	0·123	−0·144
(17) Loss of weight	0·190	0·556	0·133	−0·192
(6) Insomnia, delayed	−0·067	0·490	−0·317	−0·340
(9) Agitation	0·016	0·453	0·583	−0·032
(10) Anxiety, psychic	−0·117	0·100	0·730	0·072
(11) ,, somatic	−0·148	−0·019	0·658	0·421
(13) Somatic, general	−0·227	0·256	−0·278	0·628

Factor Saturations.—It is customary to examine the factor saturations in order to give an appropriate name to the factors. When all the variables are positively correlated, the general factor may be regarded as an overall average of the items; but when, as in this case, a group of the variables is negatively correlated with the rest, this notion of an average becomes a little tenuous. Be that as it may, there would be little objection to the proposal to call the first factor "retarded depression" on the basis of its factor saturations. The important ones are, in descending order, depressed mood 0·76, guilt 0·73, retardation 0·68, loss of insight 0·60, suicide 0·53, genital symptoms (loss of libido) 0·47, work and interest 0·46, anxiety (somatic) 0·40, anxiety (psychic) 0·37, loss of weight 0·35, and insomnia (delayed) 0·34. The correspondence with the classical descriptions is remarkably close. The saturations in the second factor are: Somatic symptoms (gastro-intestinal) 0·67, insomnia (initial) 0·61,

agitation 0·54, loss of weight 0·44, retardation 0·37, insomnia (delayed) 0·37, insomnia (middle) 0·36, hypochondriasis 0·37, anxiety (psychic) 0·33, and suicide 0·31. It might be said to be vaguely like agitated depression, which clinically shows anxiety and agitation, together with disturbed sleep (particularly initial insomnia), but the factor is deficient in depression, the first factor having taken out most of the depressive variance. The third factor might be called some sort of anxiety reaction, with saturations of anxiety (psychic) 0·56, agitation 0·50, anxiety (somatic) 0·50, genital (loss of libido) symptoms 0·40, gastrointestinal symptoms — 0·39, general somatic symptoms — 0·36, guilt 0·34, and insomnia (delayed) — 0·30. The fourth factor has saturations of insomnia (middle) 0·64, general somatic symptoms 0·63, anxiety (somatic) 0·42, and insomnia (delayed) — 0·34. It is difficult to attach any label to the third and fourth factors, as they do not bring any clinical pattern to mind.

The situation is no better with the rotated factors. Factor I is still very much like retarded depression. but the negative saturation for gastrointestinal symptoms strikes a most incongruous note. Factor II shows many somatic symptoms and disturbed sleep, but the presence in the factor of agitation without anxiety is disturbing. It cannot be regarded as a factor of objective symptoms, as opposed to subjective, since it includes loss of interest and insight. Factor III could be named "anxiety reaction", but the negative saturations of depression and loss of insight must disqualify any attempt to relate it to clinical syndromes. The fourth factor has been left unrotated.

It is not surprising that the classical clinical syndromes have not appeared from the factor analysis, since this technique is incapable of demonstrating them. It would appear from the literature that psychologists have hoped that factor analysis would elicit the classical syndromes, and perhaps even additional ones, but in practice this does not occur. The clinical syndromes are mutually exclusive, *i.e.*, a patient can be ill with endogenous depression, or reactive depression, or schizophrenia, etc., but not from two or more. Of course, there are always patients who diagnostically are doubtful in-betweens. On the other hand, factors are orthogonal, and any individual patient can have high scores in two or more factors, or conversely, low scores. The discrepancy between clinical syndromes and factors is even greater when correlated factors are obtained by non-orthogonal rotations, for with such factors, patients will tend to score high or low in all factors simultaneously.

The appropriate statistical technique for describing the clinical syndromes in terms of quantified variables is that of discriminant functions. These divide the multidimensional space into regions, the centres of which characterize the typical case, and the meeting of the regions, the "interfaces", are the sites where are located the atypical, anomalous, or half-way cases. Since this procedure requires the initial establishment of criterion groups, already diagnosed, it cannot therefore be used to find syndromes. It can be used to test the (null) hypothesis that the syndromes are not distinct, and to identify new cases.

Factor Measurements

Another way of investigating the nature of the factors is to consider the individuals who have high scores on the factors:—

Factor 1.—A man aged 39 years (Case 39) had factor scores of F_1 76, F_2 37, F_3 49, and F_4 52.

This patient was admitted to hospital after two attempts at suicide, first by electrocution, and, when this failed, by an overdose of phenobarbitone. No psychological precipitating factors were found. On admission he was severely depressed and still actively suicidal. He had strong feelings of guilt, and feared that he had acquired venereal disease and was infecting others with it. He was markedly retarded and showed loss of insight. His sleep was disturbed in all three phases, he had no interest in anything and had complete loss of libido since the onset of his illness four months previously. His symptoms cleared with six courses of electroshock treatment (E.C.T.). Two weeks later he suddenly relapsed and attempted to cut his wrists with a broken tumbler. He again recovered with a further course of E.C.T. and has remained well ever since.

This case was one of classical endogenous depression.

Case 24.—A man aged 54 had factor scores of F_1 64, F_2 51, F_3 44, and F_4 50.

This patient developed symptoms of anxiety two years ago, accompanied by impotence. As a result of physical illness, he had to change his job to one much less satisfactory and with less pay. He worried excessively over this and over his health, and became very depressed. He was given E.C.T. as an out-patient, improved and returned to work for three months. He was twice admitted to hospital, refused E.C.T., and discharged himself. Eventually he agreed to accept E.C.T. but committed suicide just before he was due to attend for treatment. When in hospital he was deeply depressed, had some guilt feelings, suicidal thoughts, and moderate retardation. He had difficulty in falling asleep and woke in the early hours. He showed loss of interest and of libido. He lacked insight, had lost weight, and complained of vague bodily symptoms. He showed little anxiety but was preoccupied with his health and his future prospects.

Psychological precipitating factors cannot be excluded, but the overall picture is that of endogenous depression.

Factor 2.—A man aged 62 years (Case 61) had factor scores of F_1 32, F_2 54, F_3 37, and F_4 38.

This patient had been off work for 11 years for "bad nerves" following an accident at work. He had many hypochondriacal complaints and had undergone many fruitless investigations. Four years ago, he was admitted to hospital for severe depression with delusions and hallucinations. This cleared after E.C.T. He was readmitted a year ago, diagnosed as a case of reactive depression, and improved slowly under general treatment. He was discharged after three months. His condition fluctuated and eventually he was readmitted, given six courses of E.C.T. and showed marked improvement. He was discharged and remained well. His symptoms were of moderate depression, without feelings of guilt or suicidal ideas. He had difficulty in falling asleep and awoke early. He showed moderate loss of interest, anxiety, both psychic and somatic, and suffered from poor appetite and constipation. He was diagnosed as a case of reactive depression, but the relation of the illness to psychological precipitating factors is not certain.

Case 17.—A man aged 72 years had factor scores of F_1 48, F_2 65, F_3 43, and F_4 45.

There was a long history of abdominal complaints, but investigations found nothing to account for them. A year ago the patient became obviously depressed and was admitted to hospital. He showed moderate depression, guilt, and some suicidal preoccupations. His sleep was disturbed in all three phases. He showed loss of interest, some agitation, severe hypochondriasis, and considerable anxiety. His appetite was poor, his bowels were constipated, and he had lost weight. Because of the poor state of his heart, he was not given E.C.T. He improved slowly, finally discharging himself against advice. Eventually he was admitted to a general hospital and died from cancer of the lung.

The clinical picture is that of reactive depression, but the psychological precipitating factors are doubtful.

Factor 3.—A man aged 61 years (Case 2) had factor scores of F_1 41, F_2 38, F_3 63, and F_4 44.

The patient had a history of several attacks of depression, the last one precipitated by the deaths of his wife and daughter. The course of the illness was fluctuating, and the patient showed a poor response to E.C.T. He showed marked depression, guilt, suicidal thinking, retardation, loss of interest, and grossly disturbed sleep. Eventually he recovered and has remained well.

Case 45.—A man aged 53 years had factor scores of F_1 60, F_2 55, F_3 78, and F_4 52.

The patient had had one previous attack of depression four years before. Two years ago, the patient again fell ill, and his symptoms have fluctuated considerably. In hospital he showed much depression, guilt, and loss of interest, much anxiety and agitation, loss of libido and loss of insight. He is a rather inadequate personality and his present illness began when he was offered a post which involved greater responsibility.

Both of these patients have had previous attacks of depression, characteristic of an endogenous type of disorder, but in both cases, there were obvious psychological stresses to account for the onset of the present attack. In the first, the symptoms were of the endogenous (retarded) type, and in the second of the reactive (agitated) type. Clinically, these patients are very unlike, but the factor scores pick them out on account of their resemblance; what this is, is not clear.

Since the factors are derived from a limited number of cases, the fourth factor is of very doubtful stability. (The question of statistical significance is ignored for the moment.) Nevertheless, it is of considerable interest. Both of the following patients showed depression with much anxiety, disturbance of sleep and many somatic symptoms, but it is the background to the illness that is noteworthy.

Factor 4.—A man aged 51 years (Case 62) had factor scores of F_1 39, F_2 41, F_3 56, and F_4 71.

This patient was a hard worker, but could not restrain his heavy drinking and gambled heavily. These caused considerable marital discord. When temporarily out of work after an accident, he stole money from his daughter to continue his "hobbies". He went off to London, stayed in a hotel and decamped without paying. When he eventually returned home, he heard that the theft had been reported to the police. He became desperate, and after a few days attempted to gas himself and was admitted to hospital. His condition cleared after E.C.T.

Case 7.—A man aged 44 years had factor scores of F_1 34, F_2 44, F_3 58, and F_4 71.

This patient came from a disturbed parental home where he had been rejected and deprived. He has always been an odd personality with marked neurotic traits and paranoid attitudes. He served in the Royal Air Force for nine years, during which he was repeatedly delinquent and resistant to authority. Eventually he was discharged for "psychoneurosis". His subsequent occupational history is irregular, with frequent loss of jobs because of quarrelling. He always feels that others are against him. He has not worked for years, has shown much anxiety and in the last six months became depressed, being finally admitted to hospital. He improved a little after E.C.T. but relapsed, subsequently recovering spontaneously.

Both of these patients have obviously abnormal personalities, although it would be an exaggeration to describe them as psychopathic personalities. It has long been recognized that abnormal personalities, particularly of the hysterical type, are liable to attacks of depression, and it is of great interest that such patients should be picked out by reason of the pattern of symptoms of their depression. Nevertheless, the present findings should not be regarded as more than suggestive and worthy of further investigation.

Another way of tackling the relation between factors and clinical syndromes is to take groups of clinically identified patients and compare their mean

factor measurements. Since this is purely a clinical problem and involves other matters, it is reported elsewhere (Hamilton and White, 1959).

Tests of significance have not been applied to these factors. It seems likely that even the smallest factor would become statistically significant if a sufficient number of patients were tested, and the ratings were repeated often enough to make the individual variables highly reliable. The value of factors lies in their use. In this connexion, although the data for the factor analysis were derived from 49 patients, the regression equations were used on the ratings obtained from 64 patients investigated for other purposes. Of these 64 patients, 49 were followed up after treatment (not the same 49). The correlation between factor measurements and total crude score after treatment is for F_1 0·23, for F_2 0·17, for F_3 0·27, and for F_4 — 0·09. Although F_3 has no obvious clinical or psychological meaning, it is the only one of the factors to be correlated with outcome after treatment at a significance level of just over 5%. This is not much, but a large correlation with outcome is not to be expected in such a highly selected group of patients (Hamilton and White, 1959). Furthermore, 16 out of the 49 cases followed up are new cases, so that some of the shrinkage to be expected in a cross-validation group has already occurred. (The situation is not quite the same as when a multiple correlation is calculated, but F_3 has been picked out because it has the highest correlation with outcome. Herein lies the interest of this factor.)

Summary

A rating scale is described for use in assessing the symptoms of patients diagnosed as suffering from depressive states. The first four latent vectors of the intercorrelation matrix obtained from 49 male patients are of interest, as shown by (*a*) the factor saturations, (*b*) the case histories of patients scoring highly in the factors, and (*c*) the correlation between factor scores and outcome after treatment. The general problem of the relationship between clinical syndromes and factors extracted from the intercorrelations of symptoms is discussed.

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APPENDIX I

ASSESSMENT OF DEPRESSION

Item No.	Score Range	Symptom	Score
1	0-4	Depressed mood	
2	0-4	Guilt	
3	0-4	Suicide	
4	0-2	Insomnia, initial	
5	0-2	,, middle	
6	0-2	,, delayed	
7	0-4	Work and interests	
8	0-4	Retardation	
9	0-2	Agitation	
10	0-4	Anxiety, psychic	
11	0-4	,, somatic	
12	0-2	Somatic symptoms, gastrointestinal	
13	0-2	,, ,, general	
14	0-2	Genital symptoms	
15	0-4	Hypochondriasis	
16	0-2	Loss of insight	
17	0-2	,, ,, weight	
18	0-2	Diurnal variation {M, E}	
19	0-4	Depersonalization, etc.	
20	0-4	Paranoid symptoms	
21	0-2	Obsessional symptoms	

Grading	
0	Absent
1	Mild or trivial
2, 3	Moderate
4	Severe
0	Absent
1	Slight or doubtful
2	Clearly present

Children's Depression Rating Scale—Revised[1] (September 1984)

Elva O. Poznanski, M.D., Linda N. Freeman, M.D.,[2] and Hartmut B. Mokros, Ph.D.[2]

Description of the Scale

The Childhood Depression Rating Scale—Revised (CDRS-R) is a clinician-rated instrument designed to measure the presence and severity of depression in children aged 6 to 12 years. The CDRS-R consists of 17 items. Fourteen of these items are rated on the basis of the subjects' responses to a series of standardized questions. This semi-standard interview can be administered to children ages 6 to 12, their parents, teachers, case workers, or other sources of information in approximately 30 minutes. The first 14 items are rated on the basis of this interview. The remaining 3 items of the CDRS-R are rated by the clinician on the basis of the *child's* nonverbal behavior. These 3 items are not rated when interviewing a subject other than the child.

The 17 items of the CDRS-R are scales from 1 to 5 for sleep, appetite, and tempo of speech items and from 1 to 7 for the remaining 14 items. A rating of 1 indicates no abnormality while a rating of 3 indicates mild symptomatology. A rating of 5 or more on all items indicates definite psychopathological symptomatology.

Reliability and validity studies on this instrument have been carried out in a hospitalized pediatric population, in a child psychiatric inpatient population, in three outpatient child psychiatric clinics, and in a elementary school sample.

[1]The CDRS-R was developed by E.O. Poznanski, M.D., with assistance of the staff of the Youth Affective Disorders Clinic. Investigators wishing to use or quote the CDRS-R should contact Dr. Poznanski at the address below.

[2]Youth Affective Disorders Clinic, Rush-Presbyterian-St. Luke's Medical Center, Department of Psychiatry, Chicago, IL 60612.

Administering the CDRS-R

Prior to administration of the scale, the clinician should familiarize himself or herself with the interview so that a freely flowing interview style is developed. Although the interview is designed so that the examination proceeds from less threatening areas of questioning to more emotionally evocative areas, some children spontaneously provide information for items out of the interview sequence. This should be accommodated in a manner that allows for the building of rapport between clinician and subject. The clinician should anticipate that some subjects are slow to become involved in the interview and may initially give bland and guarded responses. After more rapport has been developed, it may be necessary to re-question such a person about earlier items.

The developmental level of the subject being examined must always be considered in interpreting responses to questions on the CDRS-R. Some children cannot understand words such as guilt, irritability, or suicide. Suggestions are included in the interview for ways to rephrase these concepts in more concrete language that the child may better understand. The child's ability to understand time concepts must also be considered. Again, concrete time markers such as usual daily activities or meals may be helpful in assessing the duration of an unhappy, sad mood state. The clinician must make an effort to use language and time markers consistent with the child's developmental capacities throughout the interview and rating process.

The effect of various settings in which the CDRS-R may be administered must also be considered by the clinician rating the instrument. Children in psychiatric settings are more likely to give guarded responses or withhold information than those in nonpsychiatric settings such as schools. Within the pediatric liaison setting, where children have debilitating physical illness or fever, the physical state of subjects may promote apathetic withdrawn behavior, fatigue, or sleep disturbance. Children

may also suffer severe separation anxiety, appearing withdrawn, tearful, and socially isolative outside of their mother's presence, yet happily interact with peers when their mother is present. Gathering information from multiple sources is recommended to make the most valid CDRS-R rating. However, it is important to consider the source of information when determining the final, combined CDRS-R score. For example, the child's description of sleep disturbance is often more valid than the parental description since parents are often not aware of the child's sleep behavior after they have retired to bed. On the other hand, children may be reluctant to report behaviors that would promote reprimands from adults. Therefore, behaviors such as irritability and eating disturbances are more accurately reported by parents.

Determining Diagnosis

Prior experience with clinical populations indicate that a summary score of 40 or above on the CDRS-R is a strong indicator of the presence or potential for a Major Depressive Disorder. Although the score of 40 is a reliable indicator of depression, it should serve as a heuristic, not as a criterion by which a child is diagnosed Major Depressive Disorder or not. Other usual methods of psychiatric evaluation such as unstructured interviews, family history, pediatric examination, laboratory examinations, etc. may be used to determine the diagnosis using diagnostic criteria such as DSM-III (Diagnostic and Statistical Manual—3rd ed., 1980) or Research Diagnostic Criteria. When a diagnosis of depression is certain, the CDRS-R may be used as a measure of severity of the depression and to provide a basis for comparison over time.

The Individual Items

A. Schoolwork

A child's schoolwork is usually impaired while he or she is depressed. The cognitive impairment stems from a general lack of interest or enthusiasm, difficulty in concentrating, and negative cognitions (views of the world). The difficulty concentrating on external tasks is the result of a turning inward and a preoccupation with thoughts and worries rather than the result of distractibility by external stimuli. The child may be negative about the school environment and/or his or her school performance. He or she may perceive his or her schoolwork to be poorer than it objectively appears.

The depressed child's diminished academic performance represents a change as opposed to chronic and consistently poor schoolwork. There may also be variability in performance of schoolwork associated with mood shifts. Children with chronic learning problems also decline in performance relative to their usual capacity to achieve academically. Likewise, bright children may maintain high grades, but teachers or parents report a decrease in their usual enthusiasm for learning. It is necessary to assess the child's usual capabililty and motivation to perform academically, prior to the depressive episode, to accurately rate this item.

The rater should take care, further, to distinguish between general diminished school performance and disturbance with a specific subject or teacher.

If school is not in session, the clinician can assess difficulty attending to other activities, e.g., games, at-home reading, television.

Examples:

Rating of 1. "I like school, except for math. I got all B's except a C in Math—It's hard."

Rating of 3. "My teacher says I don't do enough effort . . . my mind wanders . . . I think of things people said, or about music."

Rating of 5. "I'm trying the best I can but my schoolwork is not good, I might have to go back to 5th grade . . . I don't finish homework . . . it's hard to keep what I remember in my head" (11-year-old who tested on the WISC-R in bright normal range).

Rating of 7. "I am failing all subjects . . . I don't like it . . . they ain't teaching me nothing . . . I hate my teachers and the kids."

B. Capacity to Have Fun

Loss of interest or pleasure in activities can be striking in a depressed child. Although adults

can remain very serious and get to enjoy a game of cards or chess, normal children rarely hide their pleasure and enthusiasm at their games. The presence and severity of this symptom can be assessed by the types and numbers of activities the child can enjoy, by the child's interest or enthusiasm expressed while describing the activity, and by the amount of boredom the child feels. While every child occasionally feels boredom, the depressed anhedonic child may say he or she feels bored 50 to 100% of the time. This loss of interest may be expressed more subtlely. For example, a child may describe pleasurable activities which only occur on rare occasions, or are only available in a different season of the year, e.g., ice skating in the summer. Some children cannot name any activity that they enjoy. Severely depressed children may become primarily passive watching others play without participating themselves or watch television with little awareness of the program playing. They may participate in games but only "go through the motions," not enjoying themselves.

Examples:

Rating of 1. "I like to go sledding and skating (in winter) or just play outside. Yeah, I get bored sometimes—on Sunday when I have to sit at church."

Rating of 3. "I go bike riding . . . about twice a week . . . oh, and Boy Scout outings can be fun . . . no, I don't think I'm bored *too* much."

Rating of 5. "Going fishing is fun, my Dad and I went fishing twice last year . . . I color and play with the dog. Oh yes, I got *really* bored . . . I got bored every day . . . a lot."

Rating of 7. "I don't like nothing, I want to be by myself." (Mother confirms child does not play and refused activities suggested by her.)

C. Social Withdrawal

Depressed children commonly have difficulty socializing with peers. They withdraw from peer activities, turn down opportunities to play with peers, or provoke peers to reject them. Unlike schizoid or avoidant children, depressed children usually have developed the capacity for interpersonal relationships and have been able to socialize with peers prior to the onset of the depressive episode. Therefore, it is necessary to distinguish between a chronically isolative personality style and a change in social behavior to rate this item. When the difficulty in social relating has been longstanding and unchanged, "2" is the appropriate rating for this item.

Examples:

Rating of 2. "He had a few friends in the neighborhood but they change every few weeks. He's never had any close friends."

Rating of 3. "Usually Sue calls me . . . sometimes I play with her but mostly I'd just rather stay home . . . "

Rating of 5. "He had friends in school last year and two boys he grew up with in the neighborhood—now they call him names and fight a lot . . . it's because he won't play with them anymore or he only plays with Alex."

Rating of 7. "I'd rather be alone . . . I like being by myself . . . It's better that way—all those kids smoke and drink now . . . I don't have friends any more."

D. Sleep

Although the total sleep time of depressed children is not different from that of normal children, depressed children often report initial, terminal, or middle-of-the-night insomnia. Many children have intermittent awakening because of anxiety, nightmares, etc. from which they return to sleep quickly. Depressed children have more consistent patterns of sleep disturbance and often stay awake more than 30 minutes after awakening.

Example:

Rating of 3. "About twice a week I wake up. It's dark and my parents are asleep . . . I stay awake for an hour!"

Rating of 5. "I can't sleep ever. They put me to bed at 9 p.m. but I don't go to sleep until 10 p.m. I get up at 2 a.m. and watch TV."

E. Appetite or Eating Patterns

Depressed children may have changes in their eating patterns during a depressive episode. These may be loss of appetite and weight loss or excessive appetite and weight gain. Children can describe changes in appetite. Usually

parents give more objective information regarding the child's food intake.

Examples:

Rating of 3. "I eat lunch and dinner, but I'm not really hungry . . . I lost 3 pounds on the scale."

Rating of 5. "I starve myself even though I'm hungry . . . I think the food is poisoned—and my clothes fit too big now."

F. Excessive Fatigue

While all children may feel tired during the day, depressed children feel unusually tired and heavy. They may complain frequently of fatigue or even nap frequently. Typically, even after a nap, a depressed child continues to feel tired or drowsy. The fatigue is not specifically related to boring schoolwork or a situation the child may wish to avoid, but instead is more pervasive and persists across environments or situations. When a child is persistently and frequently so tired that he or she prefers to sleep or rest, instead of to play, a severe rating of 7 is indicated.

Examples:

Rating of 1. "I feel tired sometimes like when my mother asks me to clean up my room . . . math homework makes me feel tired, too."

Rating of 3. "I usually take a nap after school . . . yeah, then I feel o.k. to do my homework (10-year-old boy).

Rating of 5. "I always go to sleep 3 times in the day" (child looks fatigued in the interview).

Rating of 7. "After school I'm too tired to play . . . I lay on the couch from 3 to 5 p.m. but I still feel tired after dinner."

G. Physical Complaints

Somatic complaints are common in depressed children and may represent either the gastrointestinal disturbances which occur in depression as well as physiological concommitants of anxiety. Pains may be subjectively experienced as more intense during a depressive episode. Since every child has occasional complaints, a pathological rating should not be considered unless the child's complaints seem excessive.

Examples:

Rating of 1. "I get headaches sometimes . . . they usually go away . . . no, I don't take an aspirin."

Rating of 3. "I get headaches . . . on hot days . . . they don't go away by themselves . . . I had a few leg aches, too. I get stomach aches a lot . . . no, I don't stop playing."

Rating of 5. "Every morning I wake up with a pain in my neck . . . my forehead hurts where a boy hit me last week."

Rating of 7. "I have pain all the time in my chest and stomach. I think I am dying because I am sick with headaches . . . my things are poisoned and there is Tylenol in my food."

H. Irritability

An irritable mood often accompanies or alternates with a depressed mood or is present in the depressive syndrome. This symptom is usually best assessed by observers—parents, teachers, or the clinician interviewing the child, but occasionally the child is also aware of feeling "grouchy," or can describe temper outbursts and can describe these feelings stated. When a child is irritable during the interview, we recommend rating a 5.

In assessing this item, the clinician should consider the duration of irritability; the appropriateness of the context in which irritability arises, as well as the appropriateness of the intensity of irritability in a given context; and the frequency of irritability. Again, as with schoolwork or social withdrawal the clinician should assess that the irritability being described represents a subjective feeling or behavioral change rather than a temperamental characteristic.

Examples:

Rating of 3. "He has little tiffs with his brother several times a week. It's because he's so grouchy . . . the brother doesn't do anything and he's mad for a half hour."

Rating of 5. "Whenever my sister talks to me I get so mad . . . I just go in my room and sit for an hour until I

feel better . . . Oh yeah, it happens 3 or 4 times a week."

Rating of 7. "Every day she gets angry and slams her door when she goes to her room . . . she says she hates Dr. H. and wants to kill him."

I. Guilt

Children can feel overwhelmingly guilty; but guilt is a difficult area to obtain consistent and reliable information from children. Developmentally, the concept of guilt is not cognitively accessible to a very young child. It is rarely grasped by a child under the age of 8 years. Lack of evidence of guilty does not necessarily mean the child does not feel guilt. A child may make a conscientious effort to make a good impression on the examiner, and not reveal misdeeds.

Pathological guilt is an important item to assess when the child is able to describe these feelings. Often, it is necessary to define guilt for the child and to be sure he or she understands the concept before proceeding with the interview. In assessing for pathological guilt—as opposed to guilty feelings appropriate for a misdeed—the clinician must evaluate the duration and intensity of the child's feelings in relation to the severity of the event reported.

It should be determined when a guilt-inducing event occurred and the length of time that the child continues to blame himself or herself for the outcome.

Example:

Rating of 1. "I broke a lamp . . . it was my fault . . . but I feel better about it now."

Rating of 3. "I hit my brother . . . I felt bad about it . . . yes, I do still think about it . . . "

Rating of 5. "I feel bad when I don't do something my mother tells me to do and then I lie and say I did it and I feel badly the *whole day*."

Rating of 7. "I said I hate my uncle . . . he died . . . it's all my fault that he died . . . why . . . because I said it!"

J. Self-Esteem

Feelings of self-reproach are common in depression. Loss of self-esteem may be difficult to determine, especially in 6- to 9-year-olds whose self-concept is less developed. Structured questions about the child's degree of satisfaction with his or her looks, personality, intelligence, and acceptance or rejection by peers yield more information than abstract questions such as "do you like yourself?." Observers often may report on the child's propensity to be teased, called names, or be picked on by other children; propensities which diminish a child's self-esteem.

Low self-esteem, however, is not specific to depression. It is seen in a variety of psychiatric diagnoses as well as in children who do not qualify for any psychiatric diagnosis.

Many children will spontaneously volunteer information about their self-concepts, but others may be modest and require encouragement before responding. If a child hesitates on every question about him or herself, or gives only half-hearted responses, we recommend a higher rating.

It is important to evaluate the overall affective tone of the child's responses. Some children will describe themselves negatively, calling themselves "stupid" or admit their peers call them nicknames such as "fatso" or "fag." Derogatory nicknames tend to lower a child's self-esteem. When children admit to being called such names, a higher rating is also recommended.

For this item, and the morbid ideation item, a pathological rating is 4 or more. A child must report two or more major areas of self-image in which he or she feels deficient to be scored a rating of 4.

Example:

Rating of 1. "Basically, I like my looks and wouldn't want to change anything . . . except maybe (offhandedly), I could be skinnier."

Rating of 3. "I'd like to change my nose. I'm smart more than dumb. Most kids like me" (mentions changing looks twice more to subsequent questions).

Rating of 4. "I wish I had my teeth straightened . . . I think I should be smarter . . . "

Rating of 5. "I hate my face . . . kids call me retardo."

Rating of 7. "I'd like to change my face, my hair, and my personality. They say I'm smart but I think I'm dumb . . . nobody likes me."

K. Depressed Feelings

This item rates *verbally* expressed depressed feelings. Since every child feels unhappy from time to time, the clinician must determine the intensity, duration, and degree of association of the sad feelings to an event. Higher ratings are indicated when either the intensity or duration of unhappiness are excessive. Lack of association with an event as well as lack of reactivity of the mood also elevates the rating score.

Examples:

Rating of 1. "I felt so sad when my dog ran away . . . I cried . . . I felt sad a lot until my mom gave me a new dog."

Rating of 2. "I cry when my mother goes away . . . I'm afraid she won't come back . . . no, I'm not sad if she's at home."

Rating of 3. "I tell my mom I feel moody . . . it's hard to shake that feeling when I feel moody . . . oh, a few times a week."

Rating of 5. "I feel sad a lot . . . I go in my room and lay down . . . nothing happened . . . I don't know why."

Rating of 7. "I feel sad a lot . . . it hurts my heart . . . I went to the doctor because my chest hurts . . . I feel so sad it hurts but they can't find anything wrong with me."

L. Morbid Ideation

Depressed children often have thoughts of death, passive wishes to die, and other morbid concerns. Concerns about one's own death are considered morbid rather than suicidal ideation, unless the child only considers his or her own death in the context of suicide. Most nondepressed latency children develop temporary fears of separation and death of the quality described in the child's prayer "If I should die before I wake, I pray the Lord my soul to take . . . ." These types of concerns should not be assessed as pathological and should receive ratings of only 1 or 2. Concerns or fears about death shortly after a traumatic environmental event, such as separation from death of a pet or family member, should not be rated pathologically (i.e., 4 or above).

Depressed children, on the other hand, may have exaggerated responses to reality events and remain excessively preoccupied with deaths which occurred in the distant past, or of people little known by the child. The thoughts may seem excessive because of the frequency or intensity with which the child recalls the precipitating event. If these thoughts are excessive but not bizarre and are related to the reality event, we recommend a rating score of 3. When the morbid thoughts preoccupy the child's thoughts and extend beyond external reality or become extensive or bizarre, we recommend a rating of 4 or higher.

Examples:

Rating of 2. "I worry that my grandfather might die." (Grandfather is in the hospital.)

Rating of 3. "Someone shot a bullet in our house . . . I'm still afraid I might die . . . I might get shot."

Rating of 4. "I worry that my father will get sick and lose his job . . . or he might die" (Father has been hospitalized twice—not currently ill or hospitalized.)

Rating of 5. "I don't think I should exist in the world . . . at night I can feel death's presence."

Rating of 7. "My dog might die . . . I have pain in my heart and stomach because I am dying . . . my food is poisoned . . . am I going to die?" (asks mother daily "am I going to die?")

M. Suicidal Ideation

Suicidal ideation, gestures, and attempts occur in childhood depression. Most children 7 years or older are familiar with the word suicide and its meaning or can readily understand once the meaning of the word is explained to them. However, the child's response to questioning about suicidal ideas is not always straightforward. Sometimes a child will deny or sharply deny suicidal thoughts when they are present. The child should be further questioned after attempts to put him or her more at ease. But, if sharp denial persists, we recommend a rating of 2. When a child admits

to thoughts of suicide, usually when angry, not accompanied by suicidal gestures or attempts, we recommend a rating of 3. Recurrent thoughts of suicide merit a rating of 5. Any child admitting to active suicidal thoughts or who has made a suicide attempt within the prior month, should be given a rating of 7.

Examples:

Rating of 3. "When my mother yelled at me and made me stay in my room, I told her "I'm going to kill myself."

Rating of 5. "Yeah, I think about walking in front of a car or jumping out of a high window . . . it makes me sad to think about it, so I try not to."

Rating of 7. "I want to kill myself . . . I think I'll go in front of a car . . . I tried to stab myself with a knife . . . last week."

N. Weeping

Weeping can be seen in childhood depression due to depressed or irritable moods. Most often, parents or other observers report excessive weeping. At times, depressed children themselves admit to feeling they are more depressed than other children, or that they often cry for no reason. Some children who have difficulty admitting to crying often, will admit to feeling like crying even though they do not cry. A mildly pathological rating of 3 is recommended for a child who cries slightly more often than peers. A rating of 5 is recommended if the child admits to crying for no reason and/or cries frequently. The severest rating of 7 is recommended for daily weeping.

O. Non-Verbal Items

The final 3 items of the CDRS-R are rated by the clinician using clinical judgment based on the child's appearance and non-verbal behavior. The guidelines for each rating on the non-verbal items are explained on the CDRS-R rating scale.

Childrens Depression Rating Scale—Revised

Schoolwork

Do you like school or dislike school? What parts do you like? What parts do you dislike? (Note: if teacher, peers, activities, e.g., recess, etc.)

What kind of grades do you get in school? Are they different now than they were last year? (Or most recent grading period.)

Do your parents or your teacher(s) think you ought to be doing better? What do they say?

Do you agree or disagree with them?

If grades are a problem, ask: Do you have trouble paying attention? Why? Do you take longer to finish your assignments than other kids? Do you daydream?

Do other children bother you? Does the teacher often ask you to listen to what he/she is saying?

If not in school, ask about ability to concentrate on a TV program or game.

Ratings

1. Performance consistent with ability.
2.
3. Decrease in school performance.
4.
5. Major interference in most subjects.
6.
7. No motivation to perform.

Capacity to Have Fun

What do you like to do for fun? (Note interest, involvement, enthusiasm.) Discuss individual activities named.

How often do you have fun? (Note whether activities available daily, weekly, seasonally, or very infrequently.)

Are you ever bored? How often?

(If very inactive) What do you like to watch on TV? Discuss favorite TV shows. (Determine if active or passive viewer.)

Ratings

1. Interest and activities realistically appropriate for age, personality, and social environment. Shows no appreciable change with present illness. Any feelings of boredom are transient.
2.
3. Describes some activities realistically available several times a week but not on a daily basis. Shows interest but not enthusiasm.

4.
5. Is easily bored. Complains of "nothing to do." Participates in structured activities with a "going through the motions" attitude. May express interest primarily in activities that are (realistically) unavailable on a daily or weekly basis.
6.
7. Has no initiative to become involved in any activities. Primarily passive. Watches others play or watches TV but shows little interest. Requires coaxing and/or pushing to get involved in activity. Shows no enthusiasm or real interest. Has difficulty naming activities.

Social Withdrawal

Do you have friends to play with? Are they at school or home? What games or things do you do? How often do you play with them?
Have you ever had a really close friend? Do you have one now?
Do your friends ever call for you and you just don't feel like going out to play? How often?
Have you ever lost friends? What happened?
Do children ever pick on you? How? What do they do? Is there anyone who will stick up for you?

Ratings

1. Enjoys friendships with peers at school and home.
2.
3. May not actively seek out friendships but waits for others to initiate a relationship or may occasionally reject opportunities to play without a describable alternative.
4.
5. Frequently avoids or refuses opportunities for desirable interaction with others and/or sets up situations where rejection is inevitable.
6.
7. Does not currently relate to other children. States he or she has "no friends" or actively rejects new or former friends.

Sleep

Do you have trouble sleeping?
Do you take a long time to go to sleep? (Differentiate from resisting going to bed.) How long? How often?
Do you wake up in the middle of the night? Do you go right back to sleep or stay awake? How often does this happen?
Do you ever wake up before you need to in the morning? How early? Do you go back to sleep or stay awake? What do you do? How often (or when) does this happen?

Ratings

1. No (or occasional) difficulty. (Goes to sleep within 1/2 hour or less.)
2.
3. Frequently has mild difficulty with sleep.
4.
5. Moderate difficulty with sleep nearly every night.

(If applicable, indicate time of difficulty)
a. Initial
b. Middle
c. Early morning awakening

Appetite or Eating Patterns

Do you like to eat?
At meals, are you hungry for some meals, most meals, all meals? Not hungry (if not hungry, record when and how often not hungry).
Does your mother complain about your eating?
Have you gained or lost weight? (If yes) How can you tell?

Ratings

1. No problems or change in eating pattern.
2.
3. Mild change from usual eating habits within onset of current behavioral problem.
4.
5. Is not hungry most of the time or has excessive food intake since onset of current behavioral problems or marked increase in appetite.

(If applicable, circle one)
Increased appetite Decreased appetite

Excessive Fatigue
(Consider age and activities of child)

Do you feel tired during the day? Even when you have had enough sleep? (During boring school subjects does not count.) After school?
How often do you feel tired after school?

Do you ever feel so tired you go and take a nap even if you don't have to? How often does this happen?

Ratings

1. No unusual complaints of "feeling tired" during the day.
2.
3. Complaints of fatigue which seem somewhat excessive and not related to boredom.
4.
5. Daily complaints of feeling tired.
6.
7. Complains of feeling tired most of the day. May voluntarily take long naps without feeling refreshed. Interferes with play activities.

Physical Complaints
(Complaints of a non-organic basis)

Do you ever get stomachaches, headaches, leg pains?
Do you get other aches and pains?
What are they like?
How often do these occur?
When you get _____ aches, how long do they last? Does anything make them go away? Do they keep you from playing? How often do they do this?

Ratings

1. Occasional complaints.
2.
3. Complaints appear mildly excessive.
4.
5. Complains daily. Some interference with the ability of the child to function.
6.
7. Preoccupied with aches and pains; interferes with play activities several times a week.

Irritability

What things make you get grouchy or mad?
How mad do you get?
Do you ever feel in a mood where everything bothers you? How long do these moods last? How often do these moods occur?

Ratings

1. Rare.
2. Occasional.
3. Several times a week for short periods.
4.
5. Several times a week for longer periods.
6.
7. Constant.

Guilt

Do you ever feel like it's your fault or blame yourself if something bad happens?
Do you ever feel bad or sorry about certain things you have done or wished you had done? What are they? (Note act and whether guilt is proportional to deed.)
Do you know what the word guilty means? Do certain things make you feel guilty?

Ratings

1. Does not express any undue feeling of guilt. Appears appropriate to precipitating event.
2.
3. Exaggerates guilt and/or shame out of proportion to the event described.
4.
5. Feels guilty over things not under his or her control. Guilt is definitely pathological.
6.
7. Severe delusions of guilt.

Self-Esteem

Do you like the way you look? Can you describe yourself? (With a young child, ask about hair, eyes, face, clothes, etc.) Would you want to change the way you look? What way?
Do you think you are smart or stupid?
Do you think you are better or worse from other kids?
Do most kids like you? Do any not like you? Why? Do you get called names? What are they? Do other kids put you down?
What things are you good at? Not so good? What?
Do you ever feel very down on yourself?
Would you like to change anything about yourself?

Ratings

1. Describes self in primarily positive terms.
2.
3. Describes self with one important area where the child feels deficit.
4.
5. Describes self in preponderance of negative terms or gives bland answers to questions.

6.
7. Refers to self in derogatory terms. Reports that other children refer to him/her frequently by using derogatory nicknames and child puts self down.

Depressed Feelings

What things make you feel unhappy?
When you feel unhappy how long does it last? An hour? A few hours? A whole day? How often do you feel like this? Every week? Every two weeks? (Note: for younger children, one hour may be equivalent of 1/2 day or more in older children.)
Do other people know when you are sad?
Do you feel sad just at certain times, like when you mother is away?
When you feel unhappy, how miserable do you feel? Do you ever feel so bad it hurts? How often does it feel bad? (Reactivity is an indicator of degree of depressed feelings.)

Ratings

1. Occasional feelings of unhappiness which quickly disappear.
2.
3. Describes sustained periods of unhappiness which appear excessive for events described.
4.
5. Feels unhappy most of the time without a major precipitating cause.
6.
7. Feels unhappy all of the time. Accompanied by psychic pain (e.g., "I can't stand it").

Morbid Ideation

Have you ever had a pet die? A friend? A relative? Do you think about it now? How often?
Do you ever think about someone dying in your family? Who? Describe. How often do you think about it?
Do you ever worry about everyone else? Who?
Do you ever think that you might die? Tell me about it.
How often do you have these kinds of thoughts?

Ratings

1. None.
2.
3. Has some morbid thoughts, all of which relate to a reality event but seem excessive.
4.
5. Preoccupied with morbid thoughts several times a week. Morbid thoughts extend beyond external reality.
6.
7. Preoccupied with death themes or morbid thoughts that are elaborate, extensive or bizarre on a daily basis.

Suicidal Ideation

Do you know what the word suicide means?
Have you ever thought of doing it? When? (If yes) How have you thought of doing it?
Have you ever said you would like to kill yourself even if you didn't mean it? Describe.
(If appropriate) Have you ever tried to kill yourself?

Ratings

1. Understands the word "suicide" but does not apply term to self.
2. Sharp denial of suicidal thoughts.
3. Has thoughts about suicide, usually when angry.
4.
5. Has recurrent thoughts of suicide.
6.
7. Has made suicide attempt within the last month or is actively suicidal.

Weeping

Do you ever cry very much?
Do you sometimes feel like crying even if you don't cry? What sort of things make you feel this way? How often do these occur?
Do you think you feel like crying more than your friends?
Do you ever feel like crying for no reason?

Ratings

1. Normal for age.
2. Suggestive statements that child cries, or feels like crying, more frequently than peers.
3. Child cries slightly more than peers.
4.
5. Cries or feels like crying frequently (several times a week). Admits to crying without knowing reason why.
6.
7. Cries nearly every day.

The following items are rated by the clinician based on the child's nonverbal behavior.

Depressed Affect

Ratings

1. Definitely not depressed. Facial expression and voice animated during interview.
2. Mild suppression of affect. Some loss of spontaneity.
3. Overall loss of spontaneity. Looks distinctly unhappy during parts of the interview. May still be able to smile when discussing non-threatening areas.
4.
5. Moderate restriction of affect throughout most of interview. Has longer and frequent periods of looking distinctly unhappy.
6.
7. Severe. Looks sad, withdrawn. Minimal verbal interaction throughout interview. Cries or may appear tearful.

Tempo of Speech

Ratings

1. Normal
2. Slow
3. Slow: delays interview.
4.
5. Severe. Low; marked interference with interview.

Hypoactivity

Ratings

1. None.
2.
3. Mild. Some body movements.
4.
5. Moderate. Definite motor retardation.
6.
7. Severe. Motionless throughout interview.

Preliminary Studies of the Reliability and Validity of the Children's Depression Rating Scale

ELVA O. POZNANSKI, M.D., JANET A. GROSSMAN, R.N., M.S.N., YAEL BUCHSBAUM, PH.D., MARTA BANEGAS, M.D., LINDA FREEMAN, M.D., AND ROBERT GIBBONS, PH.D.

The Children's Depression Rating Scale, revised version (CDRS-R), is a reliable, clinician-rated scale which differentiates the depressed from the nondepressed child. The sum score of the CDRS-R appears to provide a better estimate of depressive symptomatology than does clinical impression. The relationship of the sum of the CDRS-R with global clinical ratings of depression indicates that the scale measures the severity of depression which is its primary purpose. The scale is not affected by the age of the child in our clinical sample, and the content of the items grouped as mood, somatic, subjective, and behavior all show good correlations with depression. The CDRS-R has been shown to be useful in a variety of settings, suggesting it is useful in both primary and secondary depressions.

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The Children's Depression Rating Scale, revised version (CDRS-R), is a clinician-rated instrument for the assessment of the severity of depression in children ages 6–12 years. The majority of depression rating scales for children which have been published are self-report scales (Birleson, 1980; Kovacs, 1981). A self-report scale reliably quantifies subjective dysphoria but is less useful when the individual does not perceive his/her own affective state or rates himself or herself disproportionately high or low as compared to others in a given clinical state.

The general need for depression rating scales for children has become more evident as cross-sectional studies of the incidence of childhood depression show this is a common disorder in psychiatric populations. In addition, as treatment strategies emerge, the need to measure change both in an individual child and in groups of children is apparent.

The senior author's early stance that depression in children could be directly observed rather than inferred formed the basis from which the scale was developed (Poznanski and Zrull, 1970). The Children's Depression Rating Scale emphasizes the central importance of the child's ability to report verbally symptoms to their affective state and the direct observation of the child's behavior. Like other depression rating scales, the CDRS-R relates to the diagnosis of depression but cannot in itself make that diagnosis as information relating to other psychiatric diagnoses is lacking. The reliability of the child in reporting affective symptoms has been confirmed in several studies (Brumback and Weinberg, 1977; Carlson and Cantwell, 1979; Cytryn et al., 1980).

Review of the Literature

Rating scales can be divided into two types, namely, self-report and clinician-rated scales. Typically, a self-report protocol, with its obvious advantage of using less professional time, has not proven as reliable as clinician-rated scales. Carroll et al. (1973), in a review of the literature of depression rating scales, found a moderate correlation of self-reported symptoms of depression, with a clinician's rating of depression ($r = 0.42$) in a sample of adults. Prusoff et al. (1972) reported correlations between these two types of scales as ranging from 0.11 to 0.63. The majority of these studies have used different scales for the self-reported rating and clinician's rating. This presents a major methodological problem. The Hamilton Scale (Hamilton, 1960), which is clinician rated, is extensively used in clinical and research work with adults. The Carroll Scale (Carroll et al., 1981), which is a self-inventory, was specially designed to correspond with the Hamilton. As such, a comparison of the Carroll and Hamilton Scales overcomes the problem of using two unrelated instruments, and the correlation between these scales is higher than in the comparison of unrelated scales ($r = 0.67$) (Carroll et al., 1981).

Dr. Poznanski is Professor, Ms. Grossman is Instructor, Dr. Buchsbaum is Research Associate, and Dr. Banegas is Assistant Clinical Professor, Department of Psychiatry, University of Illinois at Chicago. Dr. Freeman is Assistant Professor of Psychiatry, Department of Psychiatry, University of Illinois at Chicago, and Staff Psychiatrist, Institute for Juvenile Research, University of Illinois at Chicago. Dr. Gibbons is Assistant Professor of Biostatistics, Department of Psychiatry, Illinois State Psychiatric Institute, Chicago.

Requests for reprints should be addressed to Dr. Poznanski, Department of Psychiatry, University of Illinois at Chicago, 912 S. Wood St., Chicago, IL 60612.

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Self-rating scales with young children need to be "interviewer-assisted" in that children can understand oral language before they can read it. Thus, most children under 9 years of age must have a scale read to them. The latter process introduces a potential bias in that the child's relationship to the adult reading the scale may influence the response. The influence and direction of this type of bias has not been studied in either adult or child populations.

The Children's Depression Inventory (CDI) (Kovacs, 1981) was the first and is the most widely used self-report measure used in childhood depression research. It was developed by Kovacs from the Beck Depression Inventory (Beck, 1969) for adults. The CDI has 27 items with a 3-point scale for severity. The CDI correlates moderately with global clinical depression rating ($r = 0.55$). Its main disadvantage is its reliability (Carlson and Cantwell, 1979), which has been a difficulty in any self-report measure.

In addition to the CDI, the only other self-report measure of depression in children that has had reported statistical analysis is a scale devised by Birleson (1980). His scale has 18 items which are simply and concretely worded and pose a forced choice situation, that is, a yes or no answer.

At least three clinical rating scales for depression in children are used in research. McKnew et al. (1979) developed and used the Children's Affective Rating Scale (CARS). The major drawback to this scale is that each item has a 10-point scale for severity without subcategory definitions, making it more difficult to obtain good interreliability. In addition, its subscale on fantasy is difficult to elicit and is subject to interpretation. Many mildly depressed children, as well as schizophrenic children with depressive affect, can provide fantasy material. However, reports by moderately to severely depressed children are characterized by slow, short answers. Therefore, eliciting fantasy material can be difficult to obtain.

Two diagnostic structured interviews, the Bellevue Index of Depression (Petti, 1978) and the Kiddies Schedule for Affective Disorders and Schizophrenia (K-SADS) (Puig-Antich et al., 1978) are used for both the diagnosis of depression in children and as a measure of severity. Both of these structured interviews for depression in childhood have been used diagnostically in clinical studies of depressed children. No statistical analyses of their data have been published relative to their use as severity rating measures of depression.

Review of the CDRS

A Depression Rating Scale for Children (CDRS) was devised and subsequently first used in a formal study of a random sample of children in an inpatient pediatric unit in a medical hospital (Poznanski et al., 1979). This population was selected primarily for ease of entry. The initial study of CDRS reliability and validity was done by two child psychiatrists, independently rating each child on a global rating of depression and the CDRS. The two sum scores of the CDRS had an inter-rater reliability of $r = 0.96$. As an index of convergent validity, the correlation of one rater's total CDRS score with a global clinical rating of depression from the other interviewer was $r = 0.89$.

Since the above study was conducted in a pediatric unit, a high occurrence of secondary depression was expected. The next step was to rate consecutive admissions to a Children's Unit of a Regional Mental Institution in the same manner as described above (Poznanski et al., 1983). In this study, four psychiatrists were used, two experienced and two inexperienced. The between-rater correlation was $r = 0.80$. Similarly, across-rater correlations (i.e. correlation between experienced and inexperienced raters) were $r = 0.75$ and $r = 0.74$. In this study, as well as in the study in the pediatric ward, a high correlation was found between global ratings of depression and the sum of the CDRS-R, indicating that the scale was indeed measuring severity.

Although the CDRS scale was performing well, since its inception 5 years of clinical research in childhood depression resulted in the recognition that several modifications would improve the clinical utility of the scale.

Scale Description and Modification

The CDRS-R is a clinician-rated scale for severity of depression of children ages 6–12 years. It usually takes about 20–30 min to interview a child in order to make a rating. Depressed children generally take longer to interview than nondepressed children. All possible sources of information can be used, i.e., additional information from the parent, child care worker, teacher or other sources. However, the emphasis is placed on information obtained from the child.

The initial items for the CDRS were selected on the basis of clinical experience, as there are not many well-developed objective methods for validating the diagnosis of depression in children. Drug response has been used in part with adults. Other measures, such as the Dexamethasone Suppression Test, are currently being developed for use in children, but are, as yet, less reliable than clinical diagnosis (Poznanski et al., 1983). Hence, the cardinal manifestations of childhood depression for the CDRS were by necessity derived from clinical experience.

The original CDRS had the following items: depressed mood, weeping, self-esteem and pathological

guilt, morbid ideation, suicidal ideation, schoolwork, social withdrawal, irritability, anhedonia, tempo of speech, appetite, sleep, hypoactivity, physical complaints and fatigue. In the CDRS-R, the items dealing with self-esteem and guilt have been split into separate categories and a verbal item for feelings of depression by the child was added. The original item of depressed mood in the CDRS is retained in the CDRS-R and is rated on the basis of nonverbal behavior. These changes were made for the following reasons. A verbal item of depressed mood is useful in order to distinguish clinically those children who relate feelings of unhappiness without showing depressive affect from children who deny feelings of unhappiness, despite manifesting depressive affect. Clinically, children in the first group, i.e., those who have only verbal dysphoria, are less depressed than children who show persistent depressive affect. A report of dysphoria by the parent is sometimes difficult to interpret. The parents' reports of depression in their child's behavior are frequently contaminated by feelings that the parents may have themselves, particularly if the parents are depressed. Guilt and self-esteem are separated so that the characteristics of each behavior could be analyzed separately. Hence the CDRS-R has 17 items, 14 of which are scored on the basis of verbal observation and three on nonverbal items: tempo of language, hypoactivity, and nonverbal expression of depressed affect.

The original CDRS had 15 items with a total score of 61 points. Since a rating of 1 = normal, the baseline is the total number of items, i.e., 15 for CDRS and 17 for the CDRS-R, rather than 0. The new CDRS-R has 17 items with a total of 113 points.

The range of possible points in each subcategory was 1–5 in the CDRS and has been increased from 1 to 7 points in the CDRS-R. The additional 2 points were added as clinicians were rating between numbers on the old scale, thus creating fractions. In addition, lengthening the pathological end of the scale increased the chances that slight lessening or worsening of symptomatology would be recorded. The lengthening of each subscale is shown in Table 1.

If the subcategory description does not seem to describe the child's behavior, the 1–7 scale can be used free of description with the following guidelines, 1 = normal, 2 = doubtful pathology, 3 = mild symptomatology, 5 = moderate symptomatology and 7 = severe symptomatology for the items.

All items have a description of normalcy and mild, moderate, and severe psychopathology. Whenever possible, the subcategory descriptions are meant to reflect increasing severity, both in terms of the *frequency* of the behavior and the intensity of such a behavior. Most of the time, the frequency and intensity of behavior increase together. However, occasionally one might encounter a child who shows a very intense behavior which occurs infrequently. The importance given to the frequency versus the intensity of behavior is ultimately dependent on clinical judgment. An example of subcategory description is shown in Table 2.

Conversion of the CDRS to the CDRS-R

The conversion formula for converting a CDRS score to a CDRS-R score was determined by linear regression. The following equation is satisfactory if the CDRS score is above 20:

$$\text{CDRS-R} = -12.1 + 1.6 \times \text{CDRS}$$

Method

Fifty-three children who were referred for possible depression were evaluated in two outpatient clinical-research units, first at the University of Michigan and later at the University of Illinois. The demographic

TABLE 1

Comparison of Scaling: CDRS and CDRS-R

CDRS		CDRS-R
0	Unable to rate	0
1	Normal	1
2	Doubtful	2
3	Mild	3
		4
4	Moderate	5
		6
5	Severe	7

TABLE 2

Description for CDRS-R Item of Anhedonia

CAPACITY TO HAVE FUN (0–7)

0 Unable to rate

1 Interest and activities realistically appropriate for age, personality, and social environment. Shows no appreciable change with present illness. Any feelings of boredom transient

2 Doubtful

3 Mild. Describes some activities realistically available several times a week but not on a daily basis. Shows interest but not enthusiasm. May express some episodes of boredom more than once a week

4 Mild to moderate

5 Moderate. Is easily bored. Complains of "nothing to do." Participates in structured activities with a "going through the motions" attitude

6 Moderate to severe. Shows no enthusiasm or real interest. Has difficulty naming activities. May express interest primarily in activities that are (realistically) *unavailable* on a daily or weekly basis

7 Severe. Has no initiative to become involved in any activities. Primarily passive. Watches others play or watches television but shows little interest in program. Requires coaxing and/or pushing to get involved in activity

characteristics of these two populations suggest it is reasonable to combine these two groups as shown in Table 3.

The age and socioeconomic status (SES) are similar in the two populations. The sex ratios show a predominance of males in both samples as reported by other researchers. The major difference in these two populations was an ethnically mixed population in the Chicago sample as compared to an entirely white population in Ann Arbor.

Children were referred for an outpatient psychiatric evaluation by a diverse group of professionals, agencies and clinics, both private and public. Children were accepted for evaluation in our clinic if they met our inclusion-exclusion criteria. For inclusion in our study, the child must have been between the ages of 6 and 12 years, not have a major physical illness, have an IQ over 70, and be off all mood altering drugs for 2 weeks prior to the evaluation. The child must also have had a reliable adult informant to give the child's past history. Legal consent to participate in our study was required.

In both the University of Michigan and the University of Illinois clinics, the diagnostic evaluation was carried out over 2 days, 2 weeks apart. During the entire evaluation, the child and parent(s) were interviewed independently by different clinicians. The research protocol included an unstructured interview of the child, the K-SADS, a clinical global rating of depression, and a Global Assessment Score (Endicott et al., 1976). The parent or parents were interviewed about the child simultaneously while the child was interviewed by a different clinician, using the same instruments in order to ensure independent data collection.

The majority of the children in the two samples were interviewed for the K-SADS and the CDRS-R by two different child psychiatrists. Also, in order to reduce rater bias effects, the CDRS-R obtained on the second visit was administered by the clinician who did not previously rate the child.

The results of the above interviews were not shared until a clinical conference was held following the second day of evaluation. Thus each child had two CDRS-R scores obtained by different raters 2 weeks apart. The purpose of the clinical conference is to share information, establish the diagnosis, and formulate the recommendations for treatment. A follow-up visit to the clinic was scheduled 6 weeks after the first visit, both to obtain a third CDRS-R and to give the parents an interpretation of our findings.

TABLE 3

Demographics of Two Clinical Populations

	Chicago	Ann Arbor	*p*
Age	$\bar{X}$ = 9.2	$\bar{X}$ = 9.8	NS
	S.D. = 2.2	S.D. = 1.10	
Sex	M = (60%)	M = (81%)	
	F = (40%)	F = (19%)	
SES	$\bar{X}$ = 4.00	$\bar{X}$ = 3.38	NS
	S.D. = 1.24	S.D. = 1.24	
Race	B 43%	W 100%	
	W 40%		
	H 17%		

Results

Relationship of CDRS-R to Diagnosis of Depression

Thirty-four of the 53 children qualified for a clinical depression by RDC criteria, combining the "Definite" and "Probable" groups (the "Definite" group by DSM-III criteria and by Poznanski criteria (Poznanski et al., 1979)). The mean CDRS-R of the RDC, DSM-III and Poznanski diagnostic groups of depressed children as previously described varied from 50 to 52, suggesting that group differences between depressed children using these diagnostic criteria were minor. Thirty-two children met all three sets of diagnostic criteria, while the additional two children varied with each set of diagnostic criteria. Poznanski criteria differ from RDC and DSM-III primarily in having a nonverbal as well as a verbal definition of dysphoria. Since there were minor changes in group composition with the different diagnostic criteria, Poznanski criteria have been used for consistency within our clinical research unit and have been used by our group since the beginning of systematic research data collection in childhood depression. Table 4 shows the relationship between a clinical diagnosis of depression using Poznanski's criteria and the mean CDRS-R.

The difference between the depressed and nondepressed CDRS-R means is probably greater in the general population than shown in the Table 4 because children are referred to our clinic for suspected dysphoria. Hence, the comparison sample probably has more borderline depressed children than a more typical outpatient psychiatric population.

Our clinical experience has been that a child with an initial CDRS-R score of 40 or more ultimately obtains a diagnosis of a clinical depression. The mean CDRS-R of 52 and 49 with a standard deviation of 10

TABLE 4

Comparison of CDRS-R with Clinical Diagnosis of Depression

Diagnosis	*N*	Mean CDRS-R	S.D.
Major depressive disorder:			
Definite group	28	52	10
"Definite" and "probable" groups	34	49	11
Nondepressed psychiatric disorder	19	29	4

and 11 fits with this clinical experience. Two children diagnosed as clinically depressed had scores below 40 and their scores were outside the range of one standard deviation of the remaining group of "Definite" and "Probable" depressed groups. Although it needs to be tested, it appears that some children with clinical depressions and low CDRS-R scores may deny depressive symptomatology if there is a stigma of depressive illness in their family.

Five children had sum scores over 60 and these children clinically appear to be severely depressed. Thus the group of children with CDRS-R scores between 40 and 60 points contain the majority of children with mild to moderate depression and a division into the two clinical subgroups of mild and moderate is purely arbitrary. In our experience, the duration of the depressive episode appears to be clinically more important than the exact CDRS-R score at the time of evaluation; however, this problem merits further study.

Correlation between a Global Rating of Depression and the CDRS-R

Prior to scoring the CDRS-R, the clinician gave the child a Global Rating of Depression based on an overall clinical impression. This rating, which is a 1–7-point scale, was then correlated with the total CDRS-R score. The correlation of the CDRS-R with the global rating was $r = 0.87$. Hence, an improvement of the CDRS-R over the CDRS is that it increases the correlation with Global Rating of Depression.

One way to study the correlation of the mean Global Rating of Depression with the mean sum of the CDRS-R scores is to assign somewhat arbitrary points to the global rating based on clinical experience. Table 5 shows the association between groups based on global ratings of depression and average CDRS-R scores.

The majority of children felt to be nondepressed clinically were given a global rating under 2.5 on a 7-point scale. Global ratings over 4 were rare for the nondepressed group, partially due to hesitancies on the part of clinicians to rate a child as moderately or severely depressed on clinical appearance alone.

The correlation of the initial global rating with the sum of the CDRS-R indicates that a wide range of scores are encountered, particularly with global ratings of 1 and 2. However, the sum of the CDRS-R at the first interview was found to be more predictive of the final clinical diagnosis of depression or a nondepressed psychiatric diagnosis after the total evaluation than the initial global rating. Hence, the value of a depression rating scale systematically to assess depressive symptomatology has some diagnostic value.

Content of the CDRS Items Relative to the Child's Age Function and Severity of Depression

The items on the CDRS-R were broken down into four groups based on clinical experience. These four groups were the following:

1. *Mood*
   Depressed feelings (verbal)
   Depressed feelings (nonverbal)
   Irritability
   Weeping
2. *Somatic*
   Appetite—either increase or decrease
   Sleep—initial, middle and/or terminal insomnia
   Excessive fatigue
   Psychomotor retardation—includes tempo of speech and hypoactivity
   Physical complaints (nonorganic).
3. *Subjective*
   Self-esteem
   Guilt
   Morbid ideation
   Suicide ideation
4. *Behavior*
   Anhedonia
   Social withdrawal
   Schoolwork

Correlation analyses (using Pearson product-moment correlation coefficient) were then carried out, to assess the strength of the relationship between each of these groups and the variables of age, Global Assessment Score (GAS), Global Rating Depression (Global) and the sum score of the CDRS-R. The correlations are shown in Table 6.

The highest correlations were obtained for each of the subgroups to items (i.e., mood, somatic, subjective and behavior) and both the global rating of depression

TABLE 5

Association between Global Ratings of Depression and CDRS-R

Mean Global	*N*	CDRS-R	S.D.
<2.4	31	33	9.1
2.5–3.5	10	45	6.5
3.5–4.5	4	60	6.5
>4.5	7	68	11

TABLE 6

*Correlations between Groups of Items and Associated Variables**

	Age	GAS	Global	CDRS-R
Mood	−0.02	−0.30	0.86**	0.88**
Somatic	0.004	−0.10	0.75**	0.86**
Subjective	0.11	−0.42*	0.75**	0.84**
Behavior	0.17	−0.25	0.53**	0.68**

*$p < 0.02$, **$p < 0.001$.

and the sum score of the CDRS-R. The correlations between each of the four groups and the CDRS-R score account for more of the variance than the correlations to the Global Rating, although both groups of scores are highly significant. These findings suggest that the scale is unidimensional and is tapping several symptom clusters which make up a depressive syndrome.

The three groups which had the highest correlation to sum scores on the CDRS-R and accounted for the greatest proportion of the variance, were the groups containing mood, somatic and subjective items. The highly significant correlation with mood items would be expected, since depression in children is both observable by trained clinicians and is verbalized by children when queried. The significant correlation between the somatic items and CDRS score suggests that the "vegetative" signs such as sleep and appetite disturbances, are as centrally important in childhood depression as they are in adult depression. The subjective items of self-esteem, guilt, morbid and suicidal ideation also had a significant correlation, suggesting that these are symptoms which can be assessed in children and which contribute to overall depressive symptomatology.

The group of behavioral items, i.e., anhedonia, social withdrawal and problems with schoolwork, are often items which depend on reports from multiple sources (e.g., parents, school 1 report) and by direct observation. While the correlation for these behavior items to sum score or the CDRS-R was still significant, it did not account for as much of the variance as the other three groups. It may be that items in this behavior grouping are not unique to depression, and this accounts for the slightly lower correlation.

The lack of correlation with age suggests that the ratings on the CDRS-R are not affected by age of the child in our psychiatric population. Therefore, children such as we see in the age range of 6–8 years can be evaluated using the CDRS-R, although it is unclear if more reliance is placed on clinical judgment when rating younger and less verbal children.

A modest significant correlation was obtained for the subjective group of items and the Global Assessment Score. It may be that symptoms such as lowered self-esteem, feelings of guilt and morbid or suicidal ideation impinge upon the child's overall level of functioning more so than mood, somatic, and behavioral items. However, further analyses which will allow us to assess the contribution of each of these items, as well as to investigate the factor structure of the CDRS-R, are clearly needed.

Test-Retest Reliability of the CDRS-R

The inter-rater reliability was determined by the correlation between the 0 and 2-week score in the Chicago sample as it is done by two different raters: $r = 0.86$ and $N = 32$.

The correlations between the 2-week and 6-week ratings ($r = 0.81$, $N = 36$) were also significant, indicating the stability of both the syndrome and the measure.

TABLE 7

Mean CDRS-R Scores in Three Samples

Sample	N	Mean CDRS-R
Children's Medical Inpatient—random sample	30	30
Children's Psychiatric Inpatient—consecutive admissions	30	36
Children's Outpatient Population—referred to dysphoria:		
Ann Arbor	22	38
Chicago	31	44

Discussion

The CDRS and the CDRS-R have been used in three different clinical populations: a pediatric unit in a medical hospital, a psychiatric inpatient unit, and psychiatric outpatient clinics. Our increasing knowledge of the clinical phenomenology of childhood depression undoubtedly influenced the clinicians' perception of depressive symptomatology and may thus affect the rating of the instrument. Nevertheless, the mean score of the CDRS-R in these populations goes in the expected direction. For example, the mean CDRS-R was lowest in a random sample of medically ill children, higher in consecutive admissions to a psychiatric inpatient unit, and highest in the groups of children specifically referred for possible depressions. Table 7 summarizes these findings.

Thus the CDRS-R has been shown to be useful in a variety of settings, and in diagnosing both primary and secondary depressions.

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16.1.9.
Ethical Review Board Information and Protocol-Specific Informed Consent Document

04/22/98 17:11 [redacted] 01

[redacted]

Institutional Review Board

April 22, 1998

[redacted]

[redacted] Fluoxetine Versus Placebo In Childhood/Adolescent Depression
(Protocol B1Y-MC-HCJE dated 17 November 1997)

Dear [redacted]

Thank you for submitting the modifications requested by the Institutional Review Board. It has been determined that you have complied with the specified conditions for approval, and this letter is notification of final IRB approval of your study. Please use the approved consent form attached here, and destroy all other drafts or undated copies. Continuing review of this study is scheduled for April 1999.

University and Federal regulations require that written consent be obtained from all human subjects in your study. A photocopy of the signed consent form should be given to each participant. The copy of the consent form bearing original signatures should be kept with other records of this research for at least five years past the completion of the study. The University attorneys have asked us to remind investigators to put a photocopy of the signed consent form in a subject's medical record.

The U. S. Department of Health and Human Services requires you to submit annual and terminal progress reports for continuing review by the IRB. Please report to the Board any adverse events or deaths that occur during the study. It is required that you keep the IRB informed of such events to prevent sanctions from being placed on the institution. If you require a modification to this protocol or the consent form, you should obtain appropriate review and approval by the Board prior to implementing any changes.

Approval by the appropriate authority at a collaborating facility is required before subjects may be enrolled on this study.

If you have any questions related to this research or the IRB, you may telephone me at [redacted]

Sincerely,

[redacted]

[redacted]

APR 22 '98 17:23 2146405941 PAGE.01

Department of Psychiatry

July 22, 1998

RE: Fluoxetine in Adolescents [redacted]

Dear [redacted]

Please find enclosed the amendments to the protocol for the Eli Lilly sponsored trial of fluoxetine in adolescents. The amendments include changes to the analysis plan and to allow the use of the MAGIC, DICA, or electronic DICA. These changes do not affect the consent form, so the original consent will continue to be used. If you have any questions, please feel free to contact me at [redacted]

Thank you,

March 23, 1999

RE: Fluoxetine in Adolescents

Dear

Please find enclosed an amendment to the Risk section of the consent form, as well as the information received regarding these changes from Eli Lilly. The changes include re-ordering the risks listed in the risk section and deleting the statement about fluoxetine being associated with increased rates of death among newborn rats.

If you have any questions, please call me at

Thank you,

04/19/99 14:44 [redacted] [redacted] [redacted]

[redacted]

Institutional Review Board

April 12, 1999

[redacted]

IRB File 0398 10400 Fluoxetine in Childhood Depression

Dear [redacted]

The Institutional Review Board voted today to update approval of the protocol and consent form for one year. Please use the approved consent form attached here, and destroy all other drafts or undated copies. Continuing review of this study is scheduled for April 10, 2000.

University and Federal regulations require that written consent be obtained from all subjects in your study. A photocopy of the signed consent form should be given to each participant. The copy of the consent form bearing original signatures should be kept with other records of this research for at least five years past the completion of the study. The University attorneys recommend that investigators file a photocopy of the signed consent form in a subject's medical record.

The U. S. Department of Health and Human Services requires you to submit annual and terminal reports for review by the IRB. Please report to the Board any adverse events or deaths that occur during the study. It is required that you keep the IRB informed of such events to prevent sanctions from being placed on the institution. If you require a modification to this protocol or the consent form, you should obtain appropriate review and approval by the Board prior to implementing any changes.

If you have any questions related to this research or the IRB, you may telephone me at [redacted]

Sincerely,

[redacted]

[redacted]

APR 19 '99 15:54 2144565941 PAGE.01

[redacted]

INSTITUTIONAL REVIEW BOARD FOR HUMAN INVESTIGATION

TO: [redacted]
Department Chairman

The [redacted] has reviewed the proposal

Submitted by: [redacted]

Entitled: Fluoxetine versus placebo in childhood/adolescent depression(06-98-24)

Please be advised that with respect to:
(1) The rights and welfare of the individuals
(2) The appropriateness of the methods to be used to secure informed consent
(3) The risks and potential medical benefits of the investigation the Board considers this project

XXXX **FULLY ACCEPTABLE, without reservation; approved through** 06/2000

☐ **NOT ACCEPTABLE for reasons noted**

REMARKS:

The annual review is due by the date noted above.
Please reference the IRB number on future reviews and correspondence

Administratively Approved
(BIY-MC-HCJE/v:6.30.98)

Date(s) of Committee Review

June 8, 1999
Date of Approval

[redacted]

TYPE PROJECT ☐ New ☐ Renewal XXXX Addendum

HUMAN RISK XXXX Yes ☐ No

SOURCE OF SUPPORT: ☐ None ☐ Departmental XXXX Outside Funding

Agency (Potential) Eli Lilly & Company Agency Number _____

ARE ANY OF THE FOLLOWING INVOLVED? ☐ No XXXX Yes, those checked

XXXX Minors ☐ Fetuses ☐ Abortuses ☐ Prisoners ☐ Pregnant Women ☐ Mentally Retarded ☐ Mentally Disabled

CC: Investigator, ORA, General Clinical Research Center

The [redacted] operates under the HHS Multiple Project Assurance of Compliance number [redacted]

Rev. 01/97

[redacted]

INSTITUTIONAL REVIEW BOARD FOR HUMAN INVESTIGATION

TO: [redacted]
Department Chairman

The [redacted] has reviewed the proposal

Submitted by: [redacted]

Entitled: Fluoxetine versus placebo in childhood/adolescent depression(06-98-24)

Please be advised that with respect to:
(1) The rights and welfare of the individuals
(2) The appropriateness of the methods to be used to secure informed consent
(3) The risks and potential medical benefits of the investigation the Board considers this project

☒ **FULLY ACCEPTABLE, without reservation; approved through** 06/99

☐ **NOT ACCEPTABLE for reasons noted**

REMARKS:

The annual review is due by the date noted above.
Please reference the IRB number on future reviews and correspondence

(BIY-MC-HCJE/v:6.30.98)

Administratively Approved
Amendment #1

Date(s) of Committee Review

January 21, 1999
Date of Approval

[redacted]

TYPE PROJECT ☐ New ☐ Renewal ☒ Addendum

HUMAN RISK ☒ Yes ☐ No

SOURCE OF SUPPORT: ☐ None ☐ Departmental ☒ Outside Funding

Agency (Potential) Eli Lilly & Company Agency Number

ARE ANY OF THE FOLLOWING INVOLVED? ☐ No ☒ Yes, those checked

☒ Minors ☐ Fetuses ☐ Abortuses ☐ Prisoners ☐ Pregnant Women ☐ Mentally Retarded ☐ Mentally Disabled

: Investigator, ORA, General Clinical Research Center

The [redacted] operates under the HHS Multiple Project Assurance of Compliance number [redacted]

Rev. 01/97

[redacted]

INSTITUTIONAL REVIEW BOARD FOR HUMAN INVESTIGATION

TO: [redacted]
Department Chairman

The University Hospitals Institutional Review Board has reviewed the proposal

Submitted by: [redacted]

Entitled: Fluoxetine versus placebo in childhood/adolescent depression(06-98-24) (Prot. BIY-MC-HCJE.v:11.17.97)

Please be advised that with respect to:
(1) The rights and welfare of the individuals
(2) The appropriateness of the methods to be used to secure informed consent
(3) The risks and potential medical benefits of the investigation the Board considers this project

☒ **FULLY ACCEPTABLE, without reservation; approved through** 06/99

☐ **NOT ACCEPTABLE for reasons noted**

REMARKS:

The annual review is due by the date noted above.
Please reference the IRB number on future reviews and correspondence

June 16, 1998
Date(s) of Committee Review

June 24, 1998
Date of Approval

[redacted]

TYPE PROJECT ☒ New ☐ Renewal ☐ Addendum

HUMAN RISK ☒ Yes ☐ No

SOURCE OF SUPPORT: ☐ None ☐ Departmental ☒ Outside Funding

Agency (Potential) Lilly & Company Agency Number _____

ARE ANY OF THE FOLLOWING INVOLVED? ☐ No ☒ Yes, those checked

☒ Minors ☐ Fetuses ☐ Abortuses ☐ Prisoners ☐ Pregnant Women ☐ Mentally Retarded ☐ Mentally Disabled

C: Investigator, ORA, General Clinical Research Center

The [redacted] *operates under the HHS Multiple Project Assurance of Compliance number* [redacted]

01/97

45

[redacted]

PATIENT CONSENT FOR INVESTIGATIONAL STUDIES

TITLE OF PROJECT: Fluoxetine versus Placebo in Childhood/ Adolescent Depression (B1Y-MC-HCJE/v:6.30.98)

5.14.99

DESCRIPTION OF STUDIES

Introduction

I/my child is being invited to take part voluntarily in a research study of a prescription drug known as fluoxetine hydrochloride (LY110140) when compared to placebo (inactive substance) in children and adolescents requiring treatment for depression. My/my child's participation in this study is expected to last up to 54 weeks. Up to 220 patients will be participating in this study.

Purpose of the Study

The purposes of this study are to determine:

* The safety of fluoxetine hydrochloride and any side effects that might be associated with it.
* Whether fluoxetine hydrochloride can help children/adolescent patients with major depression. Fluoxetine hydrochloride might not have any good effect for me/my child.
* How much fluoxetine hydrochloride should be given to patients.
* If there are any differences in the effectiveness and safety of fluoxetine hydrochloride between children (aged 8 to <13 years) and adolescents (aged 13 to <18 years).
* Blood levels of study drug (fluoxetine hydrochloride and norfluoxetine) in children and adolescents receiving different daily doses.

Qualifications to Participate

Some of the requirements to be in this study are:

* I/my child must be a child (aged 8 to <13 years) or an adolescent (aged 13 to <18 years) at the time of entry into study. If I/my child has reached my/my child's 18th birthday, I/my child will not be able to participate.
* The parent(s) or legal guardian give permission for me/my child to be in the study.
* I/my child must have been diagnosed with major depression.
* I/my child must be able to swallow whole medication without difficulty.
* I/my child must be able to have my/my child's blood tested several times during the study.
* I/my child must be able to visit the doctor's office as needed for fifty-four (54) weeks.

I/my child cannot participate in this study if:

* I/my child has a serious medical illness, such as heart, liver or kidney disease. (NOTE: If I/my child is uncertain about a particular condition, I/my child will discuss it with the study physician)
* I/my child is allergic to fluoxetine hydrochloride or I/my child has many bad reactions to medications.
* I/my child has had an illness serious enough for me/my child to go to the hospital within the last 12 months.

Fluoxetine Hydrochloride (LY110140) B1Y-US-HCJE
Protocol-Specific ICD Approved: 14 January 1998
Protocol-Specific ICD Amendment (a) Approved: 15 March 1999

[Patient/Subject] Initials_____

CONSENT FORM
APPROVED FOR USE WITH
PROTOCOL # 06-98-24
EXPIRATION DATE 6/2000

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PATIENT CONSENT FOR INVESTIGATIONAL STUDIES

TITLE OF PROJECT: Fluoxetine versus Placebo in Childhood/ Adolescent Depression (B1Y-MC-HCJE/v:6.30.98)

5.14.99

DESCRIPTION OF STUDIES

* I/my child is currently using medication for depression. It is especially important that I/my child NOT take any medication called a monoamine oxidase inhibitor (MAOI) for at least 2 weeks before starting fluoxetine hydrochloride or at least 6 weeks after stopping fluoxetine hydrochloride. (NOTE: If I/my child is uncertain about whether taking a particular medication means I/my child cannot participate in the study, or if another physician has prescribed medications for me/my child, I/my child will talk with the study doctor.)
* I/my child has used St John's Wort, melatonin, or tryptophan within 2 weeks prior to study entry or plan to use it within 6 weeks from discontinuation of treatment.
* I/my child has had a convulsion or seizure within the past 6 months.
* I/my child is using or abusing drugs or alcohol.
* I/my child is at risk of committing suicide.
* I/my child will need to undergo certain forms of talk therapy.
* I/my child has failed to get better with previous fluoxetine hydrochloride use.

In addition to the list above, I/my child cannot be in this study if:

* I/my child is pregnant or breast feeding. If I/my child possibly could become pregnant, I/my child must talk to the study doctor about the method of birth control that I/my child will use to avoid getting pregnant during the study and for two (2) months after the study is completed. The risks to the embryo or fetus from exposure to the study drug are unknown; pregnant women or nursing mothers may not participate. If I/my child suspects I/my child has become pregnant while participating in the study, I/my child is to contact the study doctor immediately. Some methods of birth control might be less effective due to a possible interaction with study drug.

The doctor in charge of this study or a member of the doctor's staff will discuss with me/my child the additional requirements for participation in this study.

Study Procedures

If I/my child participates, I/my child will visit the study doctor to have a physical examination that will include blood tests (needle sticks) [it will be possible to have up to 4 blood tests throughout the study for a total of approximately 4 teaspoons], urine tests and an ECG (a heart test). I/my child will also have a psychological examination and have to answer questions on several evaluations or questionnaires. Both I/my child and the parent/legal guardian(s) will be asked to answer questions on the evaluations. The doctor will explain the study and what will happen while I/my child is in the study. The study may last as long as 54 weeks.

When I/my child comes back to the doctor's office the second time, about one week later, the doctor will review all of the tests I/my child has had. The doctor will make sure I/my child is able to take the study medicine. The second visit will require both I/my child

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PATIENT CONSENT FOR INVESTIGATIONAL STUDIES

TITLE OF PROJECT: Fluoxetine versus Placebo in Childhood/ Adolescent Depression (B1Y-MC-HCJE/v:6.30.98)

5.14.99

DESCRIPTION OF STUDIES

and the parent/legal guardian(s) to answer several more evaluations or questionnaires. The doctor will again check to be sure I/my child can be in the study and I/my child will be scheduled to come back to the doctor's office for a third time about a week later.

Again at the 3rd visit both I/my child and the parent/legal guardian(s) will answer some questions on the evaluations or questionnaires and the doctor will again check to be sure I/my child can continue in the study. If I/my child can continue in the study I/my child will be given some pills (medication) to take every day, by mouth, and be scheduled for another (4th) visit about one week later.

Visit 4 will require some more questions to be answered and the doctor will check to be sure I/my child can continue in the study. If I/my child can continue in the study I/my child will be given some more pills (medication) to be taken every day, by mouth and scheduled for the 5th visit in about one week. I/my child will now take pills (medication) every day, by mouth, until the end of the study and I/my child will be scheduled to see the doctor about every week until visit 7. From visit 7 until visit 21 I/my child will see the doctor about every 2 weeks and from visit 21 through visit 26 I/my child will see the doctor about every 4 weeks. At each visit I/my child will have my/my child's vital signs checked and will answer questions on the evaluations or questionnaires. At visit 10, visit 15, visit 26, or when I/my child stops the study I/my child will need to have additional blood tests (needle sticks; approximately 1 teaspoon each) or laboratory tests or an ECG (heart test) and/or a physical examination.

Neither I/my child nor the doctor will know what medication I/my child is taking. Whether I/my child receives fluoxetine hydrochloride (real medication) or the placebo (sugar pill) will be determined by chance. One (1) out of every two (2) patients in the study will receive fluoxetine hydrochloride (real medication) and the other one (1) will receive the placebo (sugar pill). It will also be possible to start the study on fluoxetine hydrochloride (real medication) and then be switched during the study to the placebo (sugar pill). If I/my child is switched to placebo (sugar pill) I/my child will not have a chance of being switched back to fluoxetine hydrochloride (real medication). Again, neither I/my child nor my/my child's doctor will know whether I/my child is taking fluoxetine hydrochloride (real medication) or the placebo (sugar pill). Treatment non-responders (patients who leave the study because they do not get better) may be eligible for additional medical care by a mental health professional as determined by the primary investigator.

My/my child's blood or urine sample will be tested for certain types of drugs (known as controlled substances in the United States) that may affect behavior and that may be regulated by law. If my/my child's test results show that I/my child has taken these types of drugs, I/my child will be notified. The results of this test will be kept confidential and disclosed only as required by law.

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PATIENT CONSENT FOR INVESTIGATIONAL STUDIES

TITLE OF PROJECT: Fluoxetine versus Placebo in Childhood/ Adolescent Depression (B1Y-MC-HCJE/v:6.30.98)

5.14.99

DESCRIPTION OF STUDIES

Risks

I/my child understands that there may be risks for me/my child being in this study. Problems commonly (more than 5% of patients) experienced by subjects taking fluoxetine (Prozac®) who have participated in previous research studies including feeling tired, feeling jittery or nervous, upset stomach (nausea, diarrhea), having trouble sleeping, dry mouth sweating, tremors, feeling dizzy, or loss of appetite. Other problems experienced by between 1% and 5% of patients include rashes, itchiness, decreased interest in sex, changes in ability to have sex, problems concentrating, increased yawning, changes in pattern of passing utine or blurry vision. Problems which occur in less than 1% of patients include feeling over energized and elated with substantial social dysfunction (mania), losing hair, bruising, men having erections which last longer than normal, skin becoming sensitive to sunlight, allergic reactions with problems breathing, irritation of blood vessel cells, or irritation of liver cells as indicated by elevated levels of the blood of chemicals made in the liver, generally accompanied by clinical symptoms like stomach pain, loss of appetite, nausea, vomiting, diarrhea and skin and eyes turning yellow and a cluster of clinical symptoms that include changes in mental state and increases in muscle tension, in combination with autonomic nervous system dysfunction (e.g., faster rate of heart beating, big changes in blood pressure (up or down), severe fever, faster rate of breathing) that can be fatal in patients taking an MAOI together with fluoxetine or within 5 weeks after stopping fluoxetine.

For most people, needle punctures for blood draws do not cause any serious problems. However, they may cause bleeding, bruising, discomfort, infections and/or pain at the needle site or dizziness.

In addition to the bad experiences named above, fluoxetine hydrochloride or the study procedures may have other unknown risks.

Fluoxetine may pose risks to human pregnancy. For this reason I/my child cannot participate in this study if I/my child is (or becomes) pregnant. There may also be unknown risks to my/my child's embryo, fetus, or unborn child.

The questions on the evaluations or questionnaires include questions that are personal and that ask specifically about my/my child's illness and history. This may possibly make me/my child feel uncomfortable or upset, or bring back bad memories for me/my child.

Suicide is a risk of uncontrolled depression; therefore, I/my child will notify the study doctor immediately if I/my child has suicidal thoughts.

My/my child's condition may not improve or may worsen while participating in this study, whether I/my child takes fluoxetine hydrochloride (real medication) or placebo (sugar pill).

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PATIENT CONSENT FOR INVESTIGATIONAL STUDIES

TITLE OF PROJECT: Fluoxetine versus Placebo in Childhood/
Adolescent Depression (B1Y-MC-HCJE/v:6.30.98)

5.14.99

DESCRIPTION OF STUDIES

The study drug must be taken only by the person for whom it has been prescribed, and it must be kept out of reach of children or persons of limited capacity to read or understand.

If I/my child has any injury, bad effect, or any other unusual health experience during this study, I/my child will immediately tell the nurses o[redacted] and ask fo[redacted] I/my child can call at any time, day or night, to tell the study personnel about my/my child's health experiences.

Other Treatments

I/my child does not have to take part in this study to be treated for my/my child's illness or condition. Other treatments and therapies for my/my child's condition are available. Those might include other medications or counseling.

Voluntary Participation

My/my child's taking part in this study is entirely voluntary. I/my child may refuse to take part in the study or I/my child may stop my/my child's participation in the study at any time, without a penalty or loss of benefits to which I/my child was entitled before taking part in the study. If I/my child decides to stop being part of this study[redacted] or one of the staff members will talk to me/my child about making this choice.

Stopping the Study

The study doctors or Eli Lilly and Company (the sponsor of this study) may stop this study, or my/my child being a part of it, at any time for any reason without my/my child's consent. If this happens, it might be the result of a bad reaction that I/my child has to fluoxetine hydrochloride or new information that my/my child's physician or the sponsor learns about fluoxetine hydrochloride's safety or effectiveness.

Treatment and Compensation for Injury

If I/my child follows the directions of the doctors in charge of this study and I/my child is physically injured due to any substance or procedure properly given under the plan for this study, Eli Lilly and Company will pay the medical expenses for the treatment of that injury which are not covered by my/my child's medical insurance, by a government program, or by any other third party.

Possible Benefits

I/my child may receive information about my/my child's health from any physical examinations and laboratory tests to be done in this study and I/my child may receive medication during the study at no cost to me/my child.

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PATIENT CONSENT FOR INVESTIGATIONAL STUDIES

TITLE OF PROJECT: Fluoxetine versus Placebo in Childhood/ Adolescent Depression (B1Y-MC-HCJE/v:6.30.98)

5.14.99

DESCRIPTION OF STUDIES

Although fluoxetine hydrochloride is being tested as a treatment for a condition that I/my child may have, there is no guarantee that I/my child will receive any medical benefit. However, my/my child's condition may improve even if I/my child is taking the placebo (sugar pill).

I/my child will be paid $25 per visit ($650/completion of entire study) for participation in this study to cover expenses like travel, parking and other inconveniences.

Information obtained from this study will benefit the sponsor of the study, Eli Lilly and Company, and may benefit patients in the future.

Questions

If I/my child has any questions about this study or my/my child's rights, I/child will contact [redacted] and asking for [redacted] I/my child also may call the [redacted] at [redacted] If any important new information is found during this study that may affect my/my child's wanting to continue to be part of this study, I/my child will be told about it right away.

Confidentiality

If I/my child agrees to participate in this study, the information obtained will be shared with Eli Lilly and Company, including its agents and contractors, an ethical review board for this study, the United States Food and Drug Administration and similar agencies in other countries, all of whom may look at my/my child's medical records. Medical records that contain my/my child's identity will be treated as confidential by Eli Lilly and Company and will be shared only with these agencies, or as required by law. My/my child's medical information may be held and processed on a computer.

Signature Page

To become a part of this study, I/my child or the legal representative must sign this page.

By signing this page, I/my child is confirming the following:

* I/my child has read and understood all of the information in this Patient Information and Consent Form, and I/my child has had time to think about it.
* All of my/my child's questions have been answered to my/my child's satisfaction. If I/my child did not understand any of the words, I/my child asked the study doctor or a staff member to explain them.

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PATIENT CONSENT FOR INVESTIGATIONAL STUDIES

TITLE OF PROJECT: Fluoxetine versus Placebo in Childhood/ Adolescent Depression (B1Y-MC-HCJE/v:6.30.98)

5.14.99

DESCRIPTION OF STUDIES

* I/my child voluntarily agrees to be part of this research study, to follow the study procedures, and to provide necessary information to the doctor, nurses, or other staff members, as requested.
* I/my child understands that I/my child may freely choose to stop being a part of this study at any time.
* I/my child has received a copy of this Patient Information and Consent Form to keep.

_____ has described to me what is going to be done, the risks, hazards, and benefits involved, and will be available for questions at _____. I understand that my decision to participate or not to participate in this study will not alter my usual health care. In the use of information generated from this study, such as publications, my identity will remain anonymous. The records of studies involving treatment must be available to the FDA and the sponsor and my identity may become known to them. I am aware that I may withdraw from this study at any time. I further understand that in the event of physical injury or illness occurring to me resulting from the research procedures, care is available but [redacted] will not provide free medical care or compensation for lost wages. Further information with respect to illness or injury resulting from a research procedure as well as a research subjects' rights is available from the [redacted] I understand that by signing this consent form, I do not waive any of my legal rights nor does it relieve investigators or suppliers of liability, but merely indicates that I have been informed about the research study in which I am voluntarily agreeing to participate. A copy of this form will be provided to me.

Signature_____ Age_____ Date_____

Parent or Guardian signature (if patient is a minor)_____

Witnessed by_____ Date_____

(Revised 3/97)

LILLY APPROVED

AUG 0 3 1999

INFORMED CONSENT

Fluoxetine Hydrochloride (LY110140) B1Y-US-HCJE [Patient/Subject] Initials_____
Protocol-Specific ICD Approved: 14 January 1998
Protocol-Specific ICD Amendment (a) Approved: 15 March 1999
Page 7 of __

45

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PATIENT CONSENT FOR INVESTIGATIONAL STUDIES

TITLE OF PROJECT: Fluoxetine versus Placebo in Childhood/ Adolescent Depression (B1Y-MC-HCJE/v:6.30.98)

5.14.99

DESCRIPTION OF STUDIES

YOUTH ASSENT FORM

I am being asked to take part in a research study. This study will measure the safety of a drug called fluoxetine hydrochloride, whether it has any side effects, if it can help patients with major depression, and how much should be given to patients. I am being asked to take part because I have had some of the symptoms of depression. If I agree to take part in this study, I may be given a study medicine called fluoxetine hydrochloride or a sugar pill (placebo) for as long as 54 weeks. As part of the study, I will be asked to come to the doctor's about once a week, to start with, then the visits will go to every 2 weeks and then finish up at every 4 weeks. There will be a total of 26 visits over the 54 week period. The doctor will give me a physical examination that will include taking my blood pressure, heart rate, height, weight, blood tests (needle sticks), urine test and an ECG (heart test) to measure my heartbeats. I may have to do the tests up to 3 or 4 times during the study. The doctor will also perform a psychological examination and I will have to answer questions on several evaluations or questionnaires.

I do not have to participate in this study. If I decide to take part but change my mind, I can choose to stop at any time.

Sometimes this medicine might make people feel uncomfortable. The medication may cause difficulty falling asleep or sleeping, dry mouth, feeling tired, upset stomach (nausea, diarrhea), feeling dizzy and loss of appetite and weight. I may also feel sweaty, tingly, restless, itchy, shaky (tremors), agitated, over-energized or less hungry. I also may develop blurry vision, increased yawning, rashes, allergic reactions, problems concentrating, breathing problems, problems going to the bathroom (urinating), changes in sexual function, loss of hair, bruising more easily than normal, and/or skin becoming very sensitive to sunlight.

While I am taking part in this study, my depression may worsen, or I may experience other feelings that make me uncomfortable. I may have mild bruising and/or soreness at the place where blood is taken from my arm.

It is important that I tell my parent or guardian and the doctor if I have any problems or I don't feel well while I am taking part in the study.

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PATIENT CONSENT FOR INVESTIGATIONAL STUDIES

TITLE OF PROJECT: Fluoxetine versus Placebo in Childhood/ Adolescent Depression (B1Y-MC-HCJE/v:6.30.98)

5.14.99

DESCRIPTION OF STUDIES

Information about me will be kept confidential by the use of code names and code numbers. All information for the study will be stored in a locked room in [redacted]

By signing my name below, I agree to be in this study. All my questions about the study have been answered.

_____ has described to me what is going to be done, the risks, hazards, and benefits involved, and will be available for questions at _____. I understand that my decision to participate or not to participate in this study will not alter my usual health care. In the use of information generated from this study, such as publications, my identity will remain anonymous. The records of studies involving treatment must be available to the FDA and the sponsor and my identity may become known to them. I am aware that I may withdraw from this study at any time. I further understand that in the event of physical injury or illness occurring to me resulting from the research procedures, care is available but [redacted] will not provide free medical care or compensation for lost wages. Further information with respect to illness or injury resulting from a research procedure as well as a research subjects' rights is available from [redacted] I understand that by signing this consent form, I do not waive any of my legal rights nor does it relieve investigators or suppliers of liability, but merely indicates that I have been informed about the research study in which I am voluntarily agreeing to participate. A copy of this form will be provided to me.

Signature_____ Age_____ Date_____

Parent or Guardian signature (if patient is a minor)_____

Witnessed by_____ Date_____

(Revised 3/97)

LILLY APPROVED AUG 05 1999 INFORMED CONSENT

Fluoxetine Hydrochloride (LY110140) B1Y-US-HCJE
Protocol-Specific ICD Approved: 14 January 1998
Protocol-Specific ICD Amendment (a) Approved: 15 March 1999

[Patient/Subject] Initials_____
Page 9 of ___

45

[redacted]

PATIENT CONSENT FOR INVESTIGATIONAL STUDIES

TITLE OF PROJECT: Fluoxetine versus Placebo in Childhood/Adolescent Depression (V1Y-MC-HCJE/v:11.17.97)

6.23.98

DESCRIPTION OF STUDIES

Introduction

I/my child is being invited to take part voluntarily in a research study of a prescription drug known as fluoxetine hydrochloride (LY110140) when compared to placebo (inactive substance) in children and adolescents requiring treatment for depression. My/my child's participation in this study is expected to last up to 54 weeks. Up to 220 patients will be participating in this study.

Purpose of the Study

The purposes of this study are to determine:

* The safety of fluoxetine hydrochloride and any side effects that might be associated with it.
* Whether fluoxetine hydrochloride can help children/adolescent patients with major depression. Fluoxetine hydrochloride might not have any good effect for me/my child.
* How much fluoxetine hydrochloride should be given to patients.
* If there are any differences in the effectiveness and safety of fluoxetine hydrochloride between children (aged 8 to <13 years) and adolescents (aged 13 to <18 years).
* Blood levels of study drug (fluoxetine hydrochloride and norfluoxetine) in children and adolescents receiving different daily doses.

Qualifications to Participate

Some of the requirements to be in this study are:

* I/my child must be a child (aged 8 to <13 years) or an adolescent (aged 13 to <18 years) at the time of entry into study. If I/my child has reached my/my child's 18th birthday, I/my child will not be able to participate.
* The parent(s) or legal guardian give permission for me/my child to be in the study.
* I/my child must have been diagnosed with major depression.
* I/my child must be able to swallow whole medication without difficulty.
* I/my child must be able to have my/my child's blood tested several times during the study.
* I/my child must be able to visit the doctor's office as needed for fifty-four (54) weeks.

I/my child cannot participate in this study if:

* I/my child has a serious medical illness, such as heart, liver or kidney disease. (NOTE: If I/my child is uncertain about a particular condition, I/my child will discuss it with the study physician)
* I/my child is allergic to fluoxetine hydrochloride or I/my child has many bad reactions to medications.
* I/my child has had an illness serious enough for me/my child to go to the hospital within the last 12 months.

PROTOCOL # 06-98-24
EXPIRATION DATE 6/99

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PATIENT CONSENT FOR INVESTIGATIONAL STUDIES

TITLE OF PROJECT: Fluoxetine versus Placebo in Childhood/Adolescent Depression (V1Y-MC-HCJE/v:11.17.97)

6.23.98

DESCRIPTION OF STUDIES

* I/my child is currently using medication for depression. It is especially important that I/my child NOT take any medication called a monoamine oxidase inhibitor (MAOI) for at least 2 weeks before starting fluoxetine hydrochloride or at least 6 weeks after stopping fluoxetine hydrochloride. (NOTE: If I/my child is uncertain about whether taking a particular medication means I/my child cannot participate in the study, or if another physician has prescribed medications for me/my child, I/my child will talk with the study doctor.)
* I/my child has used St John's Wort, melatonin, or tryptophan within 2 weeks prior to study entry or plan to use it within 6 weeks from discontinuation of treatment.
* I/my child has had a convulsion or seizure within the past 6 months.
* I/my child is using or abusing drugs or alcohol.
* I/my child is at risk of committing suicide.
* I/my child will need to undergo certain forms of talk therapy.
* I/my child has failed to get better with previous fluoxetine hydrochloride use.

In addition to the list above, I/my child cannot be in this study if:

* I/my child is pregnant or breast feeding. If I/my child possibly could become pregnant, I/my child must talk to the study doctor about the method of birth control that I/my child will use to avoid getting pregnant during the study and for two (2) months after the study is completed. The risks to the embryo or fetus from exposure to the study drug are unknown; pregnant women or nursing mothers may not participate. If I/my child suspects I/my child has become pregnant while participating in the study, I/my child is to contact the study doctor immediately. Some methods of birth control might be less effective due to a possible interaction with study drug.

The doctor in charge of this study or a member of the doctor's staff will discuss with me/my child the additional requirements for participation in this study.

Study Procedures

If I/my child participates, I/my child will visit the study doctor to have a physical examination that will include blood tests (needle sticks) [it will be possible to have up to 4 blood tests throughout the study for a total of approximately 4 teaspoons], urine tests and an ECG (a heart test). I/my child will also have a psychological examination and have to answer questions on several evaluations or questionnaires. Both I/my child and the parent/legal guardian(s) will be asked to answer questions on the evaluations. The doctor will explain the study and what will happen while I/my child is in the study. The study may last as long as 54 weeks.

When I/my child comes back to the doctor's office the second time, about one week later, the doctor will review all of the tests I/my child has had. The doctor will make sure I/my child is able to take the study medicine. The second visit will require both I/my child

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PATIENT CONSENT FOR INVESTIGATIONAL STUDIES

TITLE OF PROJECT: Fluoxetine versus Placebo in Childhood/Adolescent Depression (V1Y-MC-HCJE/v:11.17.97)

6.23.98

DESCRIPTION OF STUDIES

and the parent/legal guardian(s) to answer several more evaluations or questionnaires. The doctor will again check to be sure I/my child can be in the study and I/my child will be scheduled to come back to the doctor's office for a third time about a week later.

Again at the 3rd visit both I/my child and the parent/legal guardian(s) will answer some questions on the evaluations or questionnaires and the doctor will again check to be sure I/my child can continue in the study. If I/my child can continue in the study I/my child will be given some pills (medication) to take every day, by mouth, and be scheduled for another (4th) visit about one week later.

Visit 4 will require some more questions to be answered and the doctor will check to be sure I/my child can continue in the study. If I/my child can continue in the study I/my child will be given some more pills (medication) to be taken every day, by mouth and scheduled for the 5th visit in about one week. I/my child will now take pills (medication) every day, by mouth, until the end of the study and I/my child will be scheduled to see the doctor about,every week until visit 7. From visit 7 until visit 21 I/my child will see the doctor about every 2 weeks and from visit 21 through visit 26 I/my child will see the doctor about every 4 weeks. At each visit I/my child will have my/my child's vital signs checked and will answer questions on the evaluations or questionnaires. At visit 10, visit 15, visit 26, or when I/my child stops the study I/my child will need to have additional blood tests (needle sticks; approximately 1 teaspoon each) or laboratory tests or an ECG (heart test) and/or a physical examination.

Neither I/my child nor the doctor will know what medication I/my child is taking. Whether I/my child receives fluoxetine hydrochloride (real medication) or the placebo (sugar pill) will be determined by chance. One (1) out of every two (2) patients in the study will receive fluoxetine hydrochloride (real medication) and the other one (1) will receive the placebo (sugar pill). It will also be possible to start the study on fluoxetine hydrochloride (real medication) and then be switched during the study to the placebo (sugar pill). If I/my child is switched to placebo (sugar pill) I/my child will not have a chance of being switched back to fluoxetine hydrochloride (real medication). Again, neither I/my child nor my/my child's doctor will know whether I/my child is taking fluoxetine hydrochloride (real medication) or the placebo (sugar pill). Treatment non-responders (patients who leave the study because they do not get better) may be eligible for additional medical care by a mental health professional as determined by the primary investigator.

My/my child's blood or urine sample will be tested for certain types of drugs (known as controlled substances in the United States) that may affect behavior and that may be regulated by law. If my/my child's test results show that I/my child has taken these types of drugs, I/my child will be notified. The results of this test will be kept confidential and disclosed only as required by law.

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[redacted] STUDIES

TITLE OF PROJECT: Fluoxetine versus Placebo in Childhood/Adolescent Depression (V1Y-MC-HCJE/v:11.17.97)

6.23.98

DESCRIPTION OF STUDIES

Risks

I/my child understands that there may be risks for me/my child being in this study. Problems commonly (more than 5% of people) experienced by patients taking fluoxetine hydrochloride who have participated in previous research studies include upset stomach (nausea, diarrhea), feeling tired, feeling jittery or nervous, having trouble sleeping, dry mouth, sweating, tremors, feeling dizzy or loss of appetite and weight. Other problems experienced by between 1% and 5% of patients include rashes, itchiness, swelling under the skin, changes in the interest in sex, decreased ability or inability to have sex, changes in pattern of passing urine, problems concentrating, blurry vision or increased yawning. Problems which occur in less than 1% of patients include skin becoming very sensitive to sunlight, feeling very agitated and over-energized, losing hair, bruising more easily than normal, problems breathing, inflammation of a blood vessel or men having erections which last longer than normal.

For most people, needle punctures for blood draws do not cause any serious problems. However, they may cause bleeding, bruising, discomfort, infections and/or pain at the needle site or dizziness.

In addition to the bad experiences named above, fluoxetine hydrochloride or the study procedures may have other unknown risks.

Fluoxetine hydrochloride has been associated with increased rates of death among newborn rats. Fluoxetine may pose risks to human pregnancy. For this reason I/my child cannot participate in this study if I/my child is (or becomes) pregnant. There may also be unknown risks to my/my child's embryo, fetus, or unborn child.

The questions on the evaluations or questionnaires include questions that are personal and that ask specifically about my/my child's illness and history. This may possibly make me/my child feel uncomfortable or upset, or bring back bad memories for me/my child.

Suicide is a risk of uncontrolled depression; therefore, I/my child will notify the study doctor immediately if I/my child has suicidal thoughts.

My/my child's condition may not improve or may worsen while participating in this study, whether I/my child takes fluoxetine hydrochloride (real medication) or placebo (sugar pill).

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[redacted]

PATIENT CONSENT FOR INVESTIGATIONAL STUDIES

TITLE OF PROJECT: Fluoxetine versus Placebo in Childhood/Adolescent Depression (V1Y-MC-HCJE/v:11.17.97)

6.23.98

DESCRIPTION OF STUDIES

The study drug must be taken only by the person for whom it has been prescribed, and it must be kept out of reach of children or persons of limited capacity to read or understand.

If I/my child has any injury, bad effect, or any other unusual health experience during this study, I/my child will immediately tell the nurses or [redacted] and ask for [redacted] I/my child can call at any time, day or night, to tell the study personnel about my/my child's health experiences.

Other Treatments

I/my child does not have to take part in this study to be treated for my/my child's illness or condition. Other treatments and therapies for my/my child's condition are available. Those might include other medications or counseling.

Voluntary Participation

My/my child's taking part in this study is entirely voluntary. I/my child may refuse to take part in the study or I/my child may stop my/my child's participation in the study at any time, without a penalty or loss of benefits to which I/my child was entitled before taking part in the study. If I/my child decides to stop being part of this study, [redacted] or one of the staff members will talk to me/my child about making this choice.

Stopping the Study

The study doctors or Eli Lilly and Company (the sponsor of this study) may stop this study, or my/my child being a part of it, at any time for any reason without my/my child's consent. If this happens, it might be the result of a bad reaction that I/my child has to fluoxetine hydrochloride or new information that my/my child's physician or the sponsor learns about fluoxetine hydrochloride's safety or effectiveness.

Treatment and Compensation for Injury

If I/my child follows the directions of the doctors in charge of this study and I/my child is physically injured due to any substance or procedure properly given under the plan for this study, Eli Lilly and Company will pay the medical expenses for the treatment of that injury which are not covered by my/my child's medical insurance, by a government program, or by any other third party.

Possible Benefits

I/my child may receive information about my/my child's health from any physical examinations and laboratory tests to be done in this study and I/my child may receive medication during the study at no cost to me/my child.

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[redacted]

PATIENT CONSENT FOR INVESTIGATIONAL STUDIES

TITLE OF PROJECT: Fluoxetine versus Placebo in Childhood/Adolescent Depression (V1Y-MC-HCJE/v:11.17.97)

6.23.98

DESCRIPTION OF STUDIES

Although fluoxetine hydrochloride is being tested as a treatment for a condition that I/my child may have, there is no guarantee that I/my child will receive any medical benefit. However, my/my child's condition may improve even if I/my child is taking the placebo (sugar pill).

I/my child will be paid $25 per visit ($650/completion of entire study) for participation in this study to cover expenses like travel, parking and other inconveniences.

Information obtained from this study will benefit the sponsor of the study, Eli Lilly and Company, and may benefit patients in the future.

Questions

If I/my child has any questions about this study or my/my child's rights, I/child will contact [redacted] and asking for [redacted] I/my child also may call [redacted] at [redacted] If any important new information is found during this study that may affect my/my child's wanting to continue to be part of this study, I/my child will be told about it right away.

Confidentiality

If I/my child agrees to participate in this study, the information obtained will be shared with Eli Lilly and Company, including its agents and contractors, an ethical review board for this study, the United States Food and Drug Administration and similar agencies in other countries, all of whom may look at my/my child's medical records. Medical records that contain my/my child's identity will be treated as confidential by Eli Lilly and Company and will be shared only with these agencies, or as required by law. My/my child's medical information may be held and processed on a computer.

Signature Page

To become a part of this study, I/my child or the legal representative must sign this page.

By signing this page, I/my child is confirming the following:

* I/my child has read and understood all of the information in this Patient Information and Consent Form, and I/my child has had time to think about it.
* All of my/my child's questions have been answered to my/my child's satisfaction. If I/my child did not understand any of the words, I/my child asked the study doctor or a staff member to explain them.

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[redacted]

PATIENT CONSENT FOR INVESTIGATIONAL STUDIES

TITLE OF PROJECT: Fluoxetine versus Placebo in Childhood/Adolescent Depression (V1Y-MC-HCJE/v:11.17.97)

6.23.98

DESCRIPTION OF STUDIES

* I/my child voluntarily agrees to be part of this research study, to follow the study procedures, and to provide necessary information to the doctor, nurses, or other staff members, as requested.
* I/my child understands that I/my child may freely choose to stop being a part of this study at any time.
* I/my child has received a copy of this Patient Information and Consent Form to keep.

_____ has described to me what is going to be done, the risks, hazards, and benefits involved, and will be available for questions at _____. I understand that my decision to participate or not to participate in this study will not alter my usual health care. In the use of information generated from this study, such as publications, my identity will remain anonymous. The records of studies involving treatment must be available to the FDA and the sponsor and my identity may become known to them. I am aware that I may withdraw from this study at any time. I further understand that in the event of physical injury or illness occurring to me resulting from the research procedures, care is available but [redacted] will not provide free medical care or compensation for lost wages. Further information with respect to illness or injury resulting from a research procedure as well as a research subjects' rights is available from [redacted] I understand that by signing this consent form, I do not waive any of my legal rights nor does it relieve investigators or suppliers of liability, but merely indicates that I have been informed about the research study in which I am voluntarily agreeing to participate. A copy of this form will be provided to me.

Signature_____ Age_____ Date_____

LILLY APPROVED

Parent or Guardian signature (if patient is a minor)_____

JUL 23 1998

Witnessed by_____ Date_____

INFORMED CONSENT

(Revised 3/97)

Fluoxetine Hydrochloride (LY110140) B1Y-US-HCJE
Protocol-Specific ICD: 14 January 1998

[Patient/Subject] Initials_____
Page 7 of __

16.1.10.
Listing of Patients Receiving Test Drug(s) or Investigational Product(s) From Specific Batches

Patient Number	Visit Number	Therapy	Package Assigned	Clinical Trial Lot Number	
103	3	Placebo	1037	CT09679	
103	4	Placebo	1657	CT09679	
103	5	Placebo	1662	CT09679	
103	6	Placebo	1664	CT09679	
103	7	Placebo	1658	CT09679	
104	3	Placebo	1038	CT09679	
104	4	Flx10mg	1663	CT09679	CT07620
104	5	Flx20mg	1659	CT09679	CT07620
104	6	Flx20mg	1661	CT09679	CT07620
104	7	Flx20mg	1660	CT09679	CT07620
104	8	Flx20mg	1665	CT09679	CT07620
104	9	Flx20mg	1666	CT09679	CT07620
104	10	Flx20mg	5057	CT09679	CT07620
104	11	Flx20mg	5060	CT09679	CT07620
104	12	Flx20mg	5063	CT09679	CT07620
107	3	Placebo	1039	CT09679	
107	4	Placebo	1724	CT09679	
107	5	Placebo	1728	CT09679	
107	6	Placebo	1734	CT09679	
107	7	Placebo	1667	CT09679	
107	8	Placebo	1668	CT09679	
110	3	Placebo	1041	CT09679	
110	4	Flx10mg	1729	CT09679	CT07620
110	5	Flx20mg	1725	CT09679	CT07620
110	6	Flx20mg	1735	CT09679	CT07620
110	7	Flx20mg	1727	CT09679	CT07620
112	3	Placebo	1040	CT09679	
112	4	Placebo	1739	CT09679	
112	5	Placebo	1743	CT09679	
112	6	Placebo	1753	CT09679	
112	7	Placebo	1722	CT09679	
112	8	Placebo	1730	CT09679	
112	9	Placebo	1741	CT09679	
113	3	Placebo	1043	CT09679	
113	4	Placebo	1745	CT09679	
113	5	Placebo	1749	CT09679	
113	6	Placebo	1755	CT09679	
113	7	Placebo	1723	CT09679	
113	8	Placebo	1740	CT09679	
113	9	Placebo	1750	CT09679	
113	10	Placebo	5053	CT09679	
113	11	Placebo	5055	CT09679	
113	12	Placebo	5062	CT09679	
113	13	Placebo	5067	CT09679	
113	14	Placebo	5073	CT09679	
113	15	Placebo	7183	CT10799	
113	16	Placebo	7184	CT10799	

Patient Number	Visit Number	Therapy	Package Assigned	Clinical Trial Lot Number	
113	17	Placebo	7186	CT10799	
113	18	Placebo	7191	CT10799	
113	19	Placebo	7192	CT10799	
113	20	Placebo	7196	CT10799	
114	3	Placebo	1042	CT09679	
114	4	Flx10mg	1744	CT09679	CT07620
114	5	Flx20mg	1733	CT09679	CT07620
114	6	Flx20mg	1737	CT09679	CT07620
114	7	Flx20mg	1731	CT09679	CT07620
114	8	Flx20mg	1732	CT09679	CT07620
114	9	Flx20mg	1738	CT09679	CT07620
114	10	Flx40mg	5069	CT09679	CT09678
114	11	Flx40mg	5054	CT09679	CT09678
118	3	Placebo	1045	CT09679	
118	4	Flx10mg	1752	CT09679	CT07620
118	5	Flx20mg	1748	CT09679	CT07620
118	6	Flx20mg	1757	CT09679	CT07620
118	7	Flx20mg	1736	CT09679	CT07620
118	8	Flx20mg	1742	CT09679	CT07620
118	9	Flx20mg	1754	CT09679	CT07620
118	10	Flx20mg	5064	CT09679	CT07620
119	3	Placebo	1044	CT09679	
119	4	Placebo	1765	CT09679	
119	5	Placebo	1770	CT09679	
119	6	Placebo	1773	CT09679	
119	7	Placebo	1747	CT09679	
119	8	Placebo	1759	CT09679	
119	9	Placebo	1760	CT09679	
119	10	Placebo	5056	CT09679	
119	11	Placebo	5065	CT09679	
119	12	Placebo	5070	CT09679	
119	13	Placebo	5076	CT09679	
119	14	Placebo	5078	CT09679	
120	3	Placebo	1046	CT09679	
124	3	Placebo	1047	CT09679	
124	4	Flx10mg	1767	CT09679	CT07620
124	5	Flx20mg	1761	CT09679	CT07620
124	6	Flx20mg	2395	CT09679	CT07620
124	7	Flx20mg	1756	CT09679	CT07620
124	8	Flx20mg	1764	CT09679	CT07620
124	9	Flx20mg	1772	CT09679	CT07620
124	10	Flx20mg	5068	CT09679	CT07620
124	11	Flx20mg	5071	CT09679	CT07620
124	12	Flx20mg	5077	CT09679	CT07620
124	13	Flx20mg	5523	CT09679	CT07620
124	14	Flx20mg	5524	CT09679	CT07620
124	15	Placebo	7189	CT10799	

Patient Number	Visit Number	Therapy	Package Assigned	Clinical Trial Lot Number	
124	16	Placebo	7194	CT10799	
124	17	Placebo	7197	CT10799	
124	18	Placebo	7200	CT10799	
124	19	Placebo	7201	CT10799	
124	20	Placebo	7204	CT10799	
126	3	Placebo	1229	CT09679	
126	4	Flx10mg	2408	CT09679	CT07620
126	5	Flx20mg	2389	CT09679	CT07620
126	6	Flx20mg	2407	CT09679	CT07620
126	7	Flx20mg	1758	CT09679	CT07620
126	8	Flx20mg	2385	CT09679	CT07620
127	3	Placebo	1048	CT09679	
127	4	Flx10mg	2387	CT09679	CT07620
127	5	Flx20mg	1763	CT09679	CT07620
127	6	Flx20mg	2401	CT09679	CT07620
127	7	Flx20mg	1769	CT09679	CT07620
127	8	Flx20mg	2394	CT09679	CT07620
127	9	Flx20mg	2398	CT09679	CT07620
127	10	Flx20mg	5072	CT09679	CT07620
131	3	Placebo	1230	CT09679	
131	4	Placebo	2386	CT09679	
131	5	Placebo	2392	CT09679	
131	6	Placebo	2397	CT09679	
131	7	Placebo	1762	CT09679	
131	8	Placebo	1766	CT09679	
131	9	Placebo	1768	CT09679	
131	10	Placebo	5526	CT09679	
131	11	Placebo	5528	CT09679	
133	3	Placebo	1231	CT09679	
133	4	Flx10mg	2413	CT09679	CT07620
133	5	Flx20mg	2414	CT09679	CT07620
133	6	Flx20mg	2420	CT09679	CT07620
133	7	Flx20mg	2391	CT09679	CT07620
133	8	Flx20mg	2402	CT09679	CT07620
133	9	Flx20mg	2409	CT09679	CT07620
133	10	Flx20mg	5525	CT09679	CT07620
135	3	Placebo	1232	CT09679	
135	4	Placebo	2399	CT09679	
135	5	Placebo	2404	CT09679	
135	6	Placebo	2410	CT09679	
137	3	Placebo	1233	CT09679	
137	4	Flx10mg	2768	CT09679	CT07620
137	5	Flx20mg	2771	CT09679	CT07620
137	6	Flx20mg	2773	CT09679	CT07620
137	7	Flx20mg	2415	CT09679	CT07620
137	8	Flx20mg	2763	CT09679	CT07620
137	9	Flx20mg	2775	CT09679	CT07620

Patient Number	Visit Number	Therapy	Package Assigned	Clinical Trial Lot Number	
139	3	Placebo	1234	CT09679	
139	4	Flx10mg	2783	CT09679	CT07620
139	5	Flx20mg	2781	CT09679	CT07620
139	6	Flx20mg	2790	CT09679	CT07620
139	7	Flx20mg	2417	CT09679	CT07620
139	8	Flx20mg	2767	CT09679	CT07620
139	9	Flx20mg	2797	CT09679	CT07620
139	10	Flx20mg	5530	CT09679	CT07620
139	11	Flx20mg	5628	CT09679	CT07620
139	12	Flx20mg	3379	CT09679	CT07620
139	13	Flx20mg	5923	CT09679	CT07620
139	14	Flx20mg	5943	CT09679	CT07620
140	3	Placebo	1236	CT09679	
140	4	Placebo	2411	CT09679	
140	5	Placebo	2422	CT09679	
140	6	Placebo	2764	CT09679	
141	3	Placebo	1235	CT09679	
141	4	Flx10mg	2792	CT09679	CT07620
141	5	Flx20mg	2786	CT09679	CT07620
141	6	Flx20mg	2794	CT09679	CT07620
141	7	Flx20mg	2418	CT09679	CT07620
141	8	Flx20mg	2778	CT09679	CT07620
142	3	Placebo	1237	CT09679	
142	4	Flx10mg	2809	CT09679	CT07620
142	5	Flx20mg	2805	CT09679	CT07620
142	6	Flx20mg	2810	CT09679	CT07620
142	7	Flx20mg	2766	CT09679	CT07620
142	8	Flx20mg	2787	CT09679	CT07620
142	9	Flx20mg	2802	CT09679	CT07620
142	10	Flx20mg	5626	CT09679	CT07620
142	11	Flx20mg	5631	CT09679	CT07620
142	12	Flx20mg	5919	CT09679	CT07620
142	13	Flx20mg	5941	CT09679	CT07620
142	14	Flx20mg	6018	CT09679	CT07620
143	3	Placebo	1238	CT09679	
143	4	Placebo	2423	CT09679	
143	5	Placebo	2774	CT09679	
149	3	Placebo	1239	CT09679	
149	4	Placebo	2770	CT09679	
149	5	Placebo	2779	CT09679	
149	6	Placebo	2784	CT09679	
149	7	Placebo	2388	CT09679	
149	8	Placebo	2393	CT09679	
149	9	Placebo	2403	CT09679	
149	10	Placebo	5529	CT09679	
150	3	Placebo	1240	CT09679	
150	4	Flx10mg	3378	CT09679	CT07620

Patient Number	Visit Number	Therapy	Package Assigned	Clinical Trial Lot Number	
150	5	Flx20mg	3380	CT09679	CT07620
150	6	Flx20mg	3389	CT09679	CT07620
150	7	Flx20mg	2789	CT09679	CT07620
150	8	Flx20mg	2803	CT09679	CT07620
150	9	Flx20mg	3375	CT09679	CT07620
150	10	Flx20mg	5630	CT09679	CT07620
150	11	Flx20mg	5918	CT09679	CT07620
150	12	Flx20mg	5939	CT09679	CT07620
150	13	Flx20mg	5946	CT09679	CT07620
150	14	Flx20mg	6022	CT09679	CT07620
150	15	Flx20mg	7187	CT10799	CT07620
150	16	Flx20mg	7190	CT10799	CT07620
150	17	Flx20mg	7195	CT10799	CT07620
150	18	Flx20mg	7198	CT10799	CT07620
151	3	Placebo	1349	CT09679	
151	4	Flx10mg	3390	CT09679	CT07620
151	5	Flx20mg	3382	CT09679	CT07620
151	6	Flx20mg	3397	CT09679	CT07620
151	7	Flx20mg	2798	CT09679	CT07620
151	8	Flx20mg	2812	CT09679	CT07620
151	9	Flx20mg	3377	CT09679	CT07620
151	10	Flx20mg	5912	CT09679	CT07620
153	3	Placebo	1350	CT09679	
153	4	Placebo	2785	CT09679	
153	5	Placebo	2788	CT09679	
153	6	Placebo	2793	CT09679	
153	7	Placebo	2396	CT09679	
153	8	Placebo	2405	CT09679	
153	9	Placebo	2406	CT09679	
201	3	Placebo	1109	CT09679	
201	4	Placebo	2008	CT09679	
202	3	Placebo	1110	CT09679	
202	4	Flx10mg	2012	CT09679	CT07620
202	5	Flx20mg	2016	CT09679	CT07620
202	6	Flx20mg	2018	CT09679	CT07620
203	3	Placebo	1111	CT09679	
203	4	Placebo	2010	CT09679	
203	5	Placebo	2011	CT09679	
203	6	Placebo	2255	CT09679	
203	7	Placebo	2013	CT09679	
203	8	Placebo	2014	CT09679	
203	9	Placebo	2015	CT09679	
204	3	Placebo	1112	CT09679	
204	4	Flx10mg	2267	CT09679	CT07620
204	5	Flx20mg	2258	CT09679	CT07620
204	6	Flx20mg	2259	CT09679	CT07620
204	7	Flx20mg	2009	CT09679	CT07620

Patient Number	Visit Number	Therapy	Package Assigned	Clinical Trial Lot Number	
204	8	Flx20mg	2019	CT09679	CT07620
204	9	Flx20mg	2020	CT09679	CT07620
204	10	Flx20mg	5290	CT09679	CT07620
204	11	Flx20mg	5291	CT09679	CT07620
204	12	Flx20mg	5292	CT09679	CT07620
204	13	Flx20mg	5297	CT09679	CT07620
205	3	Placebo	1113	CT09679	
205	4	Placebo	2260	CT09679	
205	5	Placebo	2266	CT09679	
205	6	Placebo	2268	CT09679	
205	7	Placebo	2256	CT09679	
206	3	Placebo	1114	CT09679	
206	4	Placebo	2275	CT09679	
206	5	Placebo	2280	CT09679	
206	6	Placebo	2289	CT09679	
206	7	Placebo	2264	CT09679	
206	8	Placebo	2265	CT09679	
206	9	Placebo	2272	CT09679	
206	10	Placebo	5287	CT09679	
206	11	Placebo	5288	CT09679	
206	12	Placebo	5294	CT09679	
206	13	Placebo	5296	CT09679	
206	14	Placebo	5299	CT09679	
206	15	Placebo	7469	CT10799	
206	16	Placebo	7471	CT10799	
206	17	Placebo	7472	CT10799	
206	18	Placebo	7474	CT10799	
208	3	Placebo	1115	CT09679	
208	4	Flx10mg	2276	CT09679	CT07620
208	5	Flx20mg	2270	CT09679	CT07620
208	6	Flx20mg	2274	CT09679	CT07620
208	7	Flx20mg	2257	CT09679	CT07620
209	3	Placebo	1117	CT09679	
209	4	Placebo	2291	CT09679	
209	5	Placebo	2303	CT09679	
209	6	Placebo	2304	CT09679	
209	7	Placebo	2278	CT09679	
209	8	Placebo	2283	CT09679	
209	9	Placebo	2293	CT09679	
209	10	Placebo	5303	CT09679	
209	11	Placebo	5304	CT09679	
209	12	Placebo	5307	CT09679	
209	13	Placebo	6073	CT09679	
209	14	Placebo	6075	CT09679	
209	15	Placebo	7477	CT10799	
209	16	Placebo	7478	CT10799	
209	17	Placebo	7479	CT10799	

Patient Number	Visit Number	Therapy	Package Assigned	Clinical Trial Lot Number	
209	18	Placebo	7482	CT10799	
209	19	Placebo	7483	CT10799	
209	20	Placebo	7485	CT10799	
210	3	Placebo	1116	CT09679	
210	4	Placebo	2290	CT09679	
210	5	Placebo	2294	CT09679	
210	6	Placebo	3647	CT09679	
210	7	Placebo	2279	CT09679	
210	8	Placebo	2284	CT09679	
210	9	Placebo	2295	CT09679	
210	10	Placebo	5305	CT09679	
210	11	Placebo	5310	CT09679	
210	12	Placebo	6070	CT09679	
210	13	Placebo	6074	CT09679	
212	3	Placebo	1118	CT09679	
301	3	Placebo	1001	CT09679	
301	4	Placebo	1501	CT09679	
301	5	Placebo	1504	CT09679	
301	6	Placebo	1508	CT09679	
301	7	Placebo	1506	CT09679	
302	3	Placebo	1003	CT09679	
302	4	Flx10mg	1509	CT09679	CT07620
302	5	Flx20mg	1505	CT09679	CT07620
302	6	Flx20mg	1517	CT09679	CT07620
302	7	Flx20mg	1502	CT09679	CT07620
302	8	Flx20mg	1514	CT09679	CT07620
303	3	Placebo	1002	CT09679	
303	4	Placebo	1515	CT09679	
303	5	Placebo	1525	CT09679	
303	6	Placebo	1536	CT09679	
303	7	Placebo	1507	CT09679	
303	8	Placebo	1518	CT09679	
303	9	Placebo	1527	CT09679	
303	10	Placebo	5121	CT09679	
303	11	Placebo	5125	CT09679	
303	12	Placebo	5130	CT09679	
303	13	Placebo	5138	CT09679	
305	3	Placebo	1006	CT09679	
305	4	Flx10mg	1531	CT09679	CT07620
305	5	Flx20mg	1532	CT09679	CT07620
305	6	Flx20mg	1537	CT09679	CT07620
305	7	Flx20mg	1512	CT09679	CT07620
305	8	Flx20mg	1529	CT09679	CT07620
305	9	Flx20mg	1540	CT09679	CT07620
305	10	Flx40mg	5120	CT09679	CT09678
305	11	Flx40mg	5142	CT09679	CT09678
305	12	Flx40mg	5170	CT09679	CT09678

Patient Number	Visit Number	Therapy	Package Assigned	Clinical Trial Lot Number	
305	13	Flx40mg	5175	CT09679	CT09678
305	14	Flx40mg	5196	CT09679	CT09678
305	15	Placebo	7100	CT10799	
305	16	Placebo	7080	CT10799	
306	3	Placebo	1004	CT09679	
306	4	Placebo	1519	CT09679	
306	5	Placebo	1528	CT09679	
306	6	Placebo	1539	CT09679	
306	7	Placebo	1513	CT09679	
306	8	Placebo	1520	CT09679	
306	9	Placebo	1534	CT09679	
306	10	Placebo	5122	CT09679	
307	3	Placebo	1005	CT09679	
307	4	Flx10mg	1516	CT09679	CT07620
307	5	Flx20mg	1510	CT09679	CT07620
307	6	Flx20mg	1526	CT09679	CT07620
307	7	Flx20mg	1503	CT09679	CT07620
307	8	Flx20mg	1521	CT09679	CT07620
307	9	Flx20mg	1533	CT09679	CT07620
307	10	Flx40mg	5119	CT09679	CT09678
307	11	Flx40mg	5131	CT09679	CT09678
309	3	Placebo	1007	CT09679	
309	4	Placebo	1546	CT09679	
309	5	Placebo	1550	CT09679	
309	6	Placebo	2094	CT09679	
309	7	Placebo	1523	CT09679	
309	8	Placebo	1542	CT09679	
309	9	Placebo	1549	CT09679	
309	10	Placebo	5127	CT09679	
309	11	Placebo	5137	CT09679	
309	12	Placebo	5141	CT09679	
309	13	Placebo	5174	CT09679	
309	14	Placebo	5320	CT09679	
312	3	Placebo	1012	CT09679	
312	4	Placebo	2102	CT09679	
312	5	Placebo	2104	CT09679	
312	6	Placebo	2122	CT09679	
312	7	Placebo	2087	CT09679	
313	3	Placebo	1008	CT09679	
313	4	Flx10mg	1548	CT09679	CT07620
313	5	Flx20mg	1541	CT09679	CT07620
313	6	Flx20mg	1545	CT09679	CT07620
313	7	Flx20mg	1524	CT09679	CT07620
313	8	Flx20mg	1538	CT09679	CT07620
315	3	Placebo	1009	CT09679	
315	4	Placebo	1551	CT09679	
315	5	Placebo	2095	CT09679	

Patient Number	Visit Number	Therapy	Package Assigned	Clinical Trial Lot Number	
315	6	Placebo	2096	CT09679	
315	7	Placebo	1530	CT09679	
315	8	Placebo	1544	CT09679	
315	9	Placebo	2088	CT09679	
315	10	Placebo	5136	CT09679	
315	11	Placebo	5140	CT09679	
315	12	Placebo	5173	CT09679	
315	13	Placebo	5177	CT09679	
315	14	Placebo	5181	CT09679	
315	15	Placebo	7081	CT10799	
315	16	Placebo	7083	CT10799	
315	17	Placebo	7085	CT10799	
315	18	Placebo	7087	CT10799	
315	19	Placebo	7089	CT10799	
315	20	Placebo	7093	CT10799	
315	21	Placebo	7094	CT10799	
315	22	Placebo	7095	CT10799	
315	23	Placebo	7099	CT10799	
315	24	Placebo	7103	CT10799	
315	25	Placebo	7104	CT10799	
318	3	Placebo	1010	CT09679	
318	4	Flx10mg	2090	CT09679	CT07620
318	5	Flx20mg	2089	CT09679	CT07620
318	6	Flx20mg	2100	CT09679	CT07620
318	7	Flx20mg	1547	CT09679	CT07620
319	3	Placebo	1011	CT09679	
319	4	Flx10mg	2103	CT09679	CT07620
319	5	Flx20mg	2097	CT09679	CT07620
319	6	Flx20mg	2111	CT09679	CT07620
319	7	Flx20mg	1552	CT09679	CT07620
319	8	Flx20mg	2086	CT09679	CT07620
319	9	Flx20mg	2093	CT09679	CT07620
319	10	Flx20mg	5123	CT09679	CT07620
319	11	Flx20mg	5126	CT09679	CT07620
319	12	Flx20mg	5323	CT09679	CT07620
319	13	Flx20mg	5129	CT09679	CT07620
320	3	Placebo	1133	CT09679	
323	3	Placebo	1134	CT09679	
323	4	Placebo	2106	CT09679	
323	5	Placebo	2118	CT09679	
323	6	Placebo	2124	CT09679	
323	7	Placebo	2091	CT09679	
323	8	Placebo	2099	CT09679	
323	9	Placebo	2105	CT09679	
326	3	Placebo	1135	CT09679	
326	4	Flx10mg	2120	CT09679	CT07620
326	5	Flx20mg	2114	CT09679	CT07620

Patient Number	Visit Number	Therapy	Package Assigned	Clinical Trial Lot Number	
326	6	Flx20mg	2121	CT09679	CT07620
326	7	Flx20mg	2098	CT09679	CT07620
326	8	Flx20mg	2101	CT09679	CT07620
326	9	Flx20mg	2249	CT09679	CT07620
326	10	Flx20mg	5128	CT09679	CT07620
326	11	Flx20mg	5132	CT09679	CT07620
326	12	Flx20mg	5134	CT09679	CT07620
326	13	Flx20mg	5135	CT09679	CT07620
326	14	Flx20mg	5143	CT09679	CT07620
326	15	Placebo	7088	CT10799	
330	3	Placebo	1137	CT09679	
330	4	Placebo	2216	CT09679	
330	5	Placebo	2218	CT09679	
330	6	Placebo	2231	CT09679	
330	7	Placebo	2110	CT09679	
330	8	Placebo	2112	CT09679	
330	9	Placebo	2119	CT09679	
330	10	Placebo	5182	CT09679	
332	3	Placebo	1136	CT09679	
332	4	Flx10mg	2220	CT09679	CT07620
332	5	Flx20mg	2224	CT09679	CT07620
332	6	Flx20mg	2226	CT09679	CT07620
332	7	Flx20mg	2108	CT09679	CT07620
332	8	Flx20mg	2109	CT09679	CT07620
334	3	Placebo	1138	CT09679	
334	4	Flx10mg	2240	CT09679	CT07620
334	5	Flx20mg	2232	CT09679	CT07620
334	6	Flx20mg	2233	CT09679	CT07620
334	7	Flx20mg	2115	CT09679	CT07620
334	8	Flx20mg	2117	CT09679	CT07620
334	9	Flx20mg	2123	CT09679	CT07620
334	10	Flx20mg	5171	CT09679	CT07620
334	11	Flx20mg	5176	CT09679	CT07620
334	12	Flx20mg	5178	CT09679	CT07620
334	13	Flx20mg	5180	CT09679	CT07620
334	14	Flx20mg	5199	CT09679	CT07620
334	15	Flx20mg	7079	CT10799	CT07620
334	16	Flx20mg	7082	CT10799	CT07620
334	17	Flx20mg	7086	CT10799	CT07620
334	18	Flx20mg	7092	CT10799	CT07620
334	19	Flx20mg	7101	CT10799	CT07620
334	20	Flx20mg	7526	CT10799	CT07620
334	21	Flx20mg	7639	CT10799	CT07620
334	22	Flx20mg	7694	CT10799	CT07620
334	23	Flx20mg	7769	CT10799	CT07620
334	24	Flx20mg	7895	CT10799	CT07620
334	25	Flx20mg	8004	CT10799	CT07620

Patient Number	Visit Number	Therapy	Package Assigned	Clinical Trial Lot Number	
335	3	Placebo	1139	CT09679	
335	4	Placebo	2225	CT09679	
335	5	Placebo	2234	CT09679	
335	6	Placebo	2237	CT09679	
335	7	Placebo	2113	CT09679	
335	8	Placebo	2217	CT09679	
335	9	Placebo	2227	CT09679	
335	10	Placebo	5197	CT09679	
335	11	Placebo	5200	CT09679	
335	12	Placebo	5205	CT09679	
335	13	Placebo	5314	CT09679	
335	14	Placebo	5601	CT09679	
336	3	Placebo	1140	CT09679	
336	4	Placebo	2244	CT09679	
336	5	Placebo	2246	CT09679	
336	6	Placebo	2252	CT09679	
336	7	Placebo	2219	CT09679	
336	8	Placebo	2229	CT09679	
336	9	Placebo	2241	CT09679	
336	10	Placebo	5203	CT09679	
336	11	Placebo	5208	CT09679	
336	12	Placebo	5316	CT09679	
336	13	Placebo	5604	CT09679	
336	14	Placebo	5611	CT09679	
339	3	Placebo	1141	CT09679	
339	4	Placebo	2815	CT09679	
339	5	Placebo	2819	CT09679	
339	6	Placebo	2828	CT09679	
339	7	Placebo	2235	CT09679	
339	8	Placebo	2247	CT09679	
339	9	Placebo	2820	CT09679	
339	10	Placebo	5315	CT09679	
343	3	Placebo	1142	CT09679	
343	4	Placebo	2825	CT09679	
343	5	Placebo	2836	CT09679	
343	6	Placebo	2846	CT09679	
343	7	Placebo	2248	CT09679	
343	8	Placebo	2253	CT09679	
343	9	Placebo	2823	CT09679	
343	10	Placebo	5321	CT09679	
343	11	Placebo	5607	CT09679	
346	3	Placebo	1143	CT09679	
346	4	Flx10mg	2245	CT09679	CT07620
346	5	Flx20mg	2251	CT09679	CT07620
346	6	Flx20mg	2254	CT09679	CT07620
346	7	Flx20mg	2221	CT09679	CT07620
346	8	Flx20mg	2223	CT09679	CT07620

Patient Number	Visit Number	Therapy	Package Assigned	Clinical Trial Lot Number	
346	9	Flx20mg	2228	CT09679	CT07620
346	10	Flx20mg	5198	CT09679	CT07620
346	11	Flx20mg	5201	CT09679	CT07620
346	12	Flx20mg	5202	CT09679	CT07620
346	13	Flx20mg	5317	CT09679	CT07620
346	14	Flx20mg	5322	CT09679	CT07620
346	15	Flx20mg	7096	CT10799	CT07620
346	16	Flx20mg	7522	CT10799	CT07620
346	17	Flx20mg	7533	CT10799	CT07620
346	18	Flx20mg	7641	CT10799	CT07620
346	19	Flx20mg	7690	CT10799	CT07620
346	20	Flx20mg	7734	CT10799	CT07620
346	21	Flx20mg	7768	CT10799	CT07620
346	22	Flx20mg	7839	CT10799	CT07620
346	23	Flx20mg	7961	CT10799	CT07620
350	3	Placebo	1144	CT09679	
350	4	Placebo	2839	CT09679	
350	5	Placebo	2850	CT09679	
350	6	Placebo	2851	CT09679	
350	7	Placebo	2818	CT09679	
350	8	Placebo	2827	CT09679	
350	9	Placebo	2830	CT09679	
350	10	Placebo	5606	CT09679	
350	11	Placebo	5704	CT09679	
350	12	Placebo	5705	CT09679	
350	13	Placebo	5710	CT09679	
350	14	Placebo	5712	CT09679	
352	3	Placebo	1265	CT09679	
352	4	Placebo	3233	CT09679	
352	5	Placebo	3237	CT09679	
352	6	Placebo	3242	CT09679	
352	7	Placebo	2834	CT09679	
352	8	Placebo	2842	CT09679	
353	3	Placebo	1266	CT09679	
353	4	Flx10mg	2816	CT09679	CT07620
353	5	Flx20mg	2817	CT09679	CT07620
353	6	Flx20mg	2826	CT09679	CT07620
353	7	Flx20mg	2230	CT09679	CT07620
353	8	Flx20mg	2236	CT09679	CT07620
353	9	Flx20mg	2239	CT09679	CT07620
353	10	Flx20mg	5319	CT09679	CT07620
353	11	Flx20mg	5599	CT09679	CT07620
353	12	Flx20mg	5605	CT09679	CT07620
353	13	Flx20mg	5608	CT09679	CT07620
353	14	Flx20mg	5708	CT09679	CT07620
353	15	Flx20mg	7647	CT10799	CT07620
353	16	Flx20mg	7693	CT10799	CT07620

Patient Number	Visit Number	Therapy	Package Assigned	Clinical Trial Lot Number	
353	17	Flx20mg	7740	CT10799	CT07620
353	18	Flx20mg	7741	CT10799	CT07620
353	19	Flx20mg	7773	CT10799	CT07620
353	20	Flx20mg	7835	CT10799	CT07620
353	21	Flx20mg	7897	CT10799	CT07620
353	22	Flx20mg	8005	CT10799	CT07620
354	3	Placebo	1268	CT09679	
354	4	Flx10mg	2848	CT09679	CT07620
354	5	Flx20mg	2841	CT09679	CT07620
354	6	Flx20mg	2845	CT09679	CT07620
354	7	Flx20mg	2250	CT09679	CT07620
354	8	Flx20mg	2821	CT09679	CT07620
354	9	Flx20mg	2829	CT09679	CT07620
354	10	Flx20mg	5709	CT09679	CT07620
354	11	Flx20mg	5862	CT09679	CT07620
354	12	Flx20mg	5864	CT09679	CT07620
354	13	Flx20mg	6106	CT09679	CT07620
354	14	Flx20mg	6109	CT09679	CT07620
354	15	Flx20mg	7834	CT10799	CT07620
354	16	Flx20mg	7885	CT10799	CT07620
354	17	Flx20mg	7954	CT10799	CT07620
354	18	Flx20mg	7957	CT10799	CT07620
354	19	Flx20mg	8008	CT10799	CT07620
355	3	Placebo	1267	CT09679	
355	4	Flx10mg	2831	CT09679	CT07620
355	5	Flx20mg	2832	CT09679	CT07620
355	6	Flx20mg	2837	CT09679	CT07620
355	7	Flx20mg	2243	CT09679	CT07620
355	8	Flx20mg	2814	CT09679	CT07620
355	9	Flx20mg	2824	CT09679	CT07620
355	10	Flx20mg	5609	CT09679	CT07620
355	11	Flx20mg	5711	CT09679	CT07620
355	12	Flx20mg	5713	CT09679	CT07620
355	13	Flx20mg	5863	CT09679	CT07620
355	14	Flx20mg	5869	CT09679	CT07620
355	15	Placebo	7524	CT10799	
355	16	Placebo	7525	CT10799	
355	17	Placebo	7529	CT10799	
355	18	Placebo	7530	CT10799	
355	19	Placebo	7531	CT10799	
355	20	Placebo	7532	CT10799	
356	3	Placebo	1269	CT09679	
356	4	Placebo	3327	CT09679	
356	5	Placebo	3330	CT09679	
356	6	Placebo	3333	CT09679	
356	7	Placebo	2844	CT09679	
356	8	Placebo	2849	CT09679	

Patient Number	Visit Number	Therapy	Package Assigned	Clinical Trial Lot Number	
356	9	Placebo	3230	CT09679	
356	10	Placebo	5715	CT09679	
356	11	Placebo	5859	CT09679	
356	12	Placebo	5860	CT09679	
356	13	Placebo	5861	CT09679	
356	14	Placebo	5865	CT09679	
356	15	Placebo	7527	CT10799	
401	3	Placebo	1049	CT09679	
401	4	Flx10mg	1680	CT09679	CT07620
401	5	Flx20mg	1674	CT09679	CT07620
401	6	Flx20mg	1682	CT09679	CT07620
401	7	Flx20mg	1673	CT09679	CT07620
401	8	Flx20mg	1675	CT09679	CT07620
401	9	Flx20mg	1777	CT09679	CT07620
401	10	Flx20mg	5002	CT09679	CT07620
401	11	Flx20mg	5008	CT09679	CT07620
403	3	Placebo	1050	CT09679	
403	4	Placebo	1672	CT09679	
403	5	Placebo	1678	CT09679	
403	6	Placebo	1679	CT09679	
403	7	Placebo	1670	CT09679	
403	8	Placebo	1671	CT09679	
403	9	Placebo	1774	CT09679	
403	10	Placebo	5003	CT09679	
403	11	Placebo	5004	CT09679	
403	12	Placebo	5009	CT09679	
403	13	Placebo	5015	CT09679	
403	14	Placebo	5017	CT09679	
403	15	Placebo	7053	CT10799	
403	16	Placebo	7056	CT10799	
403	17	Placebo	7057	CT10799	
403	18	Placebo	7058	CT10799	
403	19	Placebo	7061	CT10799	
403	20	Placebo	7062	CT10799	
403	21	Placebo	7065	CT10799	
403	22	Placebo	7066	CT10799	
403	23	Placebo	7068	CT10799	
403	24	Placebo	7069	CT10799	
403	25	Placebo	7074	CT10799	
404	3	Placebo	1051	CT09679	
404	4	Flx10mg	1778	CT09679	CT07620
404	5	Flx20mg	1781	CT09679	CT07620
404	6	Flx20mg	1785	CT09679	CT07620
404	7	Flx20mg	1681	CT09679	CT07620
404	8	Flx20mg	1782	CT09679	CT07620
404	9	Flx20mg	1784	CT09679	CT07620
404	10	Flx20mg	5010	CT09679	CT07620

Patient Number	Visit Number	Therapy	Package Assigned	Clinical Trial Lot Number	
404	11	Flx20mg	5013	CT09679	CT07620
404	12	Flx20mg	5014	CT09679	CT07620
407	3	Placebo	1052	CT09679	
407	4	Placebo	1775	CT09679	
407	5	Placebo	1783	CT09679	
407	6	Placebo	1786	CT09679	
407	7	Placebo	1677	CT09679	
407	8	Placebo	1776	CT09679	
407	9	Placebo	1779	CT09679	
407	10	Placebo	5005	CT09679	
407	11	Placebo	5011	CT09679	
407	12	Placebo	5016	CT09679	
408	3	Placebo	1053	CT09679	
408	4	Flx10mg	1793	CT09679	CT07620
408	5	Flx20mg	1796	CT09679	CT07620
408	6	Flx20mg	1797	CT09679	CT07620
408	7	Flx20mg	1790	CT09679	CT07620
408	8	Flx20mg	1791	CT09679	CT07620
408	9	Flx20mg	1794	CT09679	CT07620
411	3	Placebo	1054	CT09679	
412	3	Placebo	1056	CT09679	
412	4	Placebo	1787	CT09679	
412	5	Placebo	1789	CT09679	
412	6	Placebo	1798	CT09679	
412	7	Placebo	1788	CT09679	
412	8	Placebo	1792	CT09679	
412	9	Placebo	1799	CT09679	
412	10	Placebo	5018	CT09679	
412	11	Placebo	5020	CT09679	
412	12	Placebo	5247	CT09679	
412	13	Placebo	5236	CT09679	
412	14	Placebo	5238	CT09679	
413	3	Placebo	1055	CT09679	
413	4	Flx10mg	1804	CT09679	CT07620
413	5	Flx20mg	1808	CT09679	CT07620
413	6	Flx20mg	1810	CT09679	CT07620
413	7	Flx20mg	1801	CT09679	CT07620
413	8	Flx20mg	1805	CT09679	CT07620
413	9	Flx20mg	1807	CT09679	CT07620
413	10	Flx20mg	5019	CT09679	CT07620
413	11	Flx20mg	5021	CT09679	CT07620
413	12	Flx20mg	5026	CT09679	CT07620
413	13	Flx20mg	5240	CT09679	CT07620
413	14	Flx20mg	5244	CT09679	CT07620
415	3	Placebo	1057	CT09679	
415	4	Flx10mg	1813	CT09679	CT07620
415	5	Flx20mg	1824	CT09679	CT07620

Patient Number	Visit Number	Therapy	Package Assigned	Clinical Trial Lot Number	
415	6	Flx20mg	1825	CT09679	CT07620
415	7	Flx20mg	1816	CT09679	CT07620
415	8	Flx20mg	1822	CT09679	CT07620
415	9	Flx20mg	1823	CT09679	CT07620
415	10	Flx20mg	5237	CT09679	CT07620
415	11	Flx20mg	5420	CT09679	CT07620
415	12	Flx20mg	5423	CT09679	CT07620
415	13	Flx20mg	5422	CT09679	CT07620
415	14	Flx20mg	5537	CT09679	CT07620
415	15	Flx20mg	7054	CT10799	CT07620
415	16	Flx20mg	7055	CT10799	CT07620
416	3	Placebo	1058	CT09679	
416	4	Flx10mg	1882	CT09679	CT07620
416	5	Flx20mg	1879	CT09679	CT07620
416	6	Flx20mg	1890	CT09679	CT07620
416	7	Flx20mg	1887	CT09679	CT07620
416	8	Flx20mg	1888	CT09679	CT07620
416	9	Flx20mg	1893	CT09679	CT07620
416	10	Flx20mg	5243	CT09679	CT07620
416	11	Flx20mg	5428	CT09679	CT07620
416	12	Flx20mg	5539	CT09679	CT07620
416	13	Flx20mg	5540	CT09679	CT07620
416	14	Flx20mg	5573	CT09679	CT07620
416	15	Placebo	7070	CT10799	
416	16	Placebo	7075	CT10799	
417	3	Placebo	1059	CT09679	
417	4	Placebo	1802	CT09679	
417	5	Placebo	1806	CT09679	
417	6	Placebo	1812	CT09679	
417	7	Placebo	1800	CT09679	
419	3	Placebo	1060	CT09679	
419	4	Flx10mg	1899	CT09679	CT07620
419	5	Flx20mg	1900	CT09679	CT07620
419	6	Flx20mg	1903	CT09679	CT07620
419	7	Flx20mg	1889	CT09679	CT07620
419	8	Flx20mg	1901	CT09679	CT07620
419	9	Flx20mg	1902	CT09679	CT07620
419	10	Flx20mg	5544	CT09679	CT07620
422	3	Placebo	1169	CT09679	
422	4	Flx10mg	1912	CT09679	CT07620
422	5	Flx20mg	1906	CT09679	CT07620
422	6	Flx20mg	1914	CT09679	CT07620
422	7	Flx20mg	1904	CT09679	CT07620
422	8	Flx20mg	1907	CT09679	CT07620
422	9	Flx20mg	2681	CT09679	CT07620
422	10	Flx20mg	5575	CT09679	CT07620
422	11	Flx20mg	5583	CT09679	CT07620

Patient Number	Visit Number	Therapy	Package Assigned	Clinical Trial Lot Number	
422	12	Flx20mg	5811	CT09679	CT07620
422	13	Flx20mg	5814	CT09679	CT07620
422	14	Flx20mg	5854	CT09679	CT07620
422	15	Placebo	7077	CT10799	
422	16	Placebo	7391	CT10799	
422	17	Placebo	7392	CT10799	
424	3	Placebo	1171	CT09679	
424	4	Flx10mg	2677	CT09679	CT07620
424	5	Flx20mg	2676	CT09679	CT07620
424	6	Flx20mg	2678	CT09679	CT07620
424	7	Flx20mg	1905	CT09679	CT07620
424	8	Flx20mg	2671	CT09679	CT07620
424	9	Flx20mg	2673	CT09679	CT07620
424	10	Flx20mg	5576	CT09679	CT07620
424	11	Flx20mg	5809	CT09679	CT07620
424	12	Flx20mg	5813	CT09679	CT07620
424	13	Flx20mg	5848	CT09679	CT07620
424	14	Flx20mg	5855	CT09679	CT07620
424	15	Flx20mg	7059	CT10799	CT07620
424	16	Flx20mg	7067	CT10799	CT07620
424	17	Flx20mg	7072	CT10799	CT07620
424	18	Flx20mg	7076	CT10799	CT07620
424	19	Flx20mg	7398	CT10799	CT07620
424	20	Flx20mg	7401	CT10799	CT07620
424	21	Flx20mg	7403	CT10799	CT07620
424	22	Flx20mg	7813	CT10799	CT07620
425	3	Placebo	1170	CT09679	
425	4	Placebo	1814	CT09679	
425	5	Placebo	1820	CT09679	
425	6	Placebo	1883	CT09679	
425	7	Placebo	1803	CT09679	
425	8	Placebo	1815	CT09679	
425	9	Placebo	1818	CT09679	
425	10	Placebo	5239	CT09679	
425	11	Placebo	5242	CT09679	
425	12	Placebo	5418	CT09679	
425	13	Placebo	5421	CT09679	
425	14	Placebo	5424	CT09679	
427	3	Placebo	1172	CT09679	
427	4	Placebo	1821	CT09679	
427	5	Placebo	1881	CT09679	
427	6	Placebo	1885	CT09679	
427	7	Placebo	1811	CT09679	
431	3	Placebo	1174	CT09679	
432	3	Placebo	1173	CT09679	
432	4	Placebo	1891	CT09679	
432	5	Placebo	1894	CT09679	

Patient Number	Visit Number	Therapy	Package Assigned	Clinical Trial Lot Number	
432	6	Placebo	1897	CT09679	
433	3	Placebo	1175	CT09679	
433	4	Flx10mg	2691	CT09679	CT07620
433	5	Flx20mg	2686	CT09679	CT07620
433	6	Flx20mg	2694	CT09679	CT07620
433	7	Flx20mg	2685	CT09679	CT07620
433	8	Flx20mg	2689	CT09679	CT07620
433	9	Flx20mg	2696	CT09679	CT07620
433	10	Flx20mg	5850	CT09679	CT07620
433	11	Flx20mg	5954	CT09679	CT07620
433	12	Flx20mg	5956	CT09679	CT07620
440	3	Placebo	1176	CT09679	
441	3	Placebo	1177	CT09679	
441	4	Flx10mg	2697	CT09679	CT07620
441	5	Flx20mg	2701	CT09679	CT07620
441	6	Flx20mg	2707	CT09679	CT07620
441	7	Flx20mg	2703	CT09679	CT07620
601	3	Placebo	1073	CT09679	
601	4	Placebo	1698	CT09679	
801	3	Placebo	1097	CT09679	
803	3	Placebo	1098	CT09679	
804	3	Placebo	1099	CT09679	
804	4	Placebo	1828	CT09679	
804	5	Placebo	1830	CT09679	
804	6	Placebo	1838	CT09679	
804	7	Placebo	1827	CT09679	
804	8	Placebo	1834	CT09679	
804	9	Placebo	1835	CT09679	
804	10	Placebo	5209	CT09679	
804	11	Placebo	5211	CT09679	
804	12	Placebo	5215	CT09679	
804	13	Placebo	5216	CT09679	
804	14	Placebo	5218	CT09679	
804	15	Placebo	7147	CT10799	
804	16	Placebo	7144	CT10799	
804	17	Placebo	7148	CT10799	
804	18	Placebo	7152	CT10799	
804	19	Placebo	7153	CT10799	
804	20	Placebo	7154	CT10799	
804	21	Placebo	7156	CT10799	
806	3	Placebo	1102	CT09679	
806	4	Placebo	1963	CT09679	
806	5	Placebo	1988	CT09679	
806	6	Placebo	1973	CT09679	
806	7	Placebo	1962	CT09679	
807	3	Placebo	1101	CT09679	
807	4	Placebo	1960	CT09679	

Patient Number	Visit Number	Therapy	Package Assigned	Clinical Trial Lot Number	
808	3	Placebo	1100	CT09679	
808	4	Placebo	1956	CT09679	
808	5	Placebo	1995	CT09679	
808	6	Placebo	1972	CT09679	
808	7	Placebo	1958	CT09679	
808	8	Placebo	1967	CT09679	
808	9	Placebo	1970	CT09679	
808	10	Placebo	5223	CT09679	
808	11	Placebo	5225	CT09679	
809	3	Placebo	1103	CT09679	
809	4	Placebo	1981	CT09679	
809	5	Placebo	1993	CT09679	
809	6	Placebo	1994	CT09679	
809	7	Placebo	1976	CT09679	
809	8	Placebo	1980	CT09679	
809	9	Placebo	1986	CT09679	
809	10	Placebo	5229	CT09679	
809	11	Placebo	5231	CT09679	
810	3	Placebo	1104	CT09679	
810	4	Flx10mg	1832	CT09679	CT07620
810	5	Flx20mg	1829	CT09679	CT07620
810	6	Flx20mg	1965	CT09679	CT07620
810	7	Flx20mg	1826	CT09679	CT07620
810	8	Flx20mg	1961	CT09679	CT07620
810	9	Flx20mg	1975	CT09679	CT07620
810	10	Flx20mg	5210	CT09679	CT07620
810	11	Flx20mg	5217	CT09679	CT07620
810	12	Flx20mg	5221	CT09679	CT07620
810	13	Flx20mg	5226	CT09679	CT07620
810	14	Flx20mg	5230	CT09679	CT07620
810	15	Placebo	7157	CT10799	
810	16	Placebo	7158	CT10799	
810	17	Placebo	7160	CT10799	
811	3	Placebo	1105	CT09679	
811	4	Flx10mg	1959	CT09679	CT07620
811	5	Flx20mg	1837	CT09679	CT07620
811	6	Flx20mg	1974	CT09679	CT07620
811	7	Flx20mg	1831	CT09679	CT07620
811	8	Flx20mg	1968	CT09679	CT07620
811	9	Flx20mg	1978	CT09679	CT07620
811	10	Flx20mg	5213	CT09679	CT07620
812	3	Placebo	1106	CT09679	
812	4	Flx10mg	1979	CT09679	CT07620
812	5	Flx20mg	1964	CT09679	CT07620
812	6	Flx20mg	1977	CT09679	CT07620
812	7	Flx20mg	1836	CT09679	CT07620
812	8	Flx20mg	1969	CT09679	CT07620

Patient Number	Visit Number	Therapy	Package Assigned	Clinical Trial Lot Number	
813	3	Placebo	1107	CT09679	
813	4	Flx10mg	1982	CT09679	CT07620
813	5	Flx20mg	1987	CT09679	CT07620
813	6	Flx20mg	1989	CT09679	CT07620
813	7	Flx20mg	1957	CT09679	CT07620
813	8	Flx20mg	1983	CT09679	CT07620
813	9	Flx20mg	1985	CT09679	CT07620
813	10	Flx40mg	5212	CT09679	CT09678
813	11	Flx40mg	5220	CT09679	CT09678
813	12	Flx40mg	5222	CT09679	CT09678
814	3	Placebo	1108	CT09679	
814	4	Flx10mg	2003	CT09679	CT07620
814	5	Flx20mg	2000	CT09679	CT07620
814	6	Flx20mg	2005	CT09679	CT07620
814	7	Flx20mg	1992	CT09679	CT07620
814	8	Flx20mg	1999	CT09679	CT07620
814	9	Flx20mg	2001	CT09679	CT07620
814	10	Flx20mg	5224	CT09679	CT07620
814	11	Flx20mg	5228	CT09679	CT07620
814	12	Flx20mg	5638	CT09679	CT07620
815	3	Placebo	1301	CT09679	
815	4	Flx10mg	3132	CT09679	CT07620
815	5	Flx20mg	3129	CT09679	CT07620
815	6	Flx20mg	3137	CT09679	CT07620
815	7	Flx20mg	2006	CT09679	CT07620
815	8	Flx20mg	3126	CT09679	CT07620
815	9	Flx20mg	3131	CT09679	CT07620
815	10	Flx20mg	5640	CT09679	CT07620
815	11	Flx20mg	5641	CT09679	CT07620
815	12	Flx20mg	5642	CT09679	CT07620
815	13	Flx20mg	6042	CT09679	CT07620
815	14	Flx20mg	6050	CT09679	CT07620
815	15	Flx20mg	7145	CT10799	CT07620
815	16	Flx20mg	7150	CT10799	CT07620
901	3	Placebo	1121	CT09679	
901	4	Flx10mg	2023	CT09679	CT07620
901	5	Flx20mg	2025	CT09679	CT07620
901	6	Flx20mg	2031	CT09679	CT07620
901	7	Flx20mg	2021	CT09679	CT07620
901	8	Flx20mg	2022	CT09679	CT07620
901	9	Flx20mg	2032	CT09679	CT07620
901	10	Flx40mg	5253	CT09679	CT09678
901	11	Flx40mg	5257	CT09679	CT09678
901	12	Flx60mg	5250		CT09678
901	13	Flx60mg	5263		CT09678
905	3	Placebo	1123	CT09679	
905	4	Placebo	2027	CT09679	

Patient Number	Visit Number	Therapy	Package Assigned	Clinical Trial Lot Number	
905	5	Placebo	2030	CT09679	
905	6	Placebo	2033	CT09679	
905	7	Placebo	2024	CT09679	
905	8	Placebo	2028	CT09679	
906	3	Placebo	1124	CT09679	
906	4	Flx10mg	2311	CT09679	CT07620
906	5	Flx20mg	2315	CT09679	CT07620
906	6	Flx20mg	2317	CT09679	CT07620
906	7	Flx20mg	2312	CT09679	CT07620
906	8	Flx20mg	2313	CT09679	CT07620
906	9	Flx20mg	2318	CT09679	CT07620
906	10	Flx20mg	5249	CT09679	CT07620
906	11	Flx20mg	5251	CT09679	CT07620
906	12	Flx20mg	5255	CT09679	CT07620
906	13	Flx20mg	5260	CT09679	CT07620
906	14	Flx20mg	5261	CT09679	CT07620
911	3	Placebo	1122	CT09679	
911	4	Placebo	2309	CT09679	
911	5	Placebo	2314	CT09679	
911	6	Placebo	2323	CT09679	
911	7	Placebo	2029	CT09679	
911	8	Placebo	2308	CT09679	
911	9	Placebo	2325	CT09679	
911	10	Placebo	5252	CT09679	
911	11	Placebo	5254	CT09679	
911	12	Placebo	5259	CT09679	
911	13	Placebo	5265	CT09679	
911	14	Placebo	5269	CT09679	
911	15	Placebo	7431	CT10799	
911	16	Placebo	7432	CT10799	
911	17	Placebo	7436	CT10799	
911	18	Placebo	7439	CT10799	
911	19	Placebo	7444	CT10799	
911	20	Placebo	7446	CT10799	
911	21	Placebo	7450	CT10799	
911	22	Placebo	7976	CT10799	
912	3	Placebo	1126	CT09679	
912	4	Placebo	2310	CT09679	
912	5	Placebo	2320	CT09679	
912	6	Placebo	2332	CT09679	
912	7	Placebo	2307	CT09679	
912	8	Placebo	2319	CT09679	
912	9	Placebo	2329	CT09679	
912	10	Placebo	5248	CT09679	
912	11	Placebo	5256	CT09679	
912	12	Placebo	5262	CT09679	
912	13	Placebo	5266	CT09679	

Patient Number	Visit Number	Therapy	Package Assigned	Clinical Trial Lot Number	
912	14	Placebo	5356	CT09679	
912	15	Placebo	7430	CT10799	
912	16	Placebo	7435	CT10799	
912	17	Placebo	7438	CT10799	
912	18	Placebo	7443	CT10799	
912	19	Placebo	7445	CT10799	
912	20	Placebo	7447	CT10799	
912	21	Placebo	7455	CT10799	
912	22	Placebo	7977	CT10799	
913	3	Placebo	1125	CT09679	
913	4	Flx10mg	2330	CT09679	CT07620
913	5	Flx20mg	2322	CT09679	CT07620
913	6	Flx20mg	2328	CT09679	CT07620
913	7	Flx20mg	2321	CT09679	CT07620
913	8	Flx20mg	2326	CT09679	CT07620
913	9	Flx20mg	2327	CT09679	CT07620
913	10	Flx20mg	5264	CT09679	CT07620
913	11	Flx20mg	5267	CT09679	CT07620
915	3	Placebo	1127	CT09679	
915	4	Flx10mg	2335	CT09679	CT07620
915	5	Flx20mg	2337	CT09679	CT07620
915	6	Flx20mg	2342	CT09679	CT07620
915	7	Flx20mg	2336	CT09679	CT07620
915	8	Flx20mg	2339	CT09679	CT07620
915	9	Flx20mg	2345	CT09679	CT07620
915	10	Flx20mg	5273	CT09679	CT07620
915	11	Flx20mg	5353	CT09679	CT07620
915	12	Flx20mg	5359	CT09679	CT07620
915	13	Flx20mg	5432	CT09679	CT07620
915	14	Flx20mg	5437	CT09679	CT07620
915	15	Flx20mg	7433	CT10799	CT07620
915	16	Flx20mg	7437	CT10799	CT07620
915	17	Flx20mg	7448	CT10799	CT07620
915	18	Flx20mg	7978	CT10799	CT07620
915	19	Flx20mg	7982	CT10799	CT07620
916	3	Placebo	1128	CT09679	
916	4	Placebo	2334	CT09679	
916	5	Placebo	2338	CT09679	
916	6	Placebo	2340	CT09679	
916	7	Placebo	2331	CT09679	
916	8	Placebo	2333	CT09679	
916	9	Placebo	2344	CT09679	
916	10	Placebo	5268	CT09679	
916	11	Placebo	5358	CT09679	
918	3	Placebo	1129	CT09679	
919	3	Placebo	1130	CT09679	
919	4	Placebo	2347	CT09679	

Patient Number	Visit Number	Therapy	Package Assigned	Clinical Trial Lot Number	
919	5	Placebo	2352	CT09679	
919	6	Placebo	2354	CT09679	
919	7	Placebo	2341	CT09679	
919	8	Placebo	2355	CT09679	
919	9	Placebo	2357	CT09679	
919	10	Placebo	5361	CT09679	
920	3	Placebo	1131	CT09679	
920	4	Flx10mg	2348	CT09679	CT07620
920	5	Flx20mg	2349	CT09679	CT07620
920	6	Flx20mg	2356	CT09679	CT07620
920	7	Flx20mg	2346	CT09679	CT07620
920	8	Flx20mg	2351	CT09679	CT07620
920	9	Flx20mg	2353	CT09679	CT07620
920	10	Flx20mg	5357	CT09679	CT07620
920	11	Flx20mg	5360	CT09679	CT07620
920	12	Flx20mg	5436	CT09679	CT07620
920	13	Flx20mg	5440	CT09679	CT07620
920	14	Flx20mg	6171	CT09679	CT07620
920	15	Flx20mg	7440	CT10799	CT07620
920	16	Flx20mg	7451	CT10799	CT07620
920	17	Flx20mg	7452	CT10799	CT07620
920	18	Flx20mg	7988	CT10799	CT07620
1101	3	Placebo	1013	CT09679	
1101	4	Flx10mg	1559	CT09679	CT07620
1101	5	Flx20mg	1553	CT09679	CT07620
1101	6	Flx20mg	1560	CT09679	CT07620
1101	7	Flx20mg	1554	CT09679	CT07620
1101	8	Flx20mg	1555	CT09679	CT07620
1101	9	Flx20mg	1563	CT09679	CT07620
1101	10	Flx40mg	5082	CT09679	CT09678
1101	11	Flx40mg	5085	CT09679	CT09678
1101	12	Flx40mg	5097	CT09679	CT09678
1101	13	Flx40mg	5098	CT09679	CT09678
1101	14	Flx40mg	5105	CT09679	CT09678
1101	15	Placebo	7002	CT10799	
1101	16	Placebo	7003	CT10799	
1101	17	Placebo	7005	CT10799	
1101	18	Placebo	7009	CT10799	
1101	19	Placebo	7022	CT10799	
1101	20	Placebo	7015	CT10799	
1101	21	Placebo	7018	CT10799	
1101	22	Placebo	7131	CT10799	
1101	23	Placebo	7137	CT10799	
1101	24	Placebo	7224	CT10799	
1101	25	Placebo	7368	CT10799	
1102	3	Placebo	1014	CT09679	
1102	4	Placebo	1561	CT09679	

Patient Number	Visit Number	Therapy	Package Assigned	Clinical Trial Lot Number	
1102	5	Placebo	1562	CT09679	
1102	6	Placebo	1564	CT09679	
1102	7	Placebo	1556	CT09679	
1102	8	Placebo	1557	CT09679	
1105	3	Placebo	1015	CT09679	
1105	4	Placebo	1566	CT09679	
1105	5	Placebo	1567	CT09679	
1105	6	Placebo	1581	CT09679	
1105	7	Placebo	1565	CT09679	
1105	8	Placebo	1576	CT09679	
1105	9	Placebo	1582	CT09679	
1105	10	Placebo	5080	CT09679	
1105	11	Placebo	5086	CT09679	
1105	12	Placebo	5091	CT09679	
1105	13	Placebo	5094	CT09679	
1105	14	Placebo	5100	CT09679	
1105	15	Placebo	7004	CT10799	
1105	16	Placebo	7008	CT10799	
1105	17	Placebo	7010	CT10799	
1105	18	Placebo	7014	CT10799	
1105	19	Placebo	7017	CT10799	
1105	20	Placebo	7020	CT10799	
1105	21	Placebo	7023	CT10799	
1105	22	Placebo	7133	CT10799	
1105	23	Placebo	7223	CT10799	
1105	24	Placebo	7233	CT10799	
1107	3	Placebo	1016	CT09679	
1107	4	Placebo	1575	CT09679	
1107	5	Placebo	1584	CT09679	
1107	6	Placebo	1591	CT09679	
1107	7	Placebo	1571	CT09679	
1107	8	Placebo	1577	CT09679	
1107	9	Placebo	1586	CT09679	
1107	10	Placebo	5084	CT09679	
1107	11	Placebo	5088	CT09679	
1107	12	Placebo	5093	CT09679	
1107	13	Placebo	5099	CT09679	
1109	3	Placebo	1017	CT09679	
1109	4	Flx10mg	1573	CT09679	CT07620
1109	5	Flx20mg	1570	CT09679	CT07620
1109	6	Flx20mg	1574	CT09679	CT07620
1109	7	Flx20mg	1568	CT09679	CT07620
1109	8	Flx20mg	1569	CT09679	CT07620
1109	9	Flx20mg	1572	CT09679	CT07620
1109	10	Flx20mg	5079	CT09679	CT07620
1118	3	Placebo	1018	CT09679	
1118	4	Flx10mg	1589	CT09679	CT07620

Patient Number	Visit Number	Therapy	Package Assigned	Clinical Trial Lot Number	
1118	5	Flx20mg	1585	CT09679	CT07620
1118	6	Flx20mg	1588	CT09679	CT07620
1118	7	Flx20mg	1580	CT09679	CT07620
1118	8	Flx20mg	1583	CT09679	CT07620
1120	3	Placebo	1019	CT09679	
1120	4	Placebo	1593	CT09679	
1120	5	Placebo	1603	CT09679	
1120	6	Placebo	1924	CT09679	
1120	7	Placebo	1594	CT09679	
1120	8	Placebo	1601	CT09679	
1120	9	Placebo	1919	CT09679	
1120	10	Placebo	5104	CT09679	
1120	11	Placebo	5109	CT09679	
1120	12	Placebo	5112	CT09679	
1120	13	Placebo	5151	CT09679	
1120	14	Placebo	5331	CT09679	
1121	3	Placebo	1020	CT09679	
1121	4	Placebo	1597	CT09679	
1121	5	Placebo	1918	CT09679	
1121	6	Placebo	1929	CT09679	
1121	7	Placebo	1587	CT09679	
1121	8	Placebo	1602	CT09679	
1121	9	Placebo	1925	CT09679	
1121	10	Placebo	5106	CT09679	
1121	11	Placebo	5110	CT09679	
1121	12	Placebo	5115	CT09679	
1121	13	Placebo	5154	CT09679	
1121	14	Placebo	5152	CT09679	
1122	3	Placebo	1021	CT09679	
1122	4	Placebo	1933	CT09679	
1122	5	Placebo	1937	CT09679	
1122	6	Placebo	1942	CT09679	
1122	7	Placebo	1928	CT09679	
1122	8	Placebo	1930	CT09679	
1122	9	Placebo	1932	CT09679	
1122	10	Placebo	5147	CT09679	
1122	11	Placebo	5156	CT09679	
1122	12	Placebo	5328	CT09679	
1122	13	Placebo	5329	CT09679	
1122	14	Placebo	5332	CT09679	
1122	15	Placebo	7132	CT10799	
1122	16	Placebo	7135	CT10799	
1122	17	Placebo	7139	CT10799	
1122	18	Placebo	7140	CT10799	
1122	19	Placebo	7228	CT10799	
1122	20	Placebo	7231	CT10799	
1122	21	Placebo	7372	CT10799	

Patient Number	Visit Number	Therapy	Package Assigned	Clinical Trial Lot Number	
1122	22	Placebo	7420	CT10799	
1122	23	Placebo	7501	CT10799	
1122	24	Placebo	7542	CT10799	
1122	25	Placebo	7637	CT10799	
1126	3	Placebo	1022	CT09679	
1126	4	Placebo	1948	CT09679	
1126	5	Placebo	1949	CT09679	
1126	6	Placebo	1954	CT09679	
1126	7	Placebo	1936	CT09679	
1126	8	Placebo	1951	CT09679	
1126	9	Placebo	1952	CT09679	
1126	10	Placebo	5334	CT09679	
1126	11	Placebo	5473	CT09679	
1126	12	Placebo	5475	CT09679	
1126	13	Placebo	5478	CT09679	
1126	14	Placebo	5480	CT09679	
1126	15	Placebo	7225	CT10799	
1126	16	Placebo	7230	CT10799	
1126	17	Placebo	7369	CT10799	
1126	18	Placebo	7417	CT10799	
1126	19	Placebo	7424	CT10799	
1126	20	Placebo	7495	CT10799	
1126	21	Placebo	7504	CT10799	
1126	22	Placebo	7540	CT10799	
1126	23	Placebo	7719	CT10799	
1129	3	Placebo	1023	CT09679	
1129	4	Flx10mg	1600	CT09679	CT07620
1129	5	Flx20mg	1598	CT09679	CT07620
1129	6	Flx20mg	1599	CT09679	CT07620
1129	7	Flx20mg	1590	CT09679	CT07620
1129	8	Flx20mg	1596	CT09679	CT07620
1129	9	Flx20mg	1922	CT09679	CT07620
1129	10	Flx20mg	5081	CT09679	CT07620
1129	11	Flx20mg	5083	CT09679	CT07620
1129	12	Flx20mg	5090	CT09679	CT07620
1129	13	Flx20mg	5095	CT09679	CT07620
1129	14	Flx20mg	5096	CT09679	CT07620
1129	15	Placebo	7365	CT10799	
1129	16	Placebo	7373	CT10799	
1129	17	Placebo	7374	CT10799	
1129	18	Placebo	7421	CT10799	
1129	19	Placebo	7425	CT10799	
1129	20	Placebo	7496	CT10799	
1129	21	Placebo	7505	CT10799	
1129	22	Placebo	7625	CT10799	
1129	23	Placebo	7716	CT10799	
1129	24	Placebo	7755	CT10799	

Patient Number	Visit Number	Therapy	Package Assigned	Clinical Trial Lot Number	
1129	25	Placebo	7875	CT10799	
1131	3	Placebo	1024	CT09679	
1131	4	Flx10mg	1926	CT09679	CT07620
1131	5	Flx20mg	1920	CT09679	CT07620
1131	6	Flx20mg	1921	CT09679	CT07620
1131	7	Flx20mg	1595	CT09679	CT07620
1131	8	Flx20mg	1917	CT09679	CT07620
1131	9	Flx20mg	1592	CT09679	CT07620
1131	10	Flx40mg	5111	CT09679	CT09678
1131	11	Flx40mg	5145	CT09679	CT09678
1134	3	Placebo	1157	CT09679	
1134	4	Placebo	2606	CT09679	
1134	5	Placebo	2616	CT09679	
1134	6	Placebo	2875	CT09679	
1134	7	Placebo	1955	CT09679	
1134	8	Placebo	2614	CT09679	
1135	3	Placebo	1158	CT09679	
1135	4	Placebo	2617	CT09679	
1135	5	Placebo	2867	CT09679	
1135	6	Placebo	2972	CT09679	
1135	7	Placebo	2608	CT09679	
1135	8	Placebo	2615	CT09679	
1135	9	Placebo	2871	CT09679	
1135	10	Placebo	5479	CT09679	
1135	11	Placebo	5564	CT09679	
1135	12	Placebo	5566	CT09679	
1135	13	Placebo	5567	CT09679	
1135	14	Placebo	5569	CT09679	
1135	15	Placebo	7377	CT10799	
1135	16	Placebo	7423	CT10799	
1135	17	Placebo	7426	CT10799	
1135	18	Placebo	7499	CT10799	
1135	19	Placebo	7507	CT10799	
1135	20	Placebo	7535	CT10799	
1135	21	Placebo	7543	CT10799	
1135	22	Placebo	7717	CT10799	
1135	23	Placebo	7757	CT10799	
1135	24	Placebo	7873	CT10799	
1135	25	Placebo	7882	CT10799	
1137	3	Placebo	1159	CT09679	
1137	4	Flx10mg	1935	CT09679	CT07620
1137	5	Flx20mg	1931	CT09679	CT07620
1137	6	Flx20mg	1939	CT09679	CT07620
1137	7	Flx20mg	1927	CT09679	CT07620
1137	8	Flx20mg	1934	CT09679	CT07620
1137	9	Flx20mg	1941	CT09679	CT07620
1137	10	Flx20mg	5101	CT09679	CT07620

Patient Number	Visit Number	Therapy	Package Assigned	Clinical Trial Lot Number	
1137	11	Flx20mg	5103	CT09679	CT07620
1137	12	Flx20mg	5107	CT09679	CT07620
1137	13	Flx20mg	5108	CT09679	CT07620
1137	14	Flx20mg	5114	CT09679	CT07620
1138	3	Placebo	1160	CT09679	
1138	4	Placebo	2866	CT09679	
1138	5	Placebo	2978	CT09679	
1138	6	Placebo	2979	CT09679	
1138	7	Placebo	2876	CT09679	
1138	8	Placebo	2877	CT09679	
1138	9	Placebo	2977	CT09679	
1138	10	Placebo	5570	CT09679	
1138	11	Placebo	5666	CT09679	
1138	12	Placebo	5671	CT09679	
1138	13	Placebo	5826	CT09679	
1138	14	Placebo	5829	CT09679	
1138	15	Placebo	7534	CT10799	
1138	16	Placebo	7537	CT10799	
1138	17	Placebo	7626	CT10799	
1139	3	Placebo	1163	CT09679	
1139	4	Placebo	3168	CT09679	
1141	3	Placebo	1161	CT09679	
1141	4	Flx10mg	1953	CT09679	CT07620
1141	5	Flx20mg	1943	CT09679	CT07620
1141	6	Flx20mg	1945	CT09679	CT07620
1141	7	Flx20mg	1938	CT09679	CT07620
1141	8	Flx20mg	1944	CT09679	CT07620
1141	9	Flx20mg	1946	CT09679	CT07620
1141	10	Flx40mg	5148	CT09679	CT09678
1141	11	Flx40mg	5327	CT09679	CT09678
1143	3	Placebo	1162	CT09679	
1143	4	Placebo	3167	CT09679	
1143	5	Placebo	3171	CT09679	
1143	6	Placebo	3302	CT09679	
1143	7	Placebo	2970	CT09679	
1143	8	Placebo	3166	CT09679	
1143	9	Placebo	3176	CT09679	
1143	10	Placebo	5668	CT09679	
1143	11	Placebo	5673	CT09679	
1143	12	Placebo	5827	CT09679	
1143	13	Placebo	3298	CT09679	
1143	14	Placebo	5927	CT09679	
1143	15	Placebo	7538	CT10799	
1143	16	Placebo	7629	CT10799	
1143	17	Placebo	7634	CT10799	
1143	18	Placebo	7724	CT10799	
1143	19	Placebo	7727	CT10799	

Patient Number	Visit Number	Therapy	Package Assigned	Clinical Trial Lot Number	
1143	20	Placebo	7761	CT10799	
1143	21	Placebo	7764	CT10799	
1143	22	Placebo	7879	CT10799	
1143	23	Placebo	8031	CT10799	
1144	3	Placebo	1164	CT09679	
1144	4	Placebo	3295	CT09679	
1144	5	Placebo	3307	CT09679	
1144	6	Placebo	3418	CT09679	
1144	7	Placebo	2971	CT09679	
1144	8	Placebo	3175	CT09679	
1144	9	Placebo	3296	CT09679	
1144	10	Placebo	5669	CT09679	
1144	11	Placebo	5824	CT09679	
1144	12	Placebo	5830	CT09679	
1144	13	Placebo	5924	CT09679	
1144	14	Placebo	5929	CT09679	
1144	15	Placebo	7628	CT10799	
1144	16	Placebo	7633	CT10799	
1144	17	Placebo	7720	CT10799	
1144	18	Placebo	7725	CT10799	
1144	19	Placebo	7758	CT10799	
1144	20	Placebo	7763	CT10799	
1144	21	Placebo	7767	CT10799	
1144	22	Placebo	7883	CT10799	
1152	3	Placebo	1165	CT09679	
1152	4	Flx10mg	2612	CT09679	CT07620
1152	5	Flx20mg	2609	CT09679	CT07620
1152	6	Flx20mg	2618	CT09679	CT07620
1152	7	Flx20mg	1950	CT09679	CT07620
1153	3	Placebo	1166	CT09679	
1153	4	Flx10mg	2873	CT09679	CT07620
1153	5	Flx20mg	2870	CT09679	CT07620
1153	6	Flx20mg	2874	CT09679	CT07620
1153	7	Flx20mg	2607	CT09679	CT07620
1153	8	Flx20mg	2611	CT09679	CT07620
1153	9	Flx20mg	2613	CT09679	CT07620
1153	10	Flx20mg	5117	CT09679	CT07620
1153	11	Flx20mg	5146	CT09679	CT07620
1153	12	Flx20mg	5153	CT09679	CT07620
1153	13	Flx20mg	5155	CT09679	CT07620
1153	14	Flx20mg	5330	CT09679	CT07620
1156	3	Placebo	1167	CT09679	
1156	4	Flx10mg	2980	CT09679	CT07620
1156	5	Flx20mg	2974	CT09679	CT07620
1156	6	Flx20mg	2982	CT09679	CT07620
1156	7	Flx20mg	2868	CT09679	CT07620
1156	8	Flx20mg	2869	CT09679	CT07620

Patient Number	Visit Number	Therapy	Package Assigned	Clinical Trial Lot Number	
1156	9	Flx20mg	2872	CT09679	CT07620
1156	10	Flx20mg	5149	CT09679	CT07620
1156	11	Flx20mg	5326	CT09679	CT07620
1156	12	Flx20mg	5335	CT09679	CT07620
1156	13	Flx20mg	5336	CT09679	CT07620
1156	14	Flx20mg	5469	CT09679	CT07620
1156	15	Placebo	7876	CT10799	
1156	16	Placebo	7880	CT10799	
1156	17	Placebo	8028	CT10799	
1201	3	Placebo	1025	CT09679	
1201	4	Placebo	1607	CT09679	
1201	5	Placebo	1608	CT09679	
1201	6	Placebo	1614	CT09679	
1201	7	Placebo	1606	CT09679	
1201	8	Placebo	1616	CT09679	
1201	9	Placebo	1617	CT09679	
1201	10	Placebo	5027	CT09679	
1201	11	Placebo	5030	CT09679	
1201	12	Placebo	5033	CT09679	
1202	3	Placebo	1026	CT09679	
1202	4	Flx10mg	1611	CT09679	CT07620
1202	5	Flx20mg	1609	CT09679	CT07620
1202	6	Flx20mg	1613	CT09679	CT07620
1202	7	Flx20mg	1605	CT09679	CT07620
1202	8	Flx20mg	1610	CT09679	CT07620
1202	9	Flx20mg	1626	CT09679	CT07620
1202	10	Flx20mg	5028	CT09679	CT07620
1202	11	Flx20mg	5036	CT09679	CT07620
1202	12	Flx20mg	5038	CT09679	CT07620
1202	13	Flx20mg	5042	CT09679	CT07620
1202	14	Flx20mg	5043	CT09679	CT07620
1202	15	Flx20mg	7032	CT10799	CT07620
1202	16	Flx20mg	7038	CT10799	CT07620
1202	17	Flx20mg	7039	CT10799	CT07620
1202	18	Flx20mg	7045	CT10799	CT07620
1202	19	Flx20mg	7047	CT10799	CT07620
1202	20	Flx20mg	7050	CT10799	CT07620
1202	21	Flx20mg	7115	CT10799	CT07620
1202	22	Flx20mg	7119	CT10799	CT07620
1202	23	Flx20mg	7178	CT10799	CT07620
1202	24	Flx20mg	7265	CT10799	CT07620
1202	25	Flx20mg	7385	CT10799	CT07620
1203	3	Placebo	1027	CT09679	
1203	4	Flx10mg	1620	CT09679	CT07620
1203	5	Flx20mg	1622	CT09679	CT07620
1203	6	Flx20mg	1623	CT09679	CT07620
1203	7	Flx20mg	1612	CT09679	CT07620

Patient Number	Visit Number	Therapy	Package Assigned	Clinical Trial Lot Number	
1203	8	Flx20mg	1627	CT09679	CT07620
1203	9	Flx20mg	1632	CT09679	CT07620
1203	10	Flx20mg	5037	CT09679	CT07620
1204	3	Placebo	1028	CT09679	
1204	4	Flx10mg	1643	CT09679	CT07620
1204	5	Flx20mg	1637	CT09679	CT07620
1204	6	Flx20mg	1638	CT09679	CT07620
1204	7	Flx20mg	1624	CT09679	CT07620
1204	8	Flx20mg	1631	CT09679	CT07620
1204	9	Flx20mg	1636	CT09679	CT07620
1205	3	Placebo	1029	CT09679	
1205	4	Flx10mg	1648	CT09679	CT07620
1205	5	Flx20mg	1646	CT09679	CT07620
1205	6	Flx20mg	1656	CT09679	CT07620
1205	7	Flx20mg	1647	CT09679	CT07620
1205	8	Flx20mg	1654	CT09679	CT07620
1205	9	Flx20mg	1655	CT09679	CT07620
1205	10	Flx20mg	5047	CT09679	CT07620
1205	11	Flx20mg	5052	CT09679	CT07620
1205	12	Flx20mg	5157	CT09679	CT07620
1205	13	Flx20mg	5168	CT09679	CT07620
1205	14	Flx20mg	5195	CT09679	CT07620
1205	15	Flx20mg	7116	CT10799	CT07620
1205	16	Flx20mg	7110	CT10799	CT07620
1205	17	Flx20mg	7120	CT10799	CT07620
1205	18	Flx20mg	7129	CT10799	CT07620
1205	19	Flx20mg	7177	CT10799	CT07620
1205	20	Flx20mg	7182	CT10799	CT07620
1205	21	Flx20mg	7219	CT10799	CT07620
1205	22	Flx20mg	7358	CT10799	CT07620
1205	23	Flx20mg	7390	CT10799	CT07620
1205	24	Flx20mg	7414	CT10799	CT07620
1205	25	Flx20mg	7509	CT10799	CT07620
1206	3	Placebo	1030	CT09679	
1206	4	Placebo	1618	CT09679	
1206	5	Placebo	1630	CT09679	
1206	6	Placebo	1641	CT09679	
1206	7	Placebo	1619	CT09679	
1206	8	Placebo	1628	CT09679	
1206	9	Placebo	1635	CT09679	
1207	3	Placebo	1031	CT09679	
1207	4	Placebo	1629	CT09679	
1207	5	Placebo	1633	CT09679	
1207	6	Placebo	1642	CT09679	
1207	7	Placebo	1625	CT09679	
1207	8	Placebo	1634	CT09679	
1207	9	Placebo	1640	CT09679	

Patient Number	Visit Number	Therapy	Package Assigned	Clinical Trial Lot Number	
1207	10	Placebo	5034	CT09679	
1207	11	Placebo	5039	CT09679	
1207	12	Placebo	5040	CT09679	
1207	13	Placebo	5041	CT09679	
1207	14	Placebo	5044	CT09679	
1207	15	Placebo	7027	CT10799	
1207	16	Placebo	7028	CT10799	
1207	17	Placebo	7030	CT10799	
1207	18	Placebo	7031	CT10799	
1207	19	Placebo	7034	CT10799	
1207	20	Placebo	7035	CT10799	
1207	21	Placebo	7036	CT10799	
1207	22	Placebo	7040	CT10799	
1207	23	Placebo	7044	CT10799	
1207	24	Placebo	7049	CT10799	
1207	25	Placebo	7107	CT10799	
1208	3	Placebo	1032	CT09679	
1208	4	Flx10mg	1851	CT09679	CT07620
1208	5	Flx20mg	1842	CT09679	CT07620
1208	6	Flx20mg	1845	CT09679	CT07620
1208	7	Flx20mg	1840	CT09679	CT07620
1208	8	Flx20mg	1854	CT09679	CT07620
1208	9	Flx20mg	1862	CT09679	CT07620
1208	10	Flx20mg	5159	CT09679	CT07620
1208	11	Flx20mg	5190	CT09679	CT07620
1208	12	Flx20mg	5194	CT09679	CT07620
1208	13	Flx20mg	5286	CT09679	CT07620
1208	14	Flx20mg	5285	CT09679	CT07620
1209	3	Placebo	1033	CT09679	
1209	4	Flx10mg	1863	CT09679	CT07620
1209	5	Flx20mg	1857	CT09679	CT07620
1209	6	Flx20mg	1874	CT09679	CT07620
1209	7	Flx20mg	1844	CT09679	CT07620
1209	8	Flx20mg	1856	CT09679	CT07620
1209	9	Flx20mg	1870	CT09679	CT07620
1209	10	Flx20mg	5160	CT09679	CT07620
1211	3	Placebo	1034	CT09679	
1211	4	Flx10mg	1873	CT09679	CT07620
1211	5	Flx20mg	1860	CT09679	CT07620
1211	6	Flx20mg	1877	CT09679	CT07620
1211	7	Flx20mg	1848	CT09679	CT07620
1211	8	Flx20mg	1865	CT09679	CT07620
1211	9	Flx20mg	1872	CT09679	CT07620
1211	10	Flx20mg	5191	CT09679	CT07620
1211	11	Flx20mg	5275	CT09679	CT07620
1212	3	Placebo	1035	CT09679	
1212	4	Placebo	1645	CT09679	

Patient Number	Visit Number	Therapy	Package Assigned	Clinical Trial Lot Number	
1212	5	Placebo	1649	CT09679	
1212	6	Placebo	1650	CT09679	
1213	3	Placebo	1036	CT09679	
1213	4	Flx10mg	2181	CT09679	CT07620
1213	5	Flx20mg	2177	CT09679	CT07620
1213	6	Flx20mg	2180	CT09679	CT07620
1213	7	Flx20mg	2186	CT09679	CT07620
1213	8	Flx20mg	2187	CT09679	CT07620
1213	9	Flx20mg	2481	CT09679	CT07620
1213	10	Flx20mg	5281	CT09679	CT07620
1213	11	Flx20mg	5339	CT09679	CT07620
1213	12	Flx20mg	5341	CT09679	CT07620
1213	13	Flx20mg	5342	CT09679	CT07620
1213	14	Flx20mg	5509	CT09679	CT07620
1213	15	Flx20mg	7211	CT10799	CT07620
1213	16	Flx20mg	7214	CT10799	CT07620
1213	17	Flx20mg	7264	CT10799	CT07620
1213	18	Flx20mg	7269	CT10799	CT07620
1213	19	Flx20mg	7354	CT10799	CT07620
1213	20	Flx20mg	7359	CT10799	CT07620
1213	21	Flx20mg	7389	CT10799	CT07620
1213	22	Flx20mg	7405	CT10799	CT07620
1213	23	Flx20mg	7416	CT10799	CT07620
1213	24	Flx20mg	7516	CT10799	CT07620
1213	25	Flx20mg	7517	CT10799	CT07620
1215	3	Placebo	1145	CT09679	
1215	4	Flx10mg	2200	CT09679	CT07620
1215	5	Flx20mg	2193	CT09679	CT07620
1216	3	Placebo	1146	CT09679	
1216	4	Placebo	1843	CT09679	
1216	5	Placebo	2471	CT09679	
1216	6	Placebo	1847	CT09679	
1216	7	Placebo	1644	CT09679	
1216	8	Placebo	1651	CT09679	
1216	9	Placebo	1653	CT09679	
1216	10	Placebo	5049	CT09679	
1216	11	Placebo	5051	CT09679	
1216	12	Placebo	5158	CT09679	
1216	13	Placebo	5163	CT09679	
1216	14	Placebo	5164	CT09679	
1216	15	Placebo	7041	CT10799	
1216	16	Placebo	7043	CT10799	
1216	17	Placebo	7046	CT10799	
1216	18	Placebo	7048	CT10799	
1216	19	Placebo	7105	CT10799	
1216	20	Placebo	7106	CT10799	
1216	21	Placebo	7109	CT10799	

Patient Number	Visit Number	Therapy	Package Assigned	Clinical Trial Lot Number	
1216	22	Placebo	7118	CT10799	
1216	23	Placebo	7124	CT10799	
1216	24	Placebo	7127	CT10799	
1216	25	Placebo	7171	CT10799	
1217	3	Placebo	1147	CT09679	
1217	4	Flx10mg	2209	CT09679	CT07620
1217	5	Flx20mg	2486	CT09679	CT07620
1217	6	Flx20mg	2197	CT09679	CT07620
1217	7	Flx20mg	2189	CT09679	CT07620
1217	8	Flx20mg	2192	CT09679	CT07620
1217	9	Flx20mg	2196	CT09679	CT07620
1217	10	Flx20mg	5345	CT09679	CT07620
1218	3	Placebo	1149	CT09679	
1220	3	Placebo	1148	CT09679	
1220	4	Flx10mg	2453	CT09679	CT07620
1220	5	Flx20mg	2210	CT09679	CT07620
1220	6	Flx20mg	2214	CT09679	CT07620
1220	7	Flx20mg	2199	CT09679	CT07620
1220	8	Flx20mg	2203	CT09679	CT07620
1220	9	Flx20mg	2206	CT09679	CT07620
1220	10	Flx20mg	5512	CT09679	CT07620
1221	3	Placebo	1150	CT09679	
1221	4	Placebo	1849	CT09679	
1221	5	Placebo	1855	CT09679	
1221	6	Placebo	1861	CT09679	
1221	7	Placebo	1839	CT09679	
1221	8	Placebo	1846	CT09679	
1221	9	Placebo	1850	CT09679	
1221	10	Placebo	5166	CT09679	
1221	11	Placebo	5169	CT09679	
1221	12	Placebo	5183	CT09679	
1221	13	Placebo	5188	CT09679	
1221	14	Placebo	5189	CT09679	
1221	15	Placebo	7108	CT10799	
1221	16	Placebo	7113	CT10799	
1221	17	Placebo	7114	CT10799	
1221	18	Placebo	7121	CT10799	
1221	19	Placebo	7122	CT10799	
1221	20	Placebo	7126	CT10799	
1221	21	Placebo	7128	CT10799	
1221	22	Placebo	7170	CT10799	
1221	23	Placebo	7173	CT10799	
1222	3	Placebo	1152	CT09679	
1222	4	Placebo	1868	CT09679	
1222	5	Placebo	2178	CT09679	
1222	6	Placebo	2182	CT09679	
1222	7	Placebo	1858	CT09679	

Patient Number	Visit Number	Therapy	Package Assigned	Clinical Trial Lot Number	
1222	8	Placebo	1866	CT09679	
1222	9	Placebo	1876	CT09679	
1222	10	Placebo	5192	CT09679	
1222	11	Placebo	5277	CT09679	
1222	12	Placebo	5279	CT09679	
1222	13	Placebo	5280	CT09679	
1222	14	Placebo	5283	CT09679	
1223	3	Placebo	1151	CT09679	
1223	4	Placebo	1864	CT09679	
1223	5	Placebo	1867	CT09679	
1223	6	Placebo	1871	CT09679	
1223	7	Placebo	1852	CT09679	
1223	8	Placebo	1859	CT09679	
1223	9	Placebo	1875	CT09679	
1223	10	Placebo	5193	CT09679	
1223	11	Placebo	5278	CT09679	
1225	3	Placebo	1153	CT09679	
1225	4	Flx10mg	2465	CT09679	CT07620
1225	5	Flx20mg	2461	CT09679	CT07620
1225	6	Flx20mg	2462	CT09679	CT07620
1225	7	Flx20mg	2207	CT09679	CT07620
1225	8	Flx20mg	2454	CT09679	CT07620
1225	9	Flx20mg	2458	CT09679	CT07620
1225	10	Flx20mg	5517	CT09679	CT07620
1225	11	Flx20mg	5518	CT09679	CT07620
1225	12	Flx20mg	6003	CT09679	CT07620
1225	13	Flx20mg	6004	CT09679	CT07620
1225	14	Flx20mg	6012	CT09679	CT07620
1225	15	Flx20mg	7652	CT10799	CT07620
1225	16	Flx20mg	7661	CT10799	CT07620
1225	17	Flx20mg	7663	CT10799	CT07620
1225	18	Flx20mg	7821	CT10799	CT07620
1225	19	Flx20mg	7822	CT10799	CT07620
1225	20	Flx20mg	7832	CT10799	CT07620
1225	21	Flx20mg	8046	CT10799	CT07620
1301	3	Placebo	1205	CT09679	
1301	4	Placebo	2431	CT09679	
1301	5	Placebo	2433	CT09679	
1301	6	Placebo	2434	CT09679	
1301	7	Placebo	2424	CT09679	
1301	8	Placebo	2425	CT09679	
1301	9	Placebo	2429	CT09679	
1301	10	Placebo	5483	CT09679	
1301	11	Placebo	5486	CT09679	
1301	12	Placebo	5487	CT09679	
1301	13	Placebo	5491	CT09679	
1301	14	Placebo	5495	CT09679	

Patient Number	Visit Number	Therapy	Package Assigned	Clinical Trial Lot Number	
1301	15	Placebo	7327	CT10799	
1301	16	Placebo	7328	CT10799	
1301	17	Placebo	7329	CT10799	
1301	18	Placebo	7334	CT10799	
1301	19	Placebo	7336	CT10799	
1301	20	Placebo	7341	CT10799	
1301	21	Placebo	7345	CT10799	
1301	22	Placebo	7677	CT10799	
1301	23	Placebo	7684	CT10799	
1301	24	Placebo	7795	CT10799	
1301	25	Placebo	7801	CT10799	
1303	3	Placebo	1206	CT09679	
1303	4	Placebo	2710	CT09679	
1303	5	Placebo	2713	CT09679	
1303	6	Placebo	2719	CT09679	
1303	7	Placebo	2712	CT09679	
1303	8	Placebo	2722	CT09679	
1303	9	Placebo	2728	CT09679	
1303	10	Placebo	5494	CT09679	
1303	11	Placebo	5497	CT09679	
1303	12	Placebo	5498	CT09679	
1303	13	Placebo	5506	CT09679	
1303	14	Placebo	5507	CT09679	
1303	15	Placebo	7330	CT10799	
1303	16	Placebo	7335	CT10799	
1303	17	Placebo	7339	CT10799	
1303	18	Placebo	7342	CT10799	
1303	19	Placebo	7343	CT10799	
1303	20	Placebo	7347	CT10799	
1303	21	Placebo	7682	CT10799	
1303	22	Placebo	7686	CT10799	
1304	3	Placebo	1207	CT09679	
1304	4	Placebo	2724	CT09679	
1304	5	Placebo	2726	CT09679	
1304	6	Placebo	2727	CT09679	
1304	7	Placebo	2720	CT09679	
1304	8	Placebo	2723	CT09679	
1304	9	Placebo	2730	CT09679	
1305	3	Placebo	1208	CT09679	
1305	4	Flx10mg	2427	CT09679	CT07620
1305	5	Flx20mg	2432	CT09679	CT07620
1305	6	Flx20mg	2436	CT09679	CT07620
1305	7	Flx20mg	2428	CT09679	CT07620
1305	8	Flx20mg	2430	CT09679	CT07620
1305	9	Flx20mg	2435	CT09679	CT07620
1305	10	Flx20mg	5482	CT09679	CT07620
1305	11	Flx20mg	5484	CT09679	CT07620

Patient Number	Visit Number	Therapy	Package Assigned	Clinical Trial Lot Number	
1305	12	Flx20mg	5485	CT09679	CT07620
1305	13	Flx20mg	5492	CT09679	CT07620
1305	14	Flx20mg	5496	CT09679	CT07620
1305	15	Flx20mg	7326	CT10799	CT07620
1305	16	Flx20mg	7337	CT10799	CT07620
1305	17	Flx20mg	7338	CT10799	CT07620
1305	18	Flx20mg	7340	CT10799	CT07620
1305	19	Flx20mg	7344	CT10799	CT07620
1305	20	Flx20mg	7346	CT10799	CT07620
1305	21	Flx20mg	7678	CT10799	CT07620
1305	22	Flx20mg	7680	CT10799	CT07620
1305	23	Flx20mg	7689	CT10799	CT07620
1307	3	Placebo	1209	CT09679	
1307	4	Placebo	2742	CT09679	
1307	5	Placebo	2743	CT09679	
1307	6	Placebo	2747	CT09679	
1307	7	Placebo	2736	CT09679	
1307	8	Placebo	2737	CT09679	
1307	9	Placebo	2754	CT09679	
1307	10	Placebo	5781	CT09679	
1307	11	Placebo	5782	CT09679	
1307	12	Placebo	5790	CT09679	
1307	13	Placebo	5963	CT09679	
1307	14	Placebo	5966	CT09679	
1307	15	Placebo	7348	CT10799	
1307	16	Placebo	7681	CT10799	
1307	17	Placebo	7683	CT10799	
1307	18	Placebo	7685	CT10799	
1307	19	Placebo	7794	CT10799	
1307	20	Placebo	7797	CT10799	
1307	21	Placebo	7798	CT10799	
1307	22	Placebo	7802	CT10799	
1308	3	Placebo	1210	CT09679	
1308	4	Placebo	2753	CT09679	
1308	5	Placebo	3634	CT09679	
1308	6	Placebo	3640	CT09679	
1308	7	Placebo	2739	CT09679	
1308	8	Placebo	2760	CT09679	
1308	9	Placebo	3641	CT09679	
1308	10	Placebo	5788	CT09679	
1308	11	Placebo	5793	CT09679	
1308	12	Placebo	5965	CT09679	
1309	3	Placebo	1211	CT09679	
1309	4	Placebo	2758	CT09679	
1309	5	Placebo	3638	CT09679	
1309	6	Placebo	3731	CT09679	
1309	7	Placebo	2749	CT09679	

Patient Number	Visit Number	Therapy	Package Assigned	Clinical Trial Lot Number	
1309	8	Placebo	3633	CT09679	
1309	9	Placebo	3644	CT09679	
1310	3	Placebo	1212	CT09679	
1310	4	Placebo	2759	CT09679	
1311	3	Placebo	1213	CT09679	
1311	4	Placebo	3733	CT09679	
1311	5	Placebo	3734	CT09679	
1501	3	Placebo	1181	CT09679	
1501	4	Placebo	2359	CT09679	
1501	5	Placebo	2360	CT09679	
1501	6	Placebo	2535	CT09679	
1501	7	Placebo	2363	CT09679	
1501	8	Placebo	2364	CT09679	
1501	9	Placebo	2370	CT09679	
1501	10	Placebo	5366	CT09679	
1501	11	Placebo	5367	CT09679	
1501	12	Placebo	5370	CT09679	
1501	13	Placebo	5374	CT09679	
1501	14	Placebo	5376	CT09679	
1503	3	Placebo	1182	CT09679	
1503	4	Flx10mg	2371	CT09679	CT07620
1503	5	Flx20mg	2362	CT09679	CT07620
1503	6	Flx20mg	2367	CT09679	CT07620
1503	7	Flx20mg	2361	CT09679	CT07620
1503	8	Flx20mg	2366	CT09679	CT07620
1503	9	Flx20mg	2368	CT09679	CT07620
1503	10	Flx40mg	5369	CT09679	CT09678
1504	3	Placebo	1183	CT09679	
1504	4	Placebo	2369	CT09679	
1504	5	Placebo	2492	CT09679	
1504	6	Placebo	2496	CT09679	
1504	7	Placebo	2491	CT09679	
1504	8	Placebo	2501	CT09679	
1506	3	Placebo	1184	CT09679	
1506	4	Placebo	2495	CT09679	
1506	5	Placebo	2502	CT09679	
1506	6	Placebo	2503	CT09679	
1506	7	Placebo	2499	CT09679	
1506	8	Placebo	2504	CT09679	
1506	9	Placebo	2510	CT09679	
1506	10	Placebo	5381	CT09679	
1506	11	Placebo	5385	CT09679	
1506	12	Placebo	5387	CT09679	
1506	13	Placebo	5389	CT09679	
1506	14	Placebo	5390	CT09679	
1506	15	Placebo	7235	CT10799	
1506	16	Placebo	7236	CT10799	

Patient Number	Visit Number	Therapy	Package Assigned	Clinical Trial Lot Number	
1506	17	Placebo	7239	CT10799	
1506	18	Placebo	7240	CT10799	
1506	19	Placebo	7241	CT10799	
1506	20	Placebo	7242	CT10799	
1506	21	Placebo	7243	CT10799	
1506	22	Placebo	7250	CT10799	
1506	23	Placebo	7255	CT10799	
1506	24	Placebo	7899	CT10799	
1506	25	Placebo	7905	CT10799	
1510	3	Placebo	1185	CT09679	
1510	4	Flx10mg	2497	CT09679	CT07620
1510	5	Flx20mg	2490	CT09679	CT07620
1510	6	Flx20mg	2498	CT09679	CT07620
1510	7	Flx20mg	2489	CT09679	CT07620
1510	8	Flx20mg	2494	CT09679	CT07620
1510	9	Flx20mg	2508	CT09679	CT07620
1510	10	Flx20mg	5371	CT09679	CT07620
1510	11	Flx20mg	5372	CT09679	CT07620
1510	12	Flx20mg	5373	CT09679	CT07620
1510	13	Flx20mg	5380	CT09679	CT07620
1510	14	Flx20mg	5717	CT09679	CT07620
1510	15	Placebo	7248	CT10799	
1512	3	Placebo	1186	CT09679	
1513	3	Placebo	1188	CT09679	
1513	4	Placebo	2507	CT09679	
1513	5	Placebo	2525	CT09679	
1513	6	Placebo	2526	CT09679	
1513	7	Placebo	2512	CT09679	
1513	8	Placebo	2516	CT09679	
1514	3	Placebo	1187	CT09679	
1514	4	Flx10mg	2505	CT09679	CT07620
1514	5	Flx20mg	2509	CT09679	CT07620
1514	6	Flx20mg	2519	CT09679	CT07620
1515	3	Placebo	1189	CT09679	
1515	4	Flx10mg	2524	CT09679	CT07620
1515	5	Flx20mg	2513	CT09679	CT07620
1515	6	Flx20mg	2523	CT09679	CT07620
1515	7	Flx20mg	2500	CT09679	CT07620
1515	8	Flx20mg	2514	CT09679	CT07620
1515	9	Flx20mg	2518	CT09679	CT07620
1515	10	Flx20mg	5375	CT09679	CT07620
1515	11	Flx20mg	5379	CT09679	CT07620
1516	3	Placebo	1190	CT09679	
1516	4	Flx10mg	2536	CT09679	CT07620
1516	5	Flx20mg	2529	CT09679	CT07620
1516	6	Flx20mg	2533	CT09679	CT07620
1516	7	Flx20mg	2511	CT09679	CT07620

Patient Number	Visit Number	Therapy	Package Assigned	Clinical Trial Lot Number	
1516	8	Flx20mg	2515	CT09679	CT07620
1516	9	Flx20mg	2522	CT09679	CT07620
1516	10	Flx20mg	5378	CT09679	CT07620
1516	11	Flx20mg	5388	CT09679	CT07620
1516	12	Flx20mg	5718	CT09679	CT07620
1516	13	Flx20mg	5726	CT09679	CT07620
1516	14	Flx20mg	5728	CT09679	CT07620
1516	15	Placebo	7251	CT10799	
1516	16	Placebo	7252	CT10799	
1516	17	Placebo	7256	CT10799	
1516	18	Placebo	7257	CT10799	
1516	19	Placebo	7902	CT10799	
1516	20	Placebo	7904	CT10799	
1601	3	Placebo	1217	CT09679	
1601	4	Flx10mg	2440	CT09679	CT07620
1601	5	Flx20mg	2442	CT09679	CT07620
1601	6	Flx20mg	2582	CT09679	CT07620
1601	7	Flx20mg	2439	CT09679	CT07620
1601	8	Flx20mg	2449	CT09679	CT07620
1601	9	Flx20mg	2548	CT09679	CT07620
1601	10	Flx20mg	5393	CT09679	CT07620
1601	11	Flx20mg	5400	CT09679	CT07620
1601	12	Flx20mg	5404	CT09679	CT07620
1601	13	Flx20mg	5408	CT09679	CT07620
1601	14	Flx20mg	5414	CT09679	CT07620
1601	15	Flx20mg	7275	CT10799	CT07620
1601	16	Flx20mg	7281	CT10799	CT07620
1601	17	Flx20mg	7286	CT10799	CT07620
1601	18	Flx20mg	7293	CT10799	CT07620
1601	19	Flx20mg	7298	CT10799	CT07620
1601	20	Flx20mg	7299	CT10799	CT07620
1601	21	Flx20mg	7458	CT10799	CT07620
1601	22	Flx20mg	7466	CT10799	CT07620
1601	23	Flx20mg	7467	CT10799	CT07620
1601	24	Flx20mg	7671	CT10799	CT07620
1602	3	Placebo	1218	CT09679	
1602	4	Flx10mg	2549	CT09679	CT07620
1602	5	Flx20mg	2589	CT09679	CT07620
1602	6	Flx20mg	2448	CT09679	CT07620
1602	7	Flx20mg	2443	CT09679	CT07620
1602	8	Flx20mg	2541	CT09679	CT07620
1602	9	Flx20mg	2550	CT09679	CT07620
1602	10	Flx20mg	5398	CT09679	CT07620
1602	11	Flx20mg	5402	CT09679	CT07620
1602	12	Flx20mg	5405	CT09679	CT07620
1603	3	Placebo	1219	CT09679	
1603	4	Flx10mg	2562	CT09679	CT07620

Patient Number	Visit Number	Therapy	Package Assigned	Clinical Trial Lot Number	
1603	5	Flx20mg	2547	CT09679	CT07620
1603	6	Flx20mg	2553	CT09679	CT07620
1603	7	Flx20mg	2554	CT09679	CT07620
1604	3	Placebo	1220	CT09679	
1604	4	Flx10mg	2578	CT09679	CT07620
1604	5	Flx20mg	2565	CT09679	CT07620
1604	6	Flx20mg	2569	CT09679	CT07620
1604	7	Flx20mg	2555	CT09679	CT07620
1604	8	Flx20mg	2573	CT09679	CT07620
1604	9	Flx20mg	2587	CT09679	CT07620
1604	10	Flx40mg	5401	CT09679	CT09678
1604	11	Flx40mg	5403	CT09679	CT09678
1604	12	Flx60mg	5394		CT09678
1604	13	Flx60mg	5415		CT09678
1604	14	Flx60mg	5547		CT09678
1604	15	Placebo	7274	CT10799	
1604	16	Placebo	7276	CT10799	
1604	17	Placebo	7277	CT10799	
1604	18	Placebo	7278	CT10799	
1604	19	Placebo	7280	CT10799	
1604	20	Placebo	7282	CT10799	
1604	21	Placebo	7283	CT10799	
1604	22	Placebo	7287	CT10799	
1604	23	Placebo	7288	CT10799	
1604	24	Placebo	7291	CT10799	
1604	25	Placebo	7295	CT10799	
1605	3	Placebo	1221	CT09679	
1605	4	Flx10mg	2588	CT09679	CT07620
1605	5	Flx20mg	2566	CT09679	CT07620
1605	6	Flx20mg	2579	CT09679	CT07620
1605	7	Flx20mg	2560	CT09679	CT07620
1605	8	Flx20mg	2576	CT09679	CT07620
1605	9	Flx20mg	2590	CT09679	CT07620
1605	10	Flx20mg	5550	CT09679	CT07620
1605	11	Flx20mg	5552	CT09679	CT07620
1605	12	Flx20mg	5558	CT09679	CT07620
1605	13	Flx20mg	5620	CT09679	CT07620
1605	14	Flx20mg	5623	CT09679	CT07620
1606	3	Placebo	1222	CT09679	
1606	4	Flx10mg	2889	CT09679	CT07620
1606	5	Flx20mg	2885	CT09679	CT07620
1606	6	Flx20mg	2888	CT09679	CT07620
1606	7	Flx20mg	2577	CT09679	CT07620
1606	8	Flx20mg	2591	CT09679	CT07620
1606	9	Flx20mg	2880	CT09679	CT07620
1606	10	Flx20mg	5554	CT09679	CT07620
1606	11	Flx20mg	5617	CT09679	CT07620

Patient Number	Visit Number	Therapy	Package Assigned	Clinical Trial Lot Number	
1608	3	Placebo	1223	CT09679	
1608	4	Placebo	2444	CT09679	
1608	5	Placebo	2446	CT09679	
1609	3	Placebo	1224	CT09679	
1609	4	Flx10mg	2900	CT09679	CT07620
1609	5	Flx20mg	2898	CT09679	CT07620
1609	6	Flx20mg	2899	CT09679	CT07620
1609	7	Flx20mg	2883	CT09679	CT07620
1609	8	Flx20mg	2890	CT09679	CT07620
1609	9	Flx20mg	2892	CT09679	CT07620
1609	10	Flx20mg	5624	CT09679	CT07620
1609	11	Flx20mg	5795	CT09679	CT07620
1609	12	Flx20mg	5800	CT09679	CT07620
1609	13	Flx20mg	5806	CT09679	CT07620
1609	14	Flx20mg	6159	CT09679	CT07620
1609	15	Placebo	7289	CT10799	
1609	16	Placebo	7290	CT10799	
1612	3	Placebo	1225	CT09679	
1612	4	Flx10mg	2911	CT09679	CT07620
1612	5	Flx20mg	2909	CT09679	CT07620
1612	6	Flx20mg	2913	CT09679	CT07620
1612	7	Flx20mg	2895	CT09679	CT07620
1612	8	Flx20mg	2896	CT09679	CT07620
1612	9	Flx20mg	2905	CT09679	CT07620
1612	10	Flx20mg	5805	CT09679	CT07620
1612	11	Flx20mg	6165	CT09679	CT07620
1612	12	Flx20mg	6167	CT09679	CT07620
1651	3	Placebo	1314	CT09679	
1651	4	Placebo	3114	CT09679	
1651	5	Placebo	3183	CT09679	
1651	6	Placebo	3194	CT09679	
1651	7	Placebo	3115	CT09679	
1652	3	Placebo	1313	CT09679	
1652	4	Flx10mg	3113	CT09679	CT07620
1652	5	Flx20mg	3124	CT09679	CT07620
1652	6	Flx20mg	3179	CT09679	CT07620
1652	7	Flx20mg	3116	CT09679	CT07620
1652	8	Flx20mg	3123	CT09679	CT07620
1652	9	Flx20mg	3189	CT09679	CT07620
1652	10	Flx20mg	5680	CT09679	CT07620
1653	3	Placebo	1315	CT09679	
1653	4	Placebo	3120	CT09679	
1653	5	Placebo	3121	CT09679	
1653	6	Placebo	3191	CT09679	
1653	7	Placebo	3118	CT09679	
1654	3	Placebo	1316	CT09679	
1654	4	Flx10mg	3182	CT09679	CT07620

Patient Number	Visit Number	Therapy	Package Assigned	Clinical Trial Lot Number	
1654	5	Flx20mg	3125	CT09679	CT07620
1654	6	Flx20mg	3190	CT09679	CT07620
1654	7	Flx20mg	3122	CT09679	CT07620
1654	8	Flx20mg	3187	CT09679	CT07620
1654	9	Flx20mg	3201	CT09679	CT07620
1654	10	Flx20mg	5682	CT09679	CT07620
1654	11	Flx20mg	5685	CT09679	CT07620
1654	12	Flx20mg	5692	CT09679	CT07620
1654	13	Flx20mg	5699	CT09679	CT07620
1654	14	Flx20mg	5899	CT09679	CT07620
1654	15	Flx20mg	7574	CT10799	CT07620
1654	16	Flx20mg	7575	CT10799	CT07620
1654	17	Flx20mg	7580	CT10799	CT07620
1655	3	Placebo	1318	CT09679	
1655	4	Placebo	3197	CT09679	
1655	5	Placebo	3209	CT09679	
1655	6	Placebo	3218	CT09679	
1655	7	Placebo	3184	CT09679	
1655	8	Placebo	3186	CT09679	
1655	9	Placebo	3196	CT09679	
1655	10	Placebo	5684	CT09679	
1655	11	Placebo	5689	CT09679	
1655	12	Placebo	5694	CT09679	
1655	13	Placebo	5700	CT09679	
1655	14	Placebo	5702	CT09679	
1655	15	Placebo	7577	CT10799	
1655	16	Placebo	7579	CT10799	
1655	17	Placebo	7582	CT10799	
1655	18	Placebo	7585	CT10799	
1655	19	Placebo	7586	CT10799	
1655	20	Placebo	7587	CT10799	
1655	21	Placebo	7589	CT10799	
1655	22	Placebo	7591	CT10799	
1656	3	Placebo	1317	CT09679	
1656	4	Placebo	3181	CT09679	
1656	5	Placebo	3185	CT09679	
1656	6	Placebo	3208	CT09679	
1656	7	Placebo	3119	CT09679	
1656	8	Placebo	3178	CT09679	
1656	9	Placebo	3192	CT09679	
1656	10	Placebo	5678	CT09679	
1656	11	Placebo	5681	CT09679	
1656	12	Placebo	5686	CT09679	
1656	13	Placebo	5691	CT09679	
1656	14	Placebo	5698	CT09679	
1656	15	Placebo	7573	CT10799	
1657	3	Placebo	1319	CT09679	

Patient Number	Visit Number	Therapy	Package Assigned	Clinical Trial Lot Number	
1657	4	Placebo	3216	CT09679	
1658	3	Placebo	1320	CT09679	
1658	4	Flx10mg	3199	CT09679	CT07620
1658	5	Flx20mg	3200	CT09679	CT07620
1658	6	Flx20mg	3206	CT09679	CT07620
1658	7	Flx20mg	3188	CT09679	CT07620
1658	8	Flx20mg	3202	CT09679	CT07620
1658	9	Flx20mg	3205	CT09679	CT07620
1658	10	Flx20mg	5687	CT09679	CT07620
1658	11	Flx20mg	5697	CT09679	CT07620
1658	12	Flx20mg	5701	CT09679	CT07620
1659	3	Placebo	1321	CT09679	
1659	4	Flx10mg	3212	CT09679	CT07620
1659	5	Flx20mg	3203	CT09679	CT07620
1659	6	Flx20mg	3214	CT09679	CT07620
1659	7	Flx20mg	3193	CT09679	CT07620
1659	8	Flx20mg	3204	CT09679	CT07620
1659	9	Flx20mg	3207	CT09679	CT07620
1659	10	Flx40mg	5679	CT09679	CT09678
1659	11	Flx40mg	5688	CT09679	CT09678
1659	12	Flx40mg	5695	CT09679	CT09678
1659	13	Flx40mg	5696	CT09679	CT09678
1659	14	Flx40mg	5900	CT09679	CT09678
1659	15	Placebo	7578	CT10799	
1659	16	Placebo	7581	CT10799	
1661	3	Placebo	1322	CT09679	
1667	3	Placebo	1323	CT09679	
1667	4	Flx10mg	3226	CT09679	CT07620
1667	5	Flx20mg	3220	CT09679	CT07620
1667	6	Flx20mg	3221	CT09679	CT07620
1667	7	Flx20mg	3217	CT09679	CT07620
1667	8	Flx20mg	3222	CT09679	CT07620
1667	9	Flx20mg	3227	CT09679	CT07620
1667	10	Flx20mg	5901	CT09679	CT07620
1669	3	Placebo	1324	CT09679	
1669	4	Placebo	3224	CT09679	
1669	5	Placebo	3229	CT09679	
1669	6	Placebo	3425	CT09679	
1669	7	Placebo	3198	CT09679	
1669	8	Placebo	3211	CT09679	
1669	9	Placebo	3213	CT09679	
1669	10	Placebo	5898	CT09679	
1669	11	Placebo	5903	CT09679	
1701	3	Placebo	1253	CT09679	
1701	4	Flx10mg	2859	CT09679	CT07620
1701	5	Flx20mg	2853	CT09679	CT07620
1701	6	Flx20mg	2860	CT09679	CT07620

Patient Number	Visit Number	Therapy	Package Assigned	Clinical Trial Lot Number	
1701	7	Flx20mg	2854	CT09679	CT07620
1701	8	Flx20mg	2855	CT09679	CT07620
1701	9	Flx20mg	2863	CT09679	CT07620
1701	10	Flx20mg	5755	CT09679	CT07620
1701	11	Flx20mg	5758	CT09679	CT07620
1701	12	Flx20mg	5766	CT09679	CT07620
1701	13	Flx20mg	5775	CT09679	CT07620
1701	14	Flx20mg	5778	CT09679	CT07620
1701	15	Placebo	7599	CT10799	
1701	16	Placebo	7600	CT10799	
1701	17	Placebo	7602	CT10799	
1701	18	Placebo	7607	CT10799	
1701	19	Placebo	7612	CT10799	
1701	20	Placebo	7616	CT10799	
1701	21	Placebo	7619	CT10799	
1702	3	Placebo	1254	CT09679	
1702	4	Flx10mg	3253	CT09679	CT07620
1702	5	Flx20mg	3243	CT09679	CT07620
1702	6	Flx20mg	3245	CT09679	CT07620
1702	7	Flx20mg	3244	CT09679	CT07620
1702	8	Flx20mg	3246	CT09679	CT07620
1702	9	Flx20mg	3250	CT09679	CT07620
1702	10	Flx20mg	5760	CT09679	CT07620
1702	11	Flx20mg	5768	CT09679	CT07620
1702	12	Flx20mg	5777	CT09679	CT07620
1702	13	Flx20mg	5996	CT09679	CT07620
1702	14	Flx20mg	5998	CT09679	CT07620
1702	15	Placebo	7603	CT10799	
1702	16	Placebo	7608	CT10799	
1705	3	Placebo	1255	CT09679	
1705	4	Placebo	2861	CT09679	
1705	5	Placebo	2862	CT09679	
1705	6	Placebo	2864	CT09679	
1705	7	Placebo	2856	CT09679	
1705	8	Placebo	2857	CT09679	
1705	9	Placebo	2865	CT09679	
1705	10	Placebo	5756	CT09679	
1705	11	Placebo	5757	CT09679	
1705	12	Placebo	5759	CT09679	
1705	13	Placebo	5764	CT09679	
1705	14	Placebo	5769	CT09679	
1705	15	Placebo	7610	CT10799	
1705	16	Placebo	7615	CT10799	
1705	17	Placebo	7618	CT10799	
1705	18	Placebo	7620	CT10799	
1705	19	Placebo	7621	CT10799	
1705	20	Placebo	7911	CT10799	

Patient Number	Visit Number	Therapy	Package Assigned	Clinical Trial Lot Number	
1705	21	Placebo	7912	CT10799	
1707	3	Placebo	1256	CT09679	
1707	4	Placebo	3248	CT09679	
1707	5	Placebo	3249	CT09679	
1707	6	Placebo	3254	CT09679	
1707	7	Placebo	3251	CT09679	
1707	8	Placebo	3252	CT09679	
1707	9	Placebo	3255	CT09679	
1707	10	Placebo	5767	CT09679	
1707	11	Placebo	5772	CT09679	
1707	12	Placebo	5773	CT09679	
1707	13	Placebo	5774	CT09679	
1801	3	Placebo	1241	CT09679	
1901	3	Placebo	1193	CT09679	
1901	4	Placebo	2376	CT09679	
1901	5	Placebo	2626	CT09679	
1901	6	Placebo	2377	CT09679	
1901	7	Placebo	2372	CT09679	
1901	8	Placebo	2373	CT09679	
1901	9	Placebo	2379	CT09679	
1901	10	Placebo	5443	CT09679	
1901	11	Placebo	5444	CT09679	
1901	12	Placebo	5447	CT09679	
1901	13	Placebo	5454	CT09679	
1901	14	Placebo	5458	CT09679	
1902	3	Placebo	1198	CT09679	
1903	3	Placebo	1197	CT09679	
1903	4	Placebo	2621	CT09679	
1903	5	Placebo	2631	CT09679	
1903	6	Placebo	2637	CT09679	
1903	7	Placebo	2624	CT09679	
1903	8	Placebo	2632	CT09679	
1904	3	Placebo	1195	CT09679	
1904	4	Flx10mg	2625	CT09679	CT07620
1904	5	Flx20mg	2627	CT09679	CT07620
1904	6	Flx20mg	2636	CT09679	CT07620
1904	7	Flx20mg	2381	CT09679	CT07620
1904	8	Flx20mg	2622	CT09679	CT07620
1904	9	Flx20mg	2639	CT09679	CT07620
1904	10	Flx20mg	5450	CT09679	CT07620
1905	3	Placebo	1199	CT09679	
1905	4	Flx10mg	2644	CT09679	CT07620
1905	5	Flx20mg	2629	CT09679	CT07620
1905	6	Flx20mg	2638	CT09679	CT07620
1905	7	Flx20mg	2619	CT09679	CT07620
1905	8	Flx20mg	2634	CT09679	CT07620
1905	9	Flx20mg	2640	CT09679	CT07620

Patient Number	Visit Number	Therapy	Package Assigned	Clinical Trial Lot Number	
1905	10	Flx20mg	5452	CT09679	CT07620
1905	11	Flx20mg	5457	CT09679	CT07620
1905	12	Flx20mg	5461	CT09679	CT07620
1905	13	Flx20mg	5586	CT09679	CT07620
1905	14	Flx20mg	5596	CT09679	CT07620
1905	15	Placebo	7300	CT10799	
1905	16	Placebo	7304	CT10799	
1905	17	Placebo	7305	CT10799	
1905	18	Placebo	7308	CT10799	
1905	19	Placebo	7311	CT10799	
1905	20	Placebo	7315	CT10799	
1905	21	Placebo	7322	CT10799	
1905	22	Placebo	7707	CT10799	
1905	23	Placebo	7742	CT10799	
1905	24	Placebo	7748	CT10799	
1905	25	Placebo	7752	CT10799	
1906	3	Placebo	1194	CT09679	
1906	4	Flx10mg	2380	CT09679	CT07620
1906	5	Flx20mg	2375	CT09679	CT07620
1906	6	Flx20mg	2384	CT09679	CT07620
1906	7	Flx20mg	2374	CT09679	CT07620
1906	8	Flx20mg	2383	CT09679	CT07620
1906	9	Flx20mg	2628	CT09679	CT07620
1906	10	Flx20mg	5445	CT09679	CT07620
1906	11	Flx20mg	5453	CT09679	CT07620
1906	12	Flx20mg	5456	CT09679	CT07620
1906	13	Flx20mg	5463	CT09679	CT07620
1906	14	Flx20mg	5587	CT09679	CT07620
1906	15	Flx20mg	7301	CT10799	CT07620
1907	3	Placebo	1196	CT09679	
1907	4	Placebo	2378	CT09679	
1907	5	Placebo	2633	CT09679	
1907	6	Placebo	2635	CT09679	
1907	7	Placebo	2620	CT09679	
1907	8	Placebo	2630	CT09679	
1907	9	Placebo	2642	CT09679	
1907	10	Placebo	5451	CT09679	
1907	11	Placebo	5459	CT09679	
1907	12	Placebo	5460	CT09679	
1910	3	Placebo	1200	CT09679	
1912	3	Placebo	1201	CT09679	
1913	3	Placebo	1202	CT09679	
1913	4	Placebo	2645	CT09679	
1913	5	Placebo	2646	CT09679	
1913	6	Placebo	2652	CT09679	
1913	7	Placebo	2643	CT09679	
1913	8	Placebo	2650	CT09679	

Patient Number	Visit Number	Therapy	Package Assigned	Clinical Trial Lot Number	
1913	9	Placebo	2654	CT09679	
1913	10	Placebo	5465	CT09679	
1913	11	Placebo	5468	CT09679	
1913	12	Placebo	5590	CT09679	
1913	13	Placebo	5598	CT09679	
1913	14	Placebo	5660	CT09679	
1913	15	Placebo	7309	CT10799	
1913	16	Placebo	7312	CT10799	
1913	17	Placebo	7316	CT10799	
1913	18	Placebo	7321	CT10799	
1913	19	Placebo	7706	CT10799	
1913	20	Placebo	7712	CT10799	
1914	3	Placebo	1204	CT09679	
1914	4	Placebo	2659	CT09679	
1914	5	Placebo	2664	CT09679	
1914	6	Placebo	2918	CT09679	
1914	7	Placebo	2653	CT09679	
1914	8	Placebo	2661	CT09679	
1914	9	Placebo	2919	CT09679	
1914	10	Placebo	5588	CT09679	
1914	11	Placebo	5595	CT09679	
1914	12	Placebo	5655	CT09679	
1914	13	Placebo	5662	CT09679	
1914	14	Placebo	5873	CT09679	
1914	15	Placebo	7314	CT10799	
1914	16	Placebo	7319	CT10799	
1914	17	Placebo	7703	CT10799	
1914	18	Placebo	7709	CT10799	
1915	3	Placebo	1203	CT09679	
1915	4	Flx10mg	2651	CT09679	CT07620
1915	5	Flx20mg	2649	CT09679	CT07620
1915	6	Flx20mg	2655	CT09679	CT07620
1915	7	Flx20mg	2648	CT09679	CT07620
1915	8	Flx20mg	2656	CT09679	CT07620
1915	9	Flx20mg	2657	CT09679	CT07620
1915	10	Flx20mg	5592	CT09679	CT07620
1915	11	Flx20mg	5654	CT09679	CT07620
1918	3	Placebo	1289	CT09679	
1918	4	Placebo	2670	CT09679	
1918	5	Placebo	2929	CT09679	
1918	6	Placebo	2930	CT09679	
1918	7	Placebo	2660	CT09679	
1918	8	Placebo	2669	CT09679	
1918	9	Placebo	2925	CT09679	
1918	10	Placebo	5591	CT09679	
1918	11	Placebo	5652	CT09679	
1918	12	Placebo	5663	CT09679	

Patient Number	Visit Number	Therapy	Package Assigned	Clinical Trial Lot Number	
1918	13	Placebo	5874	CT09679	
1918	14	Placebo	5879	CT09679	
1918	15	Placebo	7320	CT10799	
1918	16	Placebo	7705	CT10799	
1918	17	Placebo	7711	CT10799	
1919	3	Placebo	1290	CT09679	
1919	4	Flx10mg	2666	CT09679	CT07620
1919	5	Flx20mg	2658	CT09679	CT07620
1919	6	Flx20mg	2665	CT09679	CT07620
1919	7	Flx20mg	2662	CT09679	CT07620
1919	8	Flx20mg	2668	CT09679	CT07620
1919	9	Flx20mg	2926	CT09679	CT07620
1919	10	Flx20mg	5656	CT09679	CT07620
1919	11	Flx20mg	5658	CT09679	CT07620
1919	12	Flx20mg	5659	CT09679	CT07620
1919	13	Flx20mg	5877	CT09679	CT07620
1919	14	Flx20mg	5882	CT09679	CT07620
1920	3	Placebo	1291	CT09679	
1921	3	Placebo	1292	CT09679	
1921	4	Flx10mg	2920	CT09679	CT07620
1921	5	Flx20mg	2922	CT09679	CT07620
1921	6	Flx20mg	2923	CT09679	CT07620
1921	7	Flx20mg	2667	CT09679	CT07620
1921	8	Flx20mg	2924	CT09679	CT07620
1921	9	Flx20mg	2931	CT09679	CT07620
1921	10	Flx40mg	5446	CT09679	CT09678
1921	11	Flx40mg	5448	CT09679	CT09678
1921	12	Flx40mg	5464	CT09679	CT09678
1921	13	Flx40mg	5466	CT09679	CT09678
1921	14	Flx40mg	5589	CT09679	CT09678
1921	15	Flx40mg	7303	CT10799	CT10738
1921	16	Flx40mg	7324	CT10799	CT10738
1921	17	Flx40mg	7710	CT10799	CT10738
1921	18	Flx40mg	7753	CT10799	CT10738
1921	19	Flx40mg	7792	CT10799	CT10738
1921	20	Flx40mg	7862	CT10799	CT10738
1921	21	Flx40mg	7934	CT10799	CT10738
1922	3	Placebo	1293	CT09679	
1924	3	Placebo	1294	CT09679	
1924	4	Flx10mg	2943	CT09679	CT07620
1924	5	Flx20mg	2937	CT09679	CT07620
1924	6	Flx20mg	2938	CT09679	CT07620
1924	7	Flx20mg	2927	CT09679	CT07620
1924	8	Flx20mg	2932	CT09679	CT07620
1924	9	Flx20mg	2936	CT09679	CT07620
1924	10	Flx20mg	5876	CT09679	CT07620
1924	11	Flx20mg	5881	CT09679	CT07620

Patient Number	Visit Number	Therapy	Package Assigned	Clinical Trial Lot Number	
1924	12	Flx20mg	6028	CT09679	CT07620
1924	13	Flx20mg	6030	CT09679	CT07620
1924	14	Flx20mg	6033	CT09679	CT07620
1925	3	Placebo	1295	CT09679	
1925	4	Placebo	2933	CT09679	
1925	5	Placebo	2941	CT09679	
1925	6	Placebo	2942	CT09679	
1925	7	Placebo	2928	CT09679	
1925	8	Placebo	2934	CT09679	
1925	9	Placebo	2935	CT09679	
1925	10	Placebo	5878	CT09679	
1925	11	Placebo	5884	CT09679	
1925	12	Placebo	6035	CT09679	
1925	13	Placebo	6039	CT09679	
1925	14	Placebo	6094	CT09679	
1927	3	Placebo	1296	CT09679	
1927	4	Placebo	2945	CT09679	
1927	5	Placebo	2949	CT09679	
1927	6	Placebo	2950	CT09679	
1927	7	Placebo	2940	CT09679	
1927	8	Placebo	2944	CT09679	
1927	9	Placebo	2951	CT09679	
1927	10	Placebo	6029	CT09679	
1927	11	Placebo	6037	CT09679	
1927	12	Placebo	6040	CT09679	
1927	13	Placebo	6097	CT09679	
1927	14	Placebo	6098	CT09679	
1927	15	Placebo	7743	CT10799	
1927	16	Placebo	7746	CT10799	
1927	17	Placebo	7750	CT10799	
1927	18	Placebo	7751	CT10799	
2201	3	Placebo	1277	CT09679	
2201	4	Placebo	2957	CT09679	
2201	5	Placebo	2962	CT09679	
2202	3	Placebo	1278	CT09679	
2202	4	Flx10mg	2963	CT09679	CT07620
2202	5	Flx20mg	2959	CT09679	CT07620
2202	6	Flx20mg	3061	CT09679	CT07620
2202	7	Flx20mg	2960	CT09679	CT07620
2202	8	Flx20mg	2966	CT09679	CT07620
2202	9	Flx20mg	3069	CT09679	CT07620
2202	10	Flx20mg	5732	CT09679	CT07620
2202	11	Flx20mg	5734	CT09679	CT07620
2202	12	Flx20mg	5741	CT09679	CT07620
2202	13	Flx20mg	5746	CT09679	CT07620
2203	3	Placebo	1279	CT09679	
2203	4	Placebo	2964	CT09679	

Patient Number	Visit Number	Therapy	Package Assigned	Clinical Trial Lot Number	
2203	5	Placebo	3065	CT09679	
2203	6	Placebo	3070	CT09679	
2203	7	Placebo	2958	CT09679	
2203	8	Placebo	2967	CT09679	
2203	9	Placebo	2968	CT09679	
2203	10	Placebo	5730	CT09679	
2203	11	Placebo	5733	CT09679	
2203	12	Placebo	5736	CT09679	
2203	13	Placebo	5739	CT09679	
2203	14	Placebo	5744	CT09679	
2203	15	Placebo	7548	CT10799	
2203	16	Placebo	7550	CT10799	
2203	17	Placebo	7552	CT10799	
2203	18	Placebo	7555	CT10799	
2203	19	Placebo	7561	CT10799	
2203	20	Placebo	7568	CT10799	
2203	21	Placebo	7849	CT10799	
2203	22	Placebo	7946	CT10799	
2204	3	Placebo	1280	CT09679	
2204	4	Flx10mg	3067	CT09679	CT07620
2204	5	Flx20mg	2961	CT09679	CT07620
2204	6	Flx20mg	3063	CT09679	CT07620
2204	7	Flx20mg	2965	CT09679	CT07620
2204	8	Flx20mg	3064	CT09679	CT07620
2204	9	Flx20mg	3072	CT09679	CT07620
2204	10	Flx40mg	5729	CT09679	CT09678
2204	11	Flx40mg	5735	CT09679	CT09678
2204	12	Flx60mg	5737		CT09678
2204	13	Flx60mg	5753		CT09678
2204	14	Flx60mg	5843		CT09678
2205	3	Placebo	1281	CT09679	
2205	4	Flx10mg	3078	CT09679	CT07620
2205	5	Flx20mg	3081	CT09679	CT07620
2205	6	Flx20mg	3085	CT09679	CT07620
2205	7	Flx20mg	3077	CT09679	CT07620
2205	8	Flx20mg	3082	CT09679	CT07620
2205	9	Flx20mg	3090	CT09679	CT07620
2205	10	Flx20mg	5738	CT09679	CT07620
2205	11	Flx20mg	5743	CT09679	CT07620
2205	12	Flx20mg	5748	CT09679	CT07620
2205	13	Flx20mg	5836	CT09679	CT07620
2205	14	Flx20mg	5844	CT09679	CT07620
2206	3	Placebo	1282	CT09679	
2206	4	Placebo	3073	CT09679	
2206	5	Placebo	3075	CT09679	
2206	6	Placebo	3086	CT09679	
2206	7	Placebo	3062	CT09679	

Patient Number	Visit Number	Therapy	Package Assigned	Clinical Trial Lot Number	
2206	8	Placebo	3068	CT09679	
2206	9	Placebo	3088	CT09679	
2206	10	Placebo	5740	CT09679	
2206	11	Placebo	5750	CT09679	
2206	12	Placebo	5754	CT09679	
2206	13	Placebo	5842	CT09679	
2206	14	Placebo	5888	CT09679	
2206	15	Placebo	7553	CT10799	
2206	16	Placebo	7559	CT10799	
2206	17	Placebo	7563	CT10799	
2206	18	Placebo	7847	CT10799	
2206	19	Placebo	6209	CT09679	
2206	20	Placebo	7941	CT10799	
2206	21	Placebo	8098	CT10799	
2207	3	Placebo	1283	CT09679	
2207	4	Placebo	3083	CT09679	
2207	5	Placebo	3087	CT09679	
2207	6	Placebo	3098	CT09679	
2207	7	Placebo	3066	CT09679	
2207	8	Placebo	3074	CT09679	
2207	9	Placebo	3099	CT09679	
2207	10	Placebo	5749	CT09679	
2207	11	Placebo	5751	CT09679	
2207	12	Placebo	5838	CT09679	
2207	13	Placebo	5845	CT09679	
2207	14	Placebo	5892	CT09679	
2207	15	Placebo	7556	CT10799	
2207	16	Placebo	7562	CT10799	
2207	17	Placebo	7569	CT10799	
2207	18	Placebo	7848	CT10799	
2207	19	Placebo	7937	CT10799	
2207	20	Placebo	8097	CT10799	
2207	21	Placebo	8109	CT10799	
2208	3	Placebo	1284	CT09679	
2208	4	Flx10mg	3093	CT09679	CT07620
2208	5	Flx20mg	3096	CT09679	CT07620
2208	6	Flx20mg	3097	CT09679	CT07620
2208	7	Flx20mg	3084	CT09679	CT07620
2208	8	Flx20mg	3091	CT09679	CT07620
2208	9	Flx20mg	3101	CT09679	CT07620
2208	10	Flx20mg	5745	CT09679	CT07620
2208	11	Flx20mg	5833	CT09679	CT07620
2208	12	Flx20mg	5839	CT09679	CT07620
2208	13	Flx20mg	5893	CT09679	CT07620
2208	14	Flx20mg	5979	CT09679	CT07620
2208	15	Placebo	7560	CT10799	
2208	16	Placebo	7564	CT10799	

Patient Number	Visit Number	Therapy	Package Assigned	Clinical Trial Lot Number	
2208	17	Placebo	7846	CT10799	
2208	18	Placebo	7856	CT10799	
2208	19	Placebo	7944	CT10799	
2208	20	Placebo	8100	CT10799	
2208	21	Placebo	8107	CT10799	
2210	3	Placebo	1285	CT09679	
2210	4	Placebo	3089	CT09679	
2210	5	Placebo	3106	CT09679	
2210	6	Placebo	3488	CT09679	
2210	7	Placebo	3079	CT09679	
2212	3	Placebo	1286	CT09679	
2212	4	Placebo	3102	CT09679	
2212	5	Placebo	3478	CT09679	
2212	6	Placebo	3482	CT09679	
2212	7	Placebo	3076	CT09679	
2212	8	Placebo	3100	CT09679	
2212	9	Placebo	3483	CT09679	
2212	10	Placebo	5837	CT09679	
2212	11	Placebo	5840	CT09679	
2212	12	Placebo	5891	CT09679	
2213	3	Placebo	1287	CT09679	
2213	4	Placebo	3112	CT09679	
2213	5	Placebo	3494	CT09679	
2213	6	Placebo	3502	CT09679	
2213	7	Placebo	3092	CT09679	
2213	8	Placebo	3111	CT09679	
2213	9	Placebo	3490	CT09679	
2214	3	Placebo	1288	CT09679	
2214	4	Flx10mg	3104	CT09679	CT07620
2214	5	Flx20mg	3110	CT09679	CT07620
2214	6	Flx20mg	3477	CT09679	CT07620
2214	7	Flx20mg	3094	CT09679	CT07620
2214	8	Flx20mg	3107	CT09679	CT07620
2214	9	Flx20mg	3492	CT09679	CT07620
2214	10	Flx40mg	5747	CT09679	CT09678
2214	11	Flx40mg	5752	CT09679	CT09678
2214	12	Flx60mg	5885		CT09678
2214	13	Flx60mg	5981		CT09678
2214	14	Flx60mg	6138		CT09678
2214	15	Placebo	7854	CT10799	
2214	16	Placebo	7938	CT10799	
2214	17	Placebo	8093	CT10799	
2214	18	Placebo	8101	CT10799	
2216	3	Placebo	9661	CT09679	
2216	4	Flx10mg	3481	CT09679	CT07620
2216	5	Flx20mg	3108	CT09679	CT07620
2216	6	Flx20mg	3480	CT09679	CT07620

Patient Number	Visit Number	Therapy	Package Assigned	Clinical Trial Lot Number	
2216	7	Flx20mg	3105	CT09679	CT07620
2216	8	Flx20mg	3487	CT09679	CT07620
2216	9	Flx20mg	3496	CT09679	CT07620
2216	10	Flx20mg	5889	CT09679	CT07620
2216	11	Flx20mg	5897	CT09679	CT07620
2216	12	Flx20mg	5980	CT09679	CT07620
2216	13	Flx20mg	6136	CT09679	CT07620
2216	14	Flx20mg	6140	CT09679	CT07620
2216	15	Flx20mg	7547	CT10799	CT07620
2216	16	Flx20mg	7551	CT10799	CT07620
2216	17	Flx20mg	7554	CT10799	CT07620
2217	3	Placebo	9662	CT09679	
2217	4	Placebo	3498	CT09679	
2217	5	Placebo	3505	CT09679	
2217	6	Placebo	3513	CT09679	
2217	7	Placebo	3103	CT09679	
2217	8	Placebo	3484	CT09679	
2217	9	Placebo	3504	CT09679	
2217	10	Placebo	5886	CT09679	
2217	11	Placebo	5894	CT09679	
2217	12	Placebo	5977	CT09679	
2217	13	Placebo	5985	CT09679	
2217	14	Placebo	6133	CT09679	
2217	15	Placebo	7855	CT10799	
2217	16	Placebo	7945	CT10799	
2217	17	Placebo	8105	CT10799	
2218	3	Placebo	9664	CT09679	
2218	4	Placebo	3512	CT09679	
2218	5	Placebo	3880	CT09679	
2218	6	Placebo	3892	CT09679	
2218	7	Placebo	3485	CT09679	
2218	8	Placebo	3495	CT09679	
2218	9	Placebo	3511	CT09679	
2218	10	Placebo	5976	CT09679	
2218	11	Placebo	5983	CT09679	
2218	12	Placebo	5987	CT09679	
2218	13	Placebo	6132	CT09679	
2218	14	Placebo	6141	CT09679	
2218	15	Placebo	7943	CT10799	
2218	16	Placebo	8096	CT10799	
2218	17	Placebo	8108	CT10799	
2220	3	Placebo	9663	CT09679	
2220	4	Flx10mg	3500	CT09679	CT07620
2220	5	Flx20mg	3493	CT09679	CT07620
2220	6	Flx20mg	3497	CT09679	CT07620
2220	7	Flx20mg	3486	CT09679	CT07620
2220	8	Flx20mg	3489	CT09679	CT07620

Patient Number	Visit Number	Therapy	Package Assigned	Clinical Trial Lot Number	
2220	9	Flx20mg	3499	CT09679	CT07620
2220	10	Flx20mg	5896	CT09679	CT07620
2220	11	Flx20mg	5978	CT09679	CT07620
2220	12	Flx20mg	5986	CT09679	CT07620
2220	13	Flx20mg	6139	CT09679	CT07620
2221	3	Placebo	9665	CT09679	
2221	4	Placebo	3886	CT09679	
2221	5	Placebo	3893	CT09679	
2221	6	Placebo	3896	CT09679	
2221	7	Placebo	3491	CT09679	
2221	8	Placebo	3508	CT09679	
2221	9	Placebo	3881	CT09679	

16.1.11.
Audit Certificates

Lilly

Eli Lilly and Company

[redacted]

AUDIT CERTIFICATE

LILLY RESEARCH CENTER

Compound:	LY 110140 Fluoxetine	Protocol:	B1Y-MC-HCJE
Study Title:	Fluoxetine Versus Placebo in Childhood / Adolescent Depression		

This study was subject to independent audit by staff of the Medical Quality Assurance Department.

Audit Subject	Date of Audit	Auditor/s
[redacted]	19 Feb 1998	[redacted]
	3 Nov 1998	
	5 Nov 1998	

Signed: [redacted]
Medical Quality Assurance Representative

Date: 11 April 2000

16.1.12.
Documentation of Inter-Laboratory Standardization Methods and Quality Assurance Procedures if Used

Inter-Laboratory Standardization Methods

Whenever possible, a central laboratory was used to maintain consistency of methods and to combine laboratory data across study sites and/or across studies. When using multiple local laboratories with different methodologies, the data were normalized, that is, laboratory results were expressed as a percentage of the upper and/or lower limits of each laboratory's reference range.

Please refer to Appendix 16.2.8 for laboratory reference ranges used in this study.

Laboratory analysis of blood and urine samples were performed at:

[redacted]

Quality Assurance Procedures

To ensure the safety of participants in the study and to ensure accurate, complete, and reliable data, Lilly or its representatives —

- provided instructional material to the study sites, as appropriate
- sponsored a start-up training session to instruct the investigators and study coordinators; gave instruction on the protocol, the completion of the clinical report forms, and study procedures
- made periodic visits to the study site
- were available for consultation; stayed in contact with the study site personnel by mail, telephone, and/or fax
- reviewed and evaluated clinical report form data and used standard computer edits to detect errors in data collection.

To ensure the safety of participants in the study and to ensure accurate, complete, and reliable data, Lilly instructed the investigator to keep records of laboratory tests, clinical notes, and patient medical records in the patient files as original source documents for the study.

The investigator was informed that —

- Lilly or its representatives might periodically check a sample of the patient data recorded against source documents at the study site.

The study might be audited by Lilly Medical Quality Assurance (MQA) and/or regulatory agencies at any time.

Blood Pressure Reference Ranges

Table 1 - Blood Pressure Levels for the 95th Percentile of Blood Pressure for Boys Age 1 to 17 years by Percentiles of Height

Age	Height Percen-tile*	Systolic BP (mm Hg)								Diastolic BP (mm Hg)						
	BP†	5%	10%	25%	50%	75%	90%	95%		5%	10%	25%	50%	75%	90%	95%
1	95th	98	99	101	102	104	106	106		55	55	56	57	58	59	59
2	95th	101	102	104	106	108	109	110		59	59	60	61	62	63	63
3	95th	104	105	107	109	111	112	113		63	63	64	65	66	67	67
4	95th	106	107	109	111	113	114	115		66	67	67	68	69	70	71
5	95th	108	109	110	112	114	115	116		69	70	70	71	72	73	74
6	95th	109	110	112	114	115	117	117		72	72	73	74	75	76	76
7	95th	110	111	113	115	116	118	119		74	74	75	76	77	78	78
8	95th	111	112	114	116	118	119	120		75	76	76	77	78	79	80
9	95th	113	114	116	117	119	121	121		76	77	78	79	80	80	81
10	95th	114	115	117	119	121	122	123		77	78	79	80	80	81	82
11	95th	116	117	119	121	123	124	125		78	79	79	80	81	82	83
12	95th	119	120	121	123	125	126	127		79	79	80	81	82	83	83
13	95th	121	122	124	126	128	129	130		79	80	81	82	83	83	84
14	95th	124	125	127	128	130	132	132		80	81	81	82	83	84	85
15	95th	127	128	129	131	133	134	135		81	82	83	83	84	85	86
16	95th	129	130	132	134	136	137	138		83	83	84	85	86	87	87
17	95th	132	133	135	136	138	140	140		85	85	86	87	88	89	89

*Height percentile determined by standard growth curves.

†Blood pressure percentile determined by a single measurement.

Data for this table taken from: http://womenshealth.medscape.com/govmt/NHLBI/1996/guidelines/NHLBI-pressure/tab-nhlbi.96-3790.html

Table 2 - Blood Pressure Levels for the 95th Percentile of Blood Pressure for Girls Age 1 to 17 years by Percentiles of Height

Age	Height Percen-tile*	Systolic BP (mm Hg)								Diastolic BP (mm Hg)						
	BP†	5%	10%	25%	50%	75%	90%	95%		5%	10%	25%	50%	75%	90%	95%
1	95th	101	102	103	104	105	107	107		57	57	57	58	59	60	60
2	95th	102	103	104	105	107	108	109		61	61	62	62	63	64	65
3	95th	104	104	105	107	108	109	110		65	65	65	66	67	67	68
4	95th	105	106	107	108	109	111	111		67	67	68	69	69	70	71
5	95th	107	107	108	110	111	112	113		69	70	70	71	72	72	73
6	95th	108	109	110	111	112	114	114		71	71	72	73	73	74	75
7	95th	110	110	112	113	114	115	116		73	73	73	74	75	76	76
8	95th	112	112	113	115	116	117	118		74	74	75	75	76	77	78
9	95th	114	114	115	117	118	119	120		75	76	76	77	78	78	79
10	95th	116	116	117	119	120	121	122		77	77	77	78	79	80	80
11	95th	118	118	119	121	122	123	124		78	78	79	79	80	81	81
12	95th	120	120	121	123	124	125	126		79	79	80	80	81	82	82
13	95th	121	122	123	125	126	127	128		80	80	81	82	82	83	84
14	95th	123	124	125	126	128	129	130		81	81	82	83	83	84	85
15	95th	124	125	126	128	129	130	131		82	82	83	83	84	85	86
16	95th	125	126	127	128	130	131	132		83	83	83	84	85	86	86
17	95th	126	126	127	129	130	131	132		83	83	83	84	85	86	86

*Height percentile determined by standard growth curves.
†Blood pressure percentile determined by a single measurement.
Data for this table taken from: http://womenshealth.medscape.com/govmt/NHLBI/1996/guidelines/NHLBI-pressure/tab-nhlbi.96-3790.html

ECG Reference Ranges

Age (years)	Heart Rate (bpm)	PR Interval (msec)	QRS Duration (msec)	QTc Interval Upper Limit[1] (msec)
8 to 12	62-130	88-171	32-85	440
12 to 16	61-120	92-176	34-88	440

Data for this table taken from Electrocardiography in Clinical Practice: Adult and Pediatric (4th ed.). 1996.
[1]Corrected using Bazett's method.
Abbreviations: bpm = beats per minute, msec = milliseconds; sec = seconds.

16.1.13.
Errors to the Locked Database

Therapy	Patient Number	Visit Number	Comments / Error
Flx	142	15	PK sample from September 1999 was not sent to [redacted] until March 2000. Sample will be assayed with the relapse PK's.
Flx	151	11	Dates of ECG recorded on CRF modules do not match dates recorded on Fisch ECG worksheets. Dates should be identical.
Placebo	153	1	Dates of ECG recorded on CRF modules do not match dates recorded on Fisch ECG worksheets. Dates should be identical.
Placebo	323	1	Dates of ECG recorded on CRF modules do not match dates recorded on Fisch ECG worksheets. Dates should be identical.
Placebo	601	5	Dates of ECG recorded on CRF modules do not match dates recorded on Fisch ECG worksheets. Dates should be identical.
Placebo	1121	15	Dates of ECG recorded on CRF modules do not match dates recorded on Fisch ECG worksheets. Dates should be identical.
Placebo	1121	1,15	ECG from visit 1 was entered as visit 15 ECG and the visit 15 ECG was never entered.
Flx	1215	7	Comments added to Comments section for visit 7 "No drug dispensed at visit 6." & "Rash ended 12/23/98"
Placebo	1307	1	ECG is checked as "abnormal" however the database reads as "Normal".
Placebo	1307	15	ECG from visit 1 was reread and entered as visit 15, same ECG used for both visits.
Placebo	1307	15	Dates of ECG recorded on CRF modules do not match dates recorded on Fisch ECG worksheets. Dates should be identical.
Flx	1510	16	Low Mood incorrectly mapped to Apathy should be Depression. (Visit onset = V16)
Placebo	1655	24	Data entry incorrectly entered frequency for Pepto Bismol as QAM instead of QPM.
Flx	1667	1	Dates of ECG recorded on CRF modules do not match dates recorded on Fisch ECG worksheets. Dates should be identical.
Placebo	1669	1	Dates of ECG recorded on CRF modules do not match dates recorded on Fisch ECG worksheets. Dates should be identical.
Placebo	1707	15	Dates of ECG recorded on CRF modules do not match dates recorded on Fisch ECG worksheets. Dates should be identical.
Placebo	1903	9	ECG from Visit 9 was not entered into the database.
Placebo	1913	1	Height changed from 66 inches to 64 inches following query of V19 height.
Flx	1919	1	Dates of ECG recorded on CRF modules do not match dates recorded on Fisch ECG worksheets. Dates should be identical.
NR	2203	26	AE Fearfulness incorrectly mapped to Anxiety - should have been Tearfulness mapped to Depression. (Visit Onset=1)
Placebo	2206	2	K-SADS Depressive Disorders -Past Changed From Yes To No
Placebo	2206	3	K-SADS Depressive Disorders -Past Changed From Yes To No
Placebo	2206	4	K-SADS Depressive Disorders -Past Changed From Yes To No
Placebo	2206	4	Comment added to Comments section for visit 4 "Patient missed 5-22-99 dose. Reason unknown."
Placebo	2207	1	Dates of ECG recorded on CRF modules do not match dates recorded on Fisch ECG worksheets. Dates should be identical.

Therapy	Patient Number	Visit Number	Comments / Error
Placebo	2207	22	Decresed Self Esteem incorrectly mapped to Personality Disorder should be Depression. (Visit onset = V17)
Flx	2216	1	Dates of ECG recorded on CRF modules do not match dates recorded on Fisch ECG worksheets. Dates should be identical.
Placebo	2218	15	Dates of ECG recorded on CRF modules do not match dates recorded on Fisch ECG worksheets. Dates should be identical.
	Site Initiated Changes to Concomitant Medications After Interim Lock (2/18/00)		
Flx	920	26	Site added Ibuprofen after interim lock with start date prior to interim lock.
Placebo	1221	26	Site deleted Claritin D after interim lock that was included in interim database.
Flx	1609	17	Site added stop date of 10/20/99 for Chloraseptic - stop date is before interim lock.
Placebo	1655	24	Site added stop date of 11/29/99 for Amoxicillin - stop date is before interim lock.
Placebo	2207	26	Site added Calamine Lotion with start date prior to interim lock after interim lock .
Flx	2214	26	Site informed us after interim lock that they had deleted Tavist.
	Site Initiated Changes to Adverse Events After Interim Lock		
Flx	354	23	Headache and Bizarre Dreams were marked "No" as possibly related at interim lock - site changed to "Yes" after lock.
Flx	355	26	Headache was marked "No" as possibly related at interim lock - site changed to "Yes" after interim lock.
Placebo	911	26	Headache was marked "No" as possibly related at interim lock - site changed to "Yes" after interim lock.
Flx	920	26	Menstrual Cramps was added by site after interim lock with onset date at V1.
Placebo	1216	26	Site added stop dates for Stomach Ache and Headache that were before interim lock.
Placebo	1221	26	Site added Sulfa and Shellfish Allergies with onset dates at V1 after interim lock.
Flx	1604	26	Headache was marked "Yes" as possibly related at interim lock - site changed to "No" after interim lock.
Flx	1604	26	Site added stop dates to Bladder and Bowel Accidents that were before interim lock.
Placebo	2203	26	Site deleted a change in severity for Rash on Face that was captured at interim lock.
Placebo	2207	26	Site added Temper Tantrums with start date at V1 that was not included in interim lock.
Placebo	2207	26	Site changed onset of Itchy Skin from V4 to V1 and changed stop date to Ongoing.
Flx	2208	26	Site added AEs Somnolence and Weight Gain with onset dates at V1 and V11 respectively after interim lock.

Therapy	Patient Number	Visit Number	Comments / Error
Flx	2208	26	Elevated Cholesterol, Increased Appetite and Stomach Ache were marked "No" as possibly related at interim lock - site changed to "Yes" after interim lock.
Flx	2214	26	Flat Affect marked "No" as possibly related at interim lock - site changed to "Yes" after interim lock.
Flx	2216	26	Site added stop dates for Decreased Motivation and Irritability after interim lock.
Placebo	2218	24	Rash on forearm and Dry Lips were marked "No" as possibly related at interim lock - site changed to "Yes" after interim lock.
Placebo	2218	24	Site changed stop date of Bronchitis from 11/8/99 to 11/2/99 after interim lock.

16.1.14.
Blinding Plan and Data Monitoring Board Information

Blinding Plan for Study B1Y-MC-HCJE

The following is Section 4.8 (Interim Analyses) of the protocol:

> One interim analysis is planned. The interim analysis will take place after all patients complete Study Period IV (Visit 10). The interim analysis will be conducted in order to obtain and communicate the results from the fixed-dose acute treatment phase in a more timely manner. The results from the fixed-dose acute treatment unblinded at the treatment level may be presented outside the company including to regulatory agencies. Additional interim analyses may take place after all patients complete Study Period V (the end of all acute treatment periods) and/or after all patients complete Visit 13 (2 weeks with doses up to 60 mg). These interim analyses will only take place if results are needed for decision-making purposes prior to the expected completion of the study. The study will not be stopped if evidence of efficacy is observed, thus adjustment of p-values is not required. To minimize the bias for the relapse prevention therapy phase, no one at the study site will be unblinded at the patient level.
>
> Planned interim analyses, and any unplanned interim analyses, will be conducted under the auspices of the data monitoring board assigned to this study. Only the data monitoring board is authorized to review completely unblinded interim efficacy and safety analyses and, if necessary, to disseminate those results. The data monitoring board will disseminate interim results in a manner that will minimize bias. Study sites will not receive information about interim results unless they need to know for the safety of their patients.

The section has been updated and although not submitted as an amendment, it has been submitted to the FDA as part of the analysis plan for B1Y-MC-HCJE.

> One interim analysis is planned. The interim analysis will take place after all patients complete Study Period V (Visit 15). The interim analysis will be conducted in order to obtain and communicate the results from the acute treatment phase in a more timely manner. The results from the acute treatment unblinded at the treatment level may be presented outside the company including to regulatory agencies. Additional interim analyses may take place after all patients complete Study Period IV (Visit 10) and/or after all patients complete Visit 13 (2 weeks with doses up to 60 mg). These interim analyses will only take place if results are needed for decision-making purposes prior to the expected completion of the study. The study will not be stopped if evidence of efficacy is observed, thus adjustment of p-values is not required. To minimize the bias for the relapse prevention therapy phase, no one at the study site will be unblinded at the patient level.
>
> Planned interim analyses, and any unplanned interim analyses, will be conducted under the auspices of the data monitoring board assigned to this study. Only the

data monitoring board is authorized to review completely unblinded interim efficacy and safety analyses and, if necessary, to disseminate those results. The data monitoring board will disseminate interim results in a manner that will minimize bias. Study sites will not receive information about interim results unless they need to know for the safety of their patients.

Blinding procedure:

1. As indicated in the above section, no one at the study site will be unblinded at the patient level until after the entire study is complete and data is locked unless this is necessary for the safety of the patient. The analyses (patients grouped) of the acute phase may be presented throughout the company and outside the company (depending on DMB decision). Since there is a re-randomization for Study Period VI, no bias can result in sharing results from the acute phase unblinded at the group level.

2. Treatment group assignments in the data will be masked using a dummy randomization code to maintain blinding during the process of data cleaning and development of statistical summary tables. Lilly study data will be formally unblinded to treatment group assignment just prior to datalock to the study statistician and systems personnel only. Any changes made to the data between unblinding and datalock will be documented.

3. Upon datalock, the Data Analysis Group (DAG) will be unblinded to the results of all analyses. The DAG consists of the study statistician, the medical writer, and systems personnel. The DAG will not share information of this analysis with anyone outside of the DAG prior to delivering it to the DMB.

4. As indicated in the protocol, only a Data Monitoring Board (DMB) can disseminate the results. Thus, a DMB will be formed prior to datalock. The study statistician will present results of the analysis to the DMB as soon as possible after datalock. The DMB will recommend whether the results of the analysis can be disseminated to people outside of the DMB and DAG. However, the study team recommends that members of the submission team (relevant personnel from the following functional areas) be unblinded after the DMB meets in order to prepare the submission:

   Pharmaceutical Projects Management
   Electronic Publishing
   Medical Writing
   IDEA Center
   Global Operations
   Regulatory (USRA/ELERT, including Global Labelling)
   Legal
   Clinical Plans (Physician and paramedical)
   Clinical Pharmacology

5. Lilly personnel in contact with study sites (e.g. CRAs and study physician), will remain blinded *on a patient basis,* until the datalock of the relapse prevention phase (early 4th quarter 2000).
6. An updated statistical analysis plan will be approved along with this blinding plan. If there are known additional changes to the analysis plan prior to unblinding the acute data, an additional updated statistical analysis plan will be prepared.

A detailed DMB charter will be completed prior to the first DMB meeting.

Your signature on this document indicates your understanding of the blinding procedures that will be utilized in this study and your commitment to preserving the integrity of the data for this study.

[redacted]

2/4/2000
Date

2/1/2000
Date

1st Feb 2000
Date

2/1/00
Date

2/1/00
Date

2/4/00
Date

Date

02/01/00
Date

Your signature on this document indicates your understanding of the blinding procedures that will be utilized in this study and your commitment to preserving the integrity of the data for this study.

[redacted]

2/4/2000
Date

2/1/2000
Date

18th Feb 2000
Date

2/1/00
Date

2/1/00
Date

2/4/00
Date

2-7-00
Date

02/01/00
Date

Data Monitoring Board Report
For Study
B1Y-MC-HCJE

February 29, 2000

Members: [redacted]

1. Study Design

The primary objective of study B1Y-MC-HCJE is to test the hypothesis that fluoxetine 20 mg is more effective than placebo in the treatment of children and adolescents with DSM-IV major depression. The primary outcome measure is response rate as measured by the Children's Depression Rating Scale-Revised (CDRS-R). The response rate is defined as a decrease in the CDRS-R total score of at least 30% from baseline to endpoint. The study consists of 6 periods:

- Periods I-II are prior to randomization and include a screening period and a 1-week placebo lead-in period.
- Period III consisted of a 1-week adaptation phase after randomization to either fluoxetine or placebo. Those patients randomized to fluoxetine received 10 mg of drug during this 1 week period.
- Period IV is an 8 week fixed-dose phase. The patients on fluoxetine titrated up to 20 mg of drug during this period. Those patients who could not tolerate 20 mg were allowed to reduce their dose back to 10 mg during this period.
- Period V was a 10-week titration phase. During this period, patients who were non-responders on fluoxetine during period IV were then re-randomized to either continue 20 mg fluoxetine treatment or to titrate up to 40 mg of drug. After 4 weeks of 40 mg, if the patient still had not responded, they were allowed to titrate up to 60 mg.
- Period VI is a 32-week relapse prevention phase. Patients with a CDRS-R score of $\leq$28 after Period V were then re-randomized to either placebo or to continue their current treatment as of the end of Period V.

The study diagram is as follows:

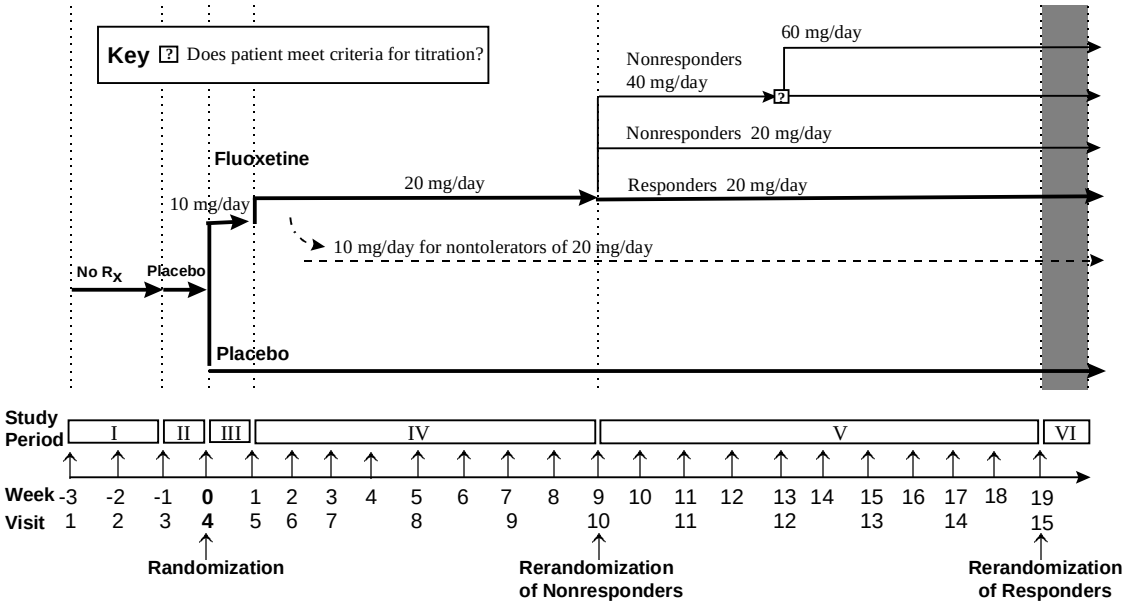


Figure 1: Study Diagram B1Y-MC-HCJE

2. Study Patients

2.1. Disposition of Patients

219 patients were randomized to at Visit 4 to receive either fluoxetine or placebo. Of these patients, 171 (78%) completed the fixed dose phase of the study (Period IV). The fluoxetine 20mg group had a significantly higher rate of completers during this period than the placebo group (86% versus 70%). There was not a significant difference in the rate of discontinuation due to an adverse event between the two treatment groups (see Table 1 below). There were no patients who could not tolerate 20mg and had to reduce their dosage down to 10mg.

Of the 219 randomized patients, 101 (46%) completed the entire acute phase, through Study Period V. There were no statistically significant differences between the groups in either rate of completers or discontinuation due to an adverse event (see Table 2).

Table 1

Summary of Reasons for Study Discontinuation
All Randomized Patients
Study Periods III-IV, B1Y-MC-HCJE

Primary Reason for Discontinuation	Flx 20 (N=109) n (%)	Placebo (N=110) n (%)	Total (N=219) n (%)	p-Value*
Study Period IV Complete	94 (86.2)	77 (70.0)	171 (78.1)	.005
Adverse Event	5 (4.6)	8 (7.3)	13 (5.9)	.569
Lack of Efficacy	4 (3.7)	7 (6.4)	11 (5.0)	.538
Patient Decision	3 (2.8)	9 (8.2)	12 (5.5)	.135
Physician Decision	1 (0.9)	0	1 (0.5)	.498
Protocol Requirement	2 (1.8)	2 (1.8)	4 (1.8)	1.00
Lost to Follow-Up	0	7 (6.4)	7 (3.2)	.014

RMP.B1YP.JCLLIB2(RDS1JEKC)
RMP.B1YO.HCJEREP(RDS1JEKC)
* Frequencies are analyzed using a Fisher's Exact test.
XRDS0001

Table 2

Summary of Reasons for Study Discontinuation
All Randomized Patients
Study Periods III-V, B1Y-MC-HCJE

Primary Reason for Discontinuation	Flx (N=109) n (%)	Placebo (N=110) n (%)	Total (N=219) n (%)	p-Value*
Acute Phase Complete	52 (47.7)	49 (44.5)	101 (46.1)	.685
Adverse Event	11 (10.1)	11 (10.0)	22 (10.0)	1.00
Lack of Efficacy	18 (16.5)	22 (20.0)	40 (18.3)	.600
Patient Decision	11 (10.1)	15 (13.6)	26 (11.9)	.532
Physician Decision	3 (2.8)	0	3 (1.4)	.122
Protocol Requirement	9 (8.3)	4 (3.6)	13 (5.9)	.165
Lost to Follow-Up	5 (4.6)	9 (8.2)	14 (6.4)	.408

RMP.B1YP.JCLLIB2(RDS1JEKD)
RMP.B1YO.HCJEREP(RDS1JEKD)
* Frequencies are analyzed using a Fisher's Exact test.
XRDS0001

2.2. Patient Characteristics

Baseline patient characteristics are given in Table 3; there were no significant differences detected between the two groups for any patient characteristics or patient habits (smoking, caffeine use, tobacco use; not shown). The average age of onset of disease was 10.4 years old for the fluoxetine group and 10.3 for the placebo group (not statistically significant). The duration of the current episode of the disease was 60.4 weeks for the fluoxetine group and 61.3 weeks for the placebo group (not statistically significant). 60% of the patients had a family history of depression and 21% had a family history of anxiety disorders (no statistically significant differences between treatment groups).

Table 3

Baseline Patient Characteristics
All Randomized Patients
B1Y-MC-HCJE

Variable	Flx 20 (N=109)	Placebo (N=110)	Total (N=219)	p-Value
Origin				
No. Patients	109	110	219	.071*
Caucasian	96 (88.1)	84 (76.4)	180 (82.2)	
East, SE Asian	1 (0.9)	0	1 (0.5)	
African American	6 (5.5)	8 (7.3)	14 (6.4)	
Hispanic	3 (2.8)	10 (9.1)	13 (5.9)	
Other	3 (2.8)	8 (7.3)	11 (5.0)	
Age				
No. Patients	109	110	219	.983**
Mean	12.70	12.69	12.70	
Median	12.56	12.50	12.56	
Standard Dev.	2.46	2.67	2.56	
Minimum	8.26	8.01	8.01	
Maximum	17.52	17.85	17.85	
Age Category				
No. Patients	109	110	219	1.00*
8 - < 13 yrs.	61 (56.0)	61 (55.5)	122 (55.7)	
13 - < 18 yrs.	48 (44.0)	49 (44.5)	97 (44.3)	
Gender				
No. Patients	109	110	219	1.00*
Female	54 (49.5)	54 (49.1)	108 (49.3)	
Male	55 (50.5)	56 (50.9)	111 (50.7)	
Height(CM)				
No. Patients	108	110	218	.432**
Mean	155.29	153.80	154.54	
Median	154.94	154.94	154.94	
Standard Dev.	14.72	13.32	14.02	
Minimum	124.46	121.92	121.92	
Maximum	187.96	182.88	187.96	
Unspecified	1	0	1	
Weight(KG)				
No. Patients	108	110	218	.937**
Mean	57.06	56.85	56.96	
Median	53.30	55.57	54.43	
Standard Dev.	19.33	19.96	19.61	
Minimum	20.87	26.76	20.87	
Maximum	102.97	140.61	140.61	
Unspecified	1	0	1	

RMP.B1YP.JCLLIB2(DES1JEAA)
RMP.B1YO.HCJEREP(DES1JEAA)
* Frequencies are analyzed using a Fishers-Exact test.
** Means are analyzed using a Type III Sum of Squares analysis of variance (ANOVA): PROC GLM model=treatment.
XDES0001

3. Efficacy Analysis

3.1. Efficacy Measures

The following efficacy measures were collected:

- **Children's Depression Rating Scale-Revised (CDRS-R):**
  The CDRS-R (Poznanski et al. 1984; 1985) is modeled after the Hamilton Depression Rating Scale (HAMD) for adults, but also includes questions about school. This is a clinician-rated instrument that measures presence and severity of depression. The scale consists of 17 items scored on a 1 to 5 or 1 to 7 scale. A rating of 1 indicates normal, thus the minimum score is 17. The maximum score is 113. In general, scores below 20 indicate an absence of depression, 20 to 30, borderline depression, 40 to 60, moderate depression.

- **Kiddie Schedule for Affective Disorders and Schizophrenia- Present and Lifetime (K-SADS-PL):**
  The K-SADS-PL (Kaufman et al. 1996) was adapted from the K-SADS (Puig-Antich and Chambers 1978; Chambers et al. 1985) which was adapted for use with children and adolescents from the Schedule for Affective Disorders and Schizophrenia (Endicott and Spitzer 1978). This clinician-rated instrument assesses the extent of depressive symptoms and allows for rating the worst part of an episode as well as for the past week. This instrument will be used in this study as both a supplementary diagnostic instrument and a measure of efficacy.

- **Clinical Global Impression of Severity (CGI-Severity):**
  The CGI-Severity scale (Guy 1976) has previously been used to assess both adults and children. This is a clinician-rated instrument that measures the severity of the patient's depression. It is a 7-point scale where 1 = normal and 7 = extremely severe case of depression.

- **Clinical Global Impression of Improvement (CGI-Improvement):**
  The CGI-Improvement scale (Guy 1976) has previously been used to assess both adults and children. This is a clinician-rated instrument that measures the improvement of the patient's depression. It is a 7-point scale where 1 = very much improved, 4 = no change, and 7 = very much worse.

- **Montgomery-Asberg Depression Rating Scale (MADRS):**
  The MADRS (Montgomery and Asberg 1979) is a clinician-rated instrument that measures the presence and severity of depression. This instrument consists of a 10-symptom scale, namely, apparent sadness, reported sadness, inner tension, reduced sleep, reduced appetite, concentration difficulties, lassitude, inability to feel, pessimistic thoughts, and suicidal ideation. Each symptom is rated on a defined step scale (0 to 6). A high numeric rating shows a greater degree of symptom severity.

- **Beck Depression Inventory (BDI):**
  The BDI (Beck and Steer 1984) has been used extensively with both adults and adolescents in research studies. This patient-rated scale assesses the major symptom categories associated with depression. The higher the total score (range, 0 to 62) the more severe the depression. The BDI scale will be completed by adolescents (patients aged 13 to <18 years).
- **Hamilton Anxiety Rating Scale (HAMA):**
  The HAMA will be administered to assess severity of anxiety, its improvement during the course of treatment, and the timing of such improvement (Riskind et al. 1987). This instrument is completed by the clinician based on his or her assessment of the patient.
- **Children's Depression Inventory (CDI):**
  The CDI was developed from the BDI (Kovacs 1985). Like the BDI, the higher the total score (range, 0 to 54) the more severe the depression. The CDI will be completed by children (patients aged 8 to <13 years).

Baseline psychiatric scores are given in Table 4. A statistically significant difference was detected between the two treatment groups for CGI-Severity with the fluoxetine patients having a slightly higher score.

Table 4

Baseline Psychiatric Evaluation
All Randomized Patients
B1Y-MC-HCJE

Variable	Flx 20 (N=109)	Placebo (N=110)	Total (N=219)	p-Value
CDRS-R Total				
No. Patients	109	110	219	.231**
Mean	57.1	55.4	56.2	
Median	55.0	55.0	55.0	
Standard Dev.	9.9	11.6	10.8	
Minimum	42.0	32.0	32.0	
Maximum	77.0	94.0	94.0	
CGI-Severity				
No. Patients	109	110	219	.037**
Mean	4.5	4.4	4.5	
Median	4.0	4.0	4.0	
Standard Dev.	0.6	0.6	0.6	
Minimum	4.0	3.0	3.0	
Maximum	6.0	6.0	6.0	
MADRS				
No. Patients	109	110	219	.908**
Mean	21.6	21.4	21.5	
Median	22.0	21.0	22.0	
Standard Dev.	7.5	8.3	7.9	
Minimum	3.0	0.0	0.0	
Maximum	38.0	44.0	44.0	
HAMA				
No. Patients	108	110	218	.216**
Mean	10.2	11.1	10.7	
Median	9.0	10.0	10.0	
Standard Dev.	5.1	5.9	5.6	
Minimum	1.0	0.0	0.0	
Maximum	29.0	28.0	29.0	
Unspecified	1	0	1	

RMT.B1YP.JCLLIB2(DES1JEKH)
RMT.B1YO.HCJEREP(DES1JEKH)
** Means are analyzed using a Type III Sum of Squares analysis of variance (ANOVA): PROC GLM model=treatment.
XDES0001

3.2. Response Rates

As defined in the protocol, the primary efficacy measure was the response rate as defined by CDRS-R total score from baseline to endpoint for Period IV. Note that in the protocol, for the primary analysis, a patient had to be on fluoxetine 20mg for at least a week. Therefore, the endpoint was the last available visit for visit 6 through 10 (Period IV). Response was defined as at least a 30% reduction in the total score from baseline. Using this definition, 65.1% of the fluoxetine patients responded compared to 53.5% of the placebo patients. This did not reach statistical significance (p=0.093). However, when the endpoint is defined as last visit available from visit 6 through visit 15 (i.e. Period IV through Period V, the titration dose period), statistical significance was detected (p=0.026, 75.2% responders on fluoxetine, 60.4% responders on placebo). This was considered a secondary analysis. Note that when using endpoint as last available measurement through Period V, all doses of fluoxetine are pooled, i.e., 20mg with the tritrated arms of 40 and 60 mg.

Other secondary analyses based on other response-type rates included the following:

- Remission rates based on the CDRS-R total. Remission was defined as a CDRS-R total score of less than 29. This was analyzed using last of visits 6-10 (Period IV) and last of visits 6-15 (Period IV-Period V) as endpoints.
- Clinical Global Impression (CGI) Improvement score where the response was defined as having a CGI score=1 (very much improved) or 2 (much improved). This was analyzed using last of visits 5-10 (Period III-Period IV) and last of visits 5-15 (Period III-Period V) as endpoints.
- Recovery rates: this was defined as having both a CDRS-R score less than 29 along with a CGI Improvement score of 1 or 2. This was analyzed using last of visits 6-10 (Period IV) and last of visits 6-15 (Period IV-Period V) as endpoints.

Results are compared below:

Table 5

Measure	Period IV as Endpoint			Period V as Endpoint		
	Flx 20 response	Placebo response	p-value*	Flx response	Placebo response	p-value*
CDRS Total Response	65.1%	53.5%	.093	75.2%	60.4%	.026
CDRS Total Remission	41.3%	19.8%	<.001	50.5%	45.5%	.493
CGI Improvement	52.3%	36.8%	.028	63.3%	51.9%	.099
Recovery rate	39.4%	19.8%	.002	50.5%	45.5%	.493

*Fisher's exact test.

To investigate different response definitions for the CDRS Total, plots were done using different cut-off values, eg, 30% reduction from baseline versus 20% reduction, 40% reduction etc. Figure 2 below plots the percent of patients who met the response criteria (vertical axis) against different possible response criteria (horizontal axis). For example, looking at the >=30% criteria, we see the points plotted are 65% and 53%, as given in the table above. As can be seen from the plot, the separation between fluoxetine and placebo is greater using some of the other criteria, e.g. >=40% or >=20%.

Figure 2
CDRS-R Total Score: Percent Change Distribution
Study Period IV as Endpoint

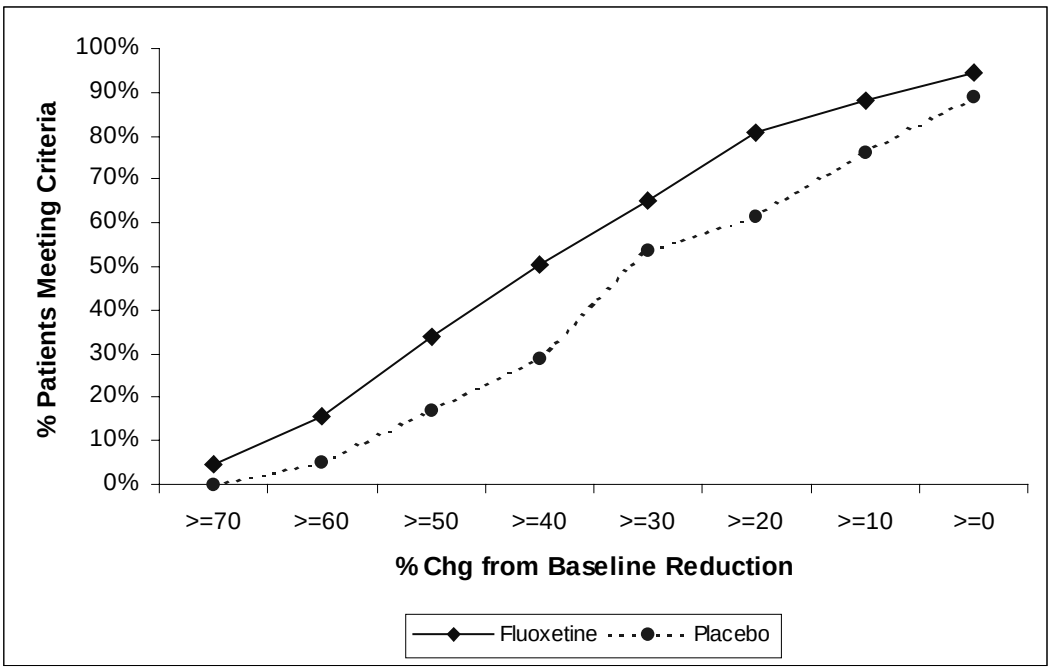
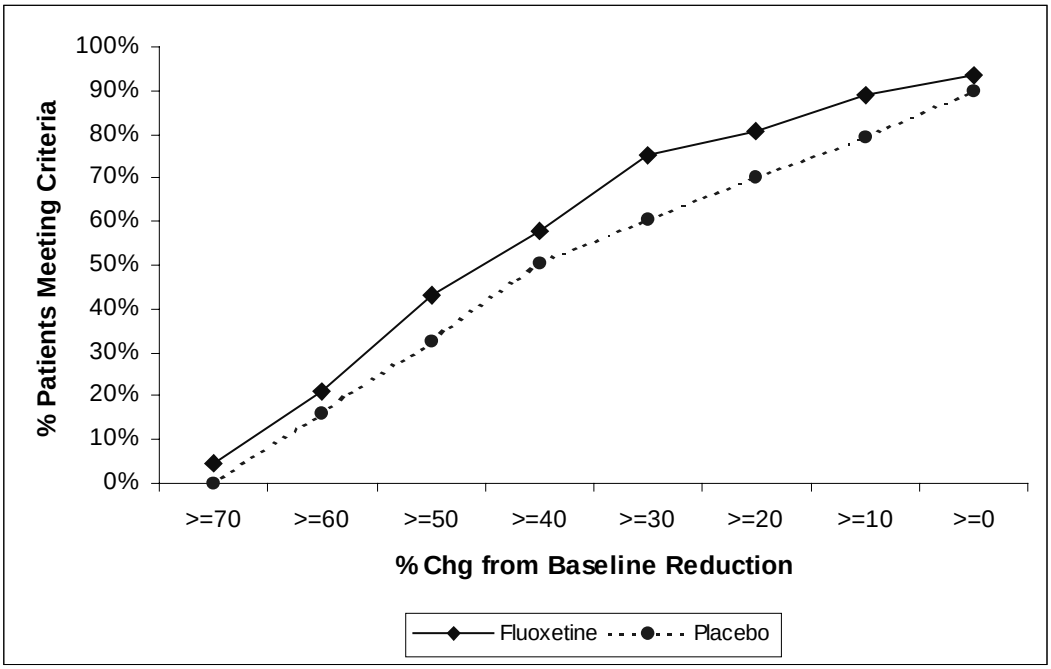


Figure 3 gives a similar plot using Study Period IV-V as endpoint (last of visits 6-15).

Figure 3
CDRS-R Total Score: Percent Change Distribution
Study Period IV-V as Endpoint



3.3. Mean Change Analysis

In addition to analyzing response rates, mean change from baseline to endpoint was also analyzed. Similar to the response rate analysis, this was done using both Period III-IV as endpoint (last of visits 5-10) as Period III-V as endpoints (last of visits 5-15). (Note that for the primary response analysis, that visit 5 was not included as a possible endpoint, i.e., endpoint was defined as last of visits 6-10 or visits 6-15). Using the CDRS-R scale, a mood subtotal, somatic subtotal, subjective subtotal and a behavioral subtotal was analyzed along with the total score[1]. These results are given in Tables 6 and 7. Statistically significant differences were detected between groups for all subtotals when using Period III-IV as endpoint, however, when using Period III-V as endpoint only the total and the behavioral subtotal reached statistical significance.

Other secondary analyses of continuous outcome measurements included change from baseline to endpoint for CGI Severity, BDI total (for adolescents only), CDI total (for children only), MADRS total and the HAMA. These results are given Tables 8 and 9. A statistically significant difference was detected between the treatment groups for the CGI severity scale using both definitions of endpoint and the MADRS total reached statistical significance for the Period III-IV endpoint definition only.

3.4. Endpoint Analysis

The CGI Improvement score was compared between groups at endpoint. These results are given in Table 10. There was a statistically significant difference detected between groups when analyzing Period III-IV but not for Period III-V.

The K-SADS assessment as to whether the patient was experiencing a current depressive or mania disorder, is presented in Table 11. A statistically significant difference was not detected between the two groups.

[1]Mood subtotal consists of a sum of scores for irritability, depressed feelings, weeping, depressed affect.
Somatic subtotal: sleep, appetite, excessive fatigue, physical complaints, tempo of speech, hypoactivity.
Behavioral subtotal: schoolwork, capacity to have fun, social withdrawal.
Subjective subtotal: guilt, self-esteem, morbid ideation, suicidal ideation.

Table 6

CDRS-R Scores
Change from Baseline to Endpoint
All Randomized Patients
Study Periods III-IV, B1Y-MC-HCJE

Variable	Therapy	n	Baseline Mean	Baseline SD	Endpoint Mean	Endpoint SD	Change Mean	Change SD	p-Value *1
TOTAL	Flx 20	109	57.1	9.9	35.1	13.5	-22.1	14.4	<.001
	Placebo	105	55.1	11.8	40.2	13.5	-14.9	13.3	
MOOD SUBTOTAL	Flx 20	109	15.9	4.0	9.4	4.7	-6.6	5.3	.002
	Placebo	105	15.4	4.8	11.2	5.0	-4.3	5.4	
SOMATIC SUBTOTAL	Flx 20	109	17.2	4.5	10.7	4.2	-6.5	5.2	.004
	Placebo	105	17.0	4.3	12.6	4.9	-4.5	4.8	
SUBJECTIVE SUBTOTAL	Flx 20	109	11.1	3.0	7.2	2.9	-3.9	3.6	.026
	Placebo	105	10.8	3.3	7.9	2.5	-2.9	3.1	
BEHAVIOR SUBTOTAL	Flx 20	109	12.9	2.9	7.8	4.0	-5.1	3.7	<.001
	Placebo	105	11.9	3.2	8.6	3.7	-3.3	3.7	

*1 Type III Sums of Squares from an analysis of variance (ANOVA): PROC GLM model=treatment.
RMP.B1YP.JCLLIB2(LAS3JEAA)
RMP.B1YO.HCJEREP(LAS3JEAA)

Table 7

CDRS-R Scores
Change from Baseline to Endpoint
All Randomized Patients
Study Periods III-V, B1Y-MC-HCJE

Variable	Therapy	n	Baseline Mean	Baseline SD	Endpoint Mean	Endpoint SD	Change Mean	Change SD	p-Value *1
TOTAL	Flx	109	57.1	9.9	33.8	14.1	-23.4	14.6	.021
	Placebo	105	55.1	11.8	36.6	14.0	-18.6	15.6	
MOOD SUBTOTAL	Flx	109	15.9	4.0	9.1	5.0	-6.9	5.6	.055
	Placebo	105	15.4	4.8	10.1	4.8	-5.3	6.2	
SOMATIC SUBTOTAL	Flx	109	17.2	4.5	10.4	4.4	-6.8	5.4	.181
	Placebo	105	17.0	4.3	11.2	5.1	-5.8	4.9	
SUBJECTIVE SUBTOTAL	Flx	109	11.1	3.0	6.9	2.9	-4.2	3.4	.078
	Placebo	105	10.8	3.3	7.5	2.6	-3.3	3.5	
BEHAVIOR SUBTOTAL	Flx	109	12.9	2.9	7.3	4.0	-5.6	3.9	.011
	Placebo	105	11.9	3.2	7.8	3.7	-4.1	4.3	

*1 Type III Sums of Squares from an analysis of variance (ANOVA): PROC GLM model=treatment.
RMP.B1YP.JCLLIB2(LAS3JEAB)
RMP.B1YO.HCJEREP(LAS3JEAB)

Table 8

Secondary Efficacy Variables
Change from Baseline to End Point
Study Periods III-IV
All Randomized Patients
B1Y-MC-HCJE

Variable	Therapy	n	Baseline Mean	Baseline SD	Endpoint Mean	Endpoint SD	Change Mean	Change SD	p-Value *1
CGI Severity	Flx 20	109	4.5	0.6	2.9	1.2	-1.6	1.3	<.001
	Placebo	106	4.4	0.6	3.4	1.1	-1.0	1.1	
BDI Total	Flx 20	46	15.5	11.1	10.9	11.8	-4.6	8.2	.700
	Placebo	38	16.6	11.6	11.3	9.3	-5.3	7.8	
CDI Total	Flx 20	56	9.2	8.3	6.8	9.1	-2.4	9.0	.822
	Placebo	53	8.4	9.3	5.6	5.4	-2.8	6.8	
MADRS Total	Flx 20	109	21.6	7.5	11.2	9.0	-10.4	9.4	.023
	Placebo	105	21.5	8.3	13.9	8.2	-7.6	8.4	
HAMA Total	Flx 20	106	10.2	5.2	5.4	4.7	-4.8	5.2	.115
	Placebo	94	11.0	5.8	7.4	5.2	-3.7	5.2	
GAF: Current Functioning	Flx 20	104	53.3	6.7	64.8	12.4	11.5	11.7	.176
	Placebo	86	54.6	7.1	63.9	9.8	9.3	10.3	

* 1 Type III Sums of Squares from an analysis of variance (ANOVA): PROC GLM model=treatment.
RMP.B1YP.JCLLIB2(LAS3JEAC)
RMP.B1YO.HCJEREP(PRCNJEAC)

Table 9

Secondary Efficacy Variables
Change from Baseline to End Point
Study Periods III-V
All Randomized Patients
B1Y-MC-HCJE

Variable	Therapy	n	Baseline Mean	Baseline SD	Endpoint Mean	Endpoint SD	Change Mean	Change SD	p-Value *1
CGI Severity	Flx	109	4.5	0.6	2.8	1.3	-1.7	1.3	.025
	Placebo	106	4.4	0.6	3.0	1.2	-1.3	1.2	
BDI Total	Flx	46	15.5	11.1	9.0	11.3	-6.5	8.6	1.00
	Placebo	38	16.6	11.6	10.1	9.0	-6.5	8.1	
CDI Total	Flx	56	9.2	8.3	7.8	11.2	-1.4	10.3	.068
	Placebo	55	9.1	10.0	4.6	5.5	-4.5	7.3	
MADRS Total	Flx	109	21.6	7.5	10.1	8.8	-11.5	9.2	.212
	Placebo	105	21.5	8.3	11.6	8.5	-9.9	9.2	
HAMA Total	Flx	106	10.2	5.2	5.1	4.8	-5.2	5.2	.669
	Placebo	94	11.0	5.8	6.2	4.8	-4.8	5.7	
GAF: Current Functioning	Flx	104	53.3	6.7	65.1	13.5	11.8	12.9	.803
	Placebo	86	54.6	7.1	66.9	10.6	12.3	12.2	

*** 1 Type III Sums of Squares from an analysis of variance (ANOVA): PROC GLM model=treatment.**
RMP.B1YP.JCLLIB2(LAS3JEAD)
RMP.B1YO.HCJEREP(PRCNJEAD

Table 10

CGI-Improvement Score
Endpoint Analysis
All Randomized Patients
Study Periods III-IV,B1Y-MC-HCJE

Variable	Flx 20 (N=109)	Placebo (N=110)	Total (N=219)	p-Value
CGI-Improvement Score				
No. Patients	109	106	215	.025**
Mean	2.50	2.86	2.67	
Median	2.00	3.00	3.00	
Standard Dev.	1.29	1.06	1.19	
Minimum	1.00	1.00	1.00	
Maximum	7.00	6.00	7.00	

RMP.B1YP.JCLLIB2(DES1JEAJ)
RMP.B1YO.HCJEREP(DES1JEAJ)
RMP.SAS.B1YM.USM037
B1Y98032
** Means are analyzed using a Type III Sum of Squares analysis of variance (ANOVA): PROC GLM model=treatment.
XDES0001

CGI-Improvement Score
Endpoint Analysis
All Randomized Patients
Study Periods III-V,B1Y-MC-HCJE

Variable	Flx (N=109)	Placebo (N=110)	Total (N=219)	p-Value
CGI-Improvement Score				
No. Patients	109	106	215	.323**
Mean	2.42	2.59	2.51	
Median	2.00	2.00	2.00	
Standard Dev.	1.36	1.19	1.27	
Minimum	1.00	1.00	1.00	
Maximum	7.00	6.00	7.00	

RMP.B1YP.JCLLIB2(DES1JEAG)
RMP.B1YO.HCJEREP(DES1JEAG)
** Means are analyzed using a Type III Sum of Squares analysis of variance (ANOVA): PROC GLM model=treatment.
XDES0001

Table 11

K-SADS
Endpoint Analysis
All Randomized Patients
Study Periods III-IV,B1Y-MC-HCJE

Variable	Flx 20 (N=109)	Placebo (N=110)	Total (N=219)	p-Value
Current Depression				
No. Patients	103	83	186	.184*
Yes	46 (44.7)	46 (55.4)	92 (49.5)	
No	57 (55.3)	37 (44.6)	94 (50.5)	
Current Mania				
No. Patients	103	83	186	.503*
Yes	2 (1.9)	0	2 (1.1)	
No	101 (98.1)	83 (100)	184 (98.9)	

RMP.B1YP.JCLLIB2(DES1JEAM)
RMP.B1YO.HCJEREP(DES1JEAM)
* Frequencies are analyzed using a Fishers-Exact test.

K-SADS
Endpoint Analysis
All Randomized Patients
Study Periods III-V,B1Y-MC-HCJE

Variable	Flx (N=109)	Placebo (N=110)	Total (N=219)	p-Value
Current Depression				
No. Patients	103	85	188	.290*
Yes	35 (34.0)	36 (42.4)	71 (37.8)	
No	68 (66.0)	49 (57.6)	117 (62.2)	
Current Mania				
No. Patients	103	85	188	.628*
Yes	3 (2.9)	1 (1.2)	4 (2.1)	
No	100 (97.1)	84 (98.8)	184 (97.9)	

RMP.B1YP.JCLLIB2(DES1JEAN)
RMP.B1YO.HCJEREP(DES1JEAN)
* Frequencies are analyzed using a Fishers-Exact test.
XDES0001

3.5. Analysis by Visit

A visit-wise analysis was performed for the CDRS-R total score change from baseline using both observed cases and a last-observation-carried-forward (LOCF) technique. In the observed case analysis, there was a statistically significant difference detected between the fluoxetine and placebo group at visits 5 through 10, however the significance was lost from visits 11 through 15. This may be explained in part due to a large number of dropouts that occurred at visit 11 in the fluoxetine group (15 patients dropped out at visit 11 in the fluoxetine group, 4 in the placebo group). When using an LOCF type of analysis, a statistically significant difference is maintained between the groups at all visits. See figures 4 and 5 below:

Figure 4
CDRS-R Total Score
Change from Baseline to Each Visit (Observed Cases)

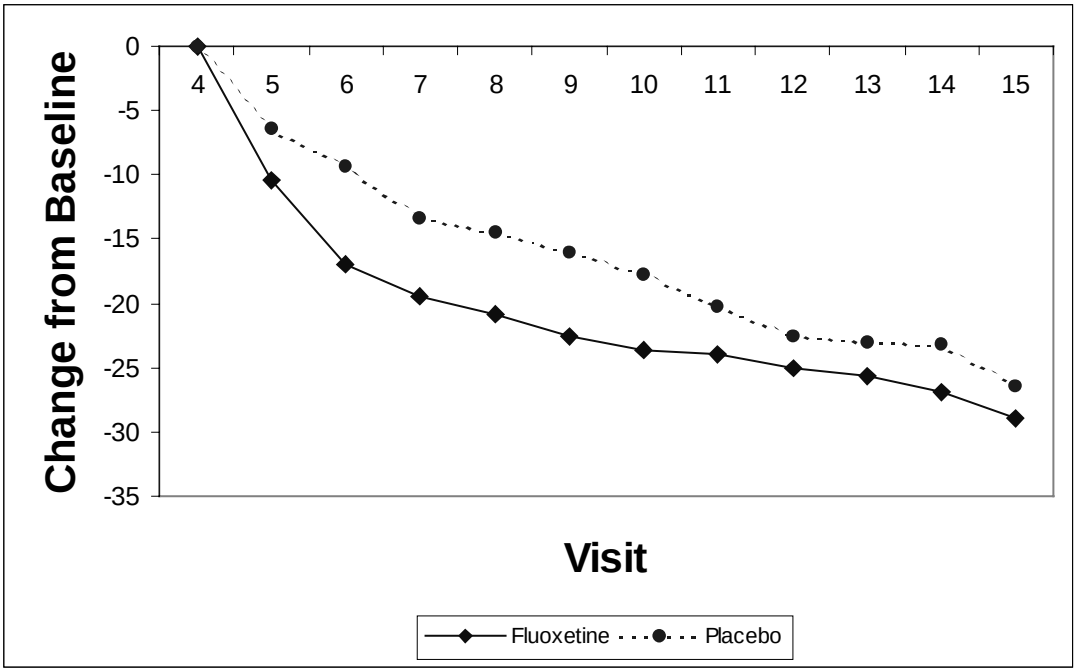
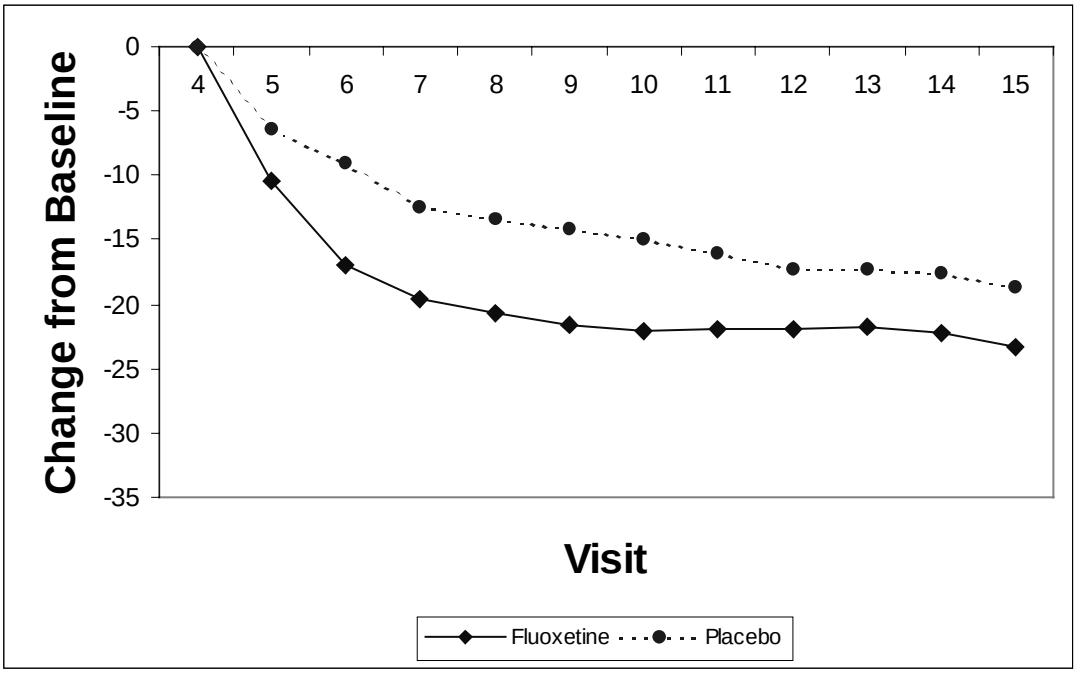


Figure 5
CDRS-R Total Score
Change from Baseline to Each Visit (LOCF)



3.6. Subgroup Analysis

Subgroup analyses were performed for three stratification variables: age group (<13 years, ≥13 years), gender and family history of depression. These analyses were done for both the CDRS-R response criteria (primary analysis of reduction ≥30%) and mean change from baseline for CDRS-R total for both study periods of interest. The analysis of response rate did not reveal anything noteworthy, i.e., there were no significant interactions between the stratification variable and treatment.

A similar analysis was done using CDRS-R total score mean change from baseline. Again, there was nothing noteworthy in the analysis, no significant treatment by strata interactions.

3.7. Analysis of Period V: Re-randomized Nonresponders

Efficacy analyses were also performed between fluoxetine non-responders who were re-randomized to either stay on fluoxetine 20mg/day or titrate up to 40mg/day during period V. There were only 14 patients randomized to increase dose to 40mg and 15 patients randomized to continue treatment of 20mg. No statistically significant differences were detected for any of the efficacy measures.

4. Safety Analysis

4.1. Adverse Events

4.1.1. Treatment Emergent Adverse Events

This study utilized a side effects checklist that was collected at every visit starting with Visit 4, which was the baseline visit. The checklist was worded such as "Since your last visit, have you been bothered with or had any trouble with any of the items listed below. Check the box which best tells how much you were bothered". Events were then listed (see Table 12) with the choices for answer as: Not at all, Just a little, Pretty much, Very much and Don't know. A treatment emergent event was defined as one that was present at baseline and worsened as defined by increase in score on the checklist at any postbaseline visit OR a new occurrence after baseline. Table 12 below gives incidence rates for those events that emerged during Study Periods III-IV. There were no statistically significant differences between the two treatment groups with the exception of "Pronouncing Words" in which the placebo group experienced a higher rate (25.5%) then the fluoxetine treated group (11.9%). Table 13 gives similar results for Study Periods III-V. In addition to the significant difference in "Pronouncing Words" there is also a statistically significant difference between groups for this study period for the event "Wetness in Mouth" with the placebo group experiencing a higher incidence of 21.8% compared to the fluoxetine treated group rate of 10.1%

In addition to the side effects checklist, spontaneous adverse events were also recorded and analyzed. Rates of treatment emergent events (for events that occurred in more than 2 fluoxetine treated patients) are given in Table 14 for Study Periods III-IV and in Table 15 for Study Periods III-V. The only event that occurred statistically significantly higher in the fluoxetine group than the placebo group was headache.

Treatment-emergent adverse events were also analyzed for only those patients *entering* Study Period V using baseline as Visits 4-10. There were no statistically significant differences detected between fluoxetine (pooled across doses) and placebo for any spontaneous event. For the solicited events, 2 events were statistically significant between the groups: Wetness in mouth occurred more frequently in the placebo group (8.8%) compared to the fluoxetine group (1.1%) and rash occurred more frequently in the placebo group (11.8%) than then fluoxetine group (1.1%). (No, this is not a typo- it occurred higher in the placebo group.)

Finally, treatment-emergent adverse events were compared between the fluoxetine nonresponders re-randomized to 20mg versus those randomized to 40/60mg. There were no statistically significant differences detected between the groups for any event, spontaneous or solicited.

Adverse events leading to discontinuation are given in Table 16. There were no events that led to discontinuation that occurred in more than 1 fluoxetine patient.

Table 12

Treatment-Emergent(1) Solicited Adverse Events
Side-Effects Checklist
Incidence by Decreasing Frequency (Ordered by Fluoxetine)
All Randomized Patients
Study Periods III-IV, B1Y-MC-HCJE

Event Classification	Flx 20 (N=109) n (%)	Placebo (N=110) n (%)	Total (N=219) n (%)	p-Value*
PATIENTS WITH >= 1 TESS	105 (96.3)	100 (90.9)	205 (93.6)	.165
PATIENTS WITH NO TESS	4 (3.7)	10 (9.1)	14 (6.4)	.165
23. FEELING SLEEPY	52 (47.7)	47 (42.7)	99 (45.2)	.499
22. TIREDNESS	50 (45.9)	46 (41.8)	96 (43.8)	.587
15. HEADACHE	49 (45.0)	41 (37.3)	90 (41.1)	.273
26. GETTING ALONG WITH PARENTS	43 (39.4)	45 (40.9)	88 (40.2)	.891
32. PAYING ATTENTION	43 (39.4)	31 (28.2)	74 (33.8)	.088
14. COLD OR SNIFFLES	41 (37.6)	50 (45.5)	91 (41.6)	.273
31. BEING SAD	41 (37.6)	32 (29.1)	73 (33.3)	.199
29. GETTING MAD	40 (36.7)	47 (42.7)	87 (39.7)	.408
30. NOT BEING HAPPY	40 (36.7)	34 (30.9)	74 (33.8)	.394
09. BEING SICK TO YOUR STOMACH	39 (35.8)	33 (30.0)	72 (32.9)	.390
24. SLEEPING	39 (35.8)	45 (40.9)	84 (38.4)	.488
28. CRYING	39 (35.8)	39 (35.5)	78 (35.6)	1.00
07. STOMACHACHES	37 (33.9)	43 (39.1)	80 (36.5)	.484
16. DIZZINESS	34 (31.2)	23 (20.9)	57 (26.0)	.092
27. GETTING ALONG WITH KIDS	33 (30.3)	31 (28.2)	64 (29.2)	.768
03. DRY MOUTH AND LIPS	32 (29.4)	38 (34.5)	70 (32.0)	.469
01. EATING	31 (28.4)	35 (31.8)	66 (30.1)	.659
21. SITTING STILL	30 (27.5)	42 (38.2)	72 (32.9)	.114
08. MUSCLE CRAMPS	27 (24.8)	34 (30.9)	61 (27.9)	.366
12. ITCHY OR SCRATCHY SKIN	27 (24.8)	32 (29.1)	59 (26.9)	.543
25. BAD DREAMS	27 (24.8)	27 (24.5)	54 (24.7)	1.00
06. DIARRHEA	22 (20.2)	19 (17.3)	41 (18.7)	.607
18. SHAKINESS	21 (19.3)	23 (20.9)	44 (20.1)	.866
13. RASHES	17 (15.6)	18 (16.4)	35 (16.0)	1.00
17. PLAYING SPORTS	17 (15.6)	20 (18.2)	37 (16.9)	.719
02. DRINKING	14 (12.8)	20 (18.2)	34 (15.5)	.351
19. PRONOUNCING WORDS	13 (11.9)	28 (25.5)	41 (18.7)	.015
20. DOING THINGS WITH YOUR HANDS	13 (11.9)	19 (17.3)	32 (14.6)	.339
04. WETNESS IN MOUTH	10 (9.2)	19 (17.3)	29 (13.2)	.110
11. URINATING	10 (9.2)	12 (10.9)	22 (10.0)	.823
05. CONSTIPATION	9 (8.3)	10 (9.1)	19 (8.7)	1.00
10. WETTING THE BED	3 (2.8)	5 (4.5)	8 (3.7)	.721

1 Treatment-Emergent = was present at baseline (Visit 4) and worsened as defined by increase in score on the side-effects checklist at any postbaseline visit (Visits 5-10) or new occurrence after baseline.
RMT.B1YP.JCLLIB2(AES2JEKI)
RMT.B1YO.HCJEREP(AES2JEKI)
*** Frequencies are analyzed using a Fisher's Exact test.**
XAES0002

Table 13

Treatment-Emergent(1) Solicited Adverse Events
Side-Effects Checklist
Incidence by Decreasing Frequency (Ordered by Fluoxetine)
All Randomized Patients
Study Periods III-V, B1Y-MC-HCJE

Event Classification	Flx (N=109) n (%)	Placebo (N=110) n (%)	Total (N=219) n (%)	p-Value*
PATIENTS WITH >= 1 TESS	107 (98.2)	101 (91.8)	208 (95.0)	.059
PATIENTS WITH NO TESS	2 (1.8)	9 (8.2)	11 (5.0)	.059
15. HEADACHE	57 (52.3)	44 (40.0)	101 (46.1)	.079
23. FEELING SLEEPY	56 (51.4)	49 (44.5)	105 (47.9)	.345
22. TIREDNESS	55 (50.5)	48 (43.6)	103 (47.0)	.345
14. COLD OR SNIFFLES	51 (46.8)	56 (50.9)	107 (48.9)	.590
26. GETTING ALONG WITH PARENTS	51 (46.8)	48 (43.6)	99 (45.2)	.685
07. STOMACHACHES	48 (44.0)	49 (44.5)	97 (44.3)	1.00
28. CRYING	47 (43.1)	44 (40.0)	91 (41.6)	.682
31. BEING SAD	47 (43.1)	36 (32.7)	83 (37.9)	.127
32. PAYING ATTENTION	47 (43.1)	37 (33.6)	84 (38.4)	.166
24. SLEEPING	45 (41.3)	50 (45.5)	95 (43.4)	.586
29. GETTING MAD	45 (41.3)	51 (46.4)	96 (43.8)	.497
09. BEING SICK TO YOUR STOMACH	44 (40.4)	39 (35.5)	83 (37.9)	.488
30. NOT BEING HAPPY	44 (40.4)	39 (35.5)	83 (37.9)	.488
16. DIZZINESS	38 (34.9)	32 (29.1)	70 (32.0)	.387
08. MUSCLE CRAMPS	35 (32.1)	42 (38.2)	77 (35.2)	.396
01. EATING	34 (31.2)	39 (35.5)	73 (33.3)	.567
03. DRY MOUTH AND LIPS	34 (31.2)	42 (38.2)	76 (34.7)	.321
21. SITTING STILL	34 (31.2)	43 (39.1)	77 (35.2)	.258
27. GETTING ALONG WITH KIDS	34 (31.2)	33 (30.0)	67 (30.6)	.884
12. ITCHY OR SCRATCHY SKIN	32 (29.4)	36 (32.7)	68 (31.1)	.662
25. BAD DREAMS	30 (27.5)	35 (31.8)	65 (29.7)	.555
06. DIARRHEA	28 (25.7)	23 (20.9)	51 (23.3)	.428
18. SHAKINESS	26 (23.9)	24 (21.8)	50 (22.8)	.750
17. PLAYING SPORTS	19 (17.4)	21 (19.1)	40 (18.3)	.861
13. RASHES	18 (16.5)	25 (22.7)	43 (19.6)	.308
19. PRONOUNCING WORDS	18 (16.5)	33 (30.0)	51 (23.3)	.025
02. DRINKING	16 (14.7)	21 (19.1)	37 (16.9)	.471
20. DOING THINGS WITH YOUR HANDS	15 (13.8)	25 (22.7)	40 (18.3)	.115
04. WETNESS IN MOUTH	11 (10.1)	24 (21.8)	35 (16.0)	.026
05. CONSTIPATION	11 (10.1)	14 (12.7)	25 (11.4)	.672
11. URINATING	10 (9.2)	13 (11.8)	23 (10.5)	.660
10. WETTING THE BED	3 (2.8)	5 (4.5)	8 (3.7)	.721

1 Treatment-Emergent = was present at baseline (Visit 4) and worsened as defined by increase in score on the side-effects checklist at any postbaseline visit (Visits 5-15) or new occurrence after baseline.
RMT.B1YP.JCLLIB2(AES2JEKK)
RMT.B1YO.HCJEREP(AES2JEKK)
*** Frequencies are analyzed using a Fisher's Exact test.**
XAES0002

Table 14

Treatment-Emergent Adverse Events
Incidence by Decreasing Frequency (Ordered by Fluoxetine)
All Randomized Patients
Study Periods III-IV, B1Y-MC-HCJE

Event Classification	Flx 20 (N=109) n (%)	Placebo (N=110) n (%)	Total (N=219) n (%)	p-Value*
PATIENTS WITH >= 1 TESS	94 (86.2)	80 (72.7)	174 (79.5)	.019
PATIENTS WITH NO TESS	15 (13.8)	30 (27.3)	45 (20.5)	.019
HEADACHE	33 (30.3)	18 (16.4)	51 (23.3)	.017
RHINITIS	24 (22.0)	21 (19.1)	45 (20.5)	.619
ABDOMINAL PAIN	17 (15.6)	16 (14.5)	33 (15.1)	.852
PHARYNGITIS	16 (14.7)	9 (8.2)	25 (11.4)	.143
ACCIDENTAL INJURY	13 (11.9)	8 (7.3)	21 (9.6)	.261
DIARRHEA	11 (10.1)	11 (10.0)	22 (10.0)	1.00
DIZZINESS	10 (9.2)	4 (3.6)	14 (6.4)	.106
RASH	10 (9.2)	4 (3.6)	14 (6.4)	.106
ANOREXIA	9 (8.3)	6 (5.5)	15 (6.8)	.437
COUGH INCREASED	9 (8.3)	7 (6.4)	16 (7.3)	.615
NAUSEA	9 (8.3)	8 (7.3)	17 (7.8)	.806
NERVOUSNESS	9 (8.3)	6 (5.5)	15 (6.8)	.437
ASTHENIA	8 (7.3)	6 (5.5)	14 (6.4)	.594
PAIN	8 (7.3)	9 (8.2)	17 (7.8)	1.00
VOMITING	8 (7.3)	8 (7.3)	16 (7.3)	1.00
FEVER	7 (6.4)	5 (4.5)	12 (5.5)	.569
ABNORMAL DREAMS	6 (5.5)	3 (2.7)	9 (4.1)	.332
EPISTAXIS	5 (4.6)	1 (0.9)	6 (2.7)	.119
DRY MOUTH	4 (3.7)	5 (4.5)	9 (4.1)	1.00
DYSMENORRHEA	4 (3.7)	3 (2.7)	7 (3.2)	.721
EAR PAIN	4 (3.7)	3 (2.7)	7 (3.2)	.721
FLU SYNDROME	4 (3.7)	3 (2.7)	7 (3.2)	.721
INSOMNIA	4 (3.7)	5 (4.5)	9 (4.1)	1.00
PRURITUS	4 (3.7)	5 (4.5)	9 (4.1)	1.00
AGITATION	3 (2.8)	0	3 (1.4)	.122
BACK PAIN	3 (2.8)	5 (4.5)	8 (3.7)	.721
CHEST PAIN	3 (2.8)	2 (1.8)	5 (2.3)	.683
CONSTIPATION	3 (2.8)	2 (1.8)	5 (2.3)	.683
DYSPEPSIA	3 (2.8)	4 (3.6)	7 (3.2)	1.00
ECCHYMOSIS	3 (2.8)	2 (1.8)	5 (2.3)	.683
NECK PAIN	3 (2.8)	0	3 (1.4)	.122
SINUSITIS	3 (2.8)	2 (1.8)	5 (2.3)	.683
SOMNOLENCE	3 (2.8)	3 (2.7)	6 (2.7)	1.00
TREMOR	3 (2.8)	0	3 (1.4)	.122

Table 15

Treatment-Emergent Adverse Events
Incidence by Decreasing Frequency (Ordered by Fluoxetine)
All Randomized Patients
Study Periods III-V, B1Y-MC-HCJE

Event Classification	Flx (N=109) n (%)	Placebo (N=110) n (%)	Total (N=219) n (%)	p-Value*
PATIENTS WITH >= 1 TESS	101 (92.7)	87 (79.1)	188 (85.8)	.006
PATIENTS WITH NO TESS	8 (7.3)	23 (20.9)	31 (14.2)	.006
HEADACHE	37 (33.9)	21 (19.1)	58 (26.5)	.014
RHINITIS	34 (31.2)	29 (26.4)	63 (28.8)	.458
ABDOMINAL PAIN	22 (20.2)	22 (20.0)	44 (20.1)	1.00
PHARYNGITIS	21 (19.3)	14 (12.7)	35 (16.0)	.202
ACCIDENTAL INJURY	19 (17.4)	10 (9.1)	29 (13.2)	.076
COUGH INCREASED	16 (14.7)	9 (8.2)	25 (11.4)	.143
DIARRHEA	14 (12.8)	13 (11.8)	27 (12.3)	.840
RASH	13 (11.9)	10 (9.1)	23 (10.5)	.517
DIZZINESS	11 (10.1)	8 (7.3)	19 (8.7)	.483
NERVOUSNESS	11 (10.1)	6 (5.5)	17 (7.8)	.218
VOMITING	11 (10.1)	12 (10.9)	23 (10.5)	1.00
ANOREXIA	10 (9.2)	9 (8.2)	19 (8.7)	.815
ASTHENIA	10 (9.2)	7 (6.4)	17 (7.8)	.462
FEVER	10 (9.2)	8 (7.3)	18 (8.2)	.632
PAIN	10 (9.2)	12 (10.9)	22 (10.0)	.823
NAUSEA	9 (8.3)	11 (10.0)	20 (9.1)	.815
ABNORMAL DREAMS	7 (6.4)	3 (2.7)	10 (4.6)	.215
BACK PAIN	6 (5.5)	5 (4.5)	11 (5.0)	.768
DRY MOUTH	6 (5.5)	6 (5.5)	12 (5.5)	1.00
EAR PAIN	6 (5.5)	3 (2.7)	9 (4.1)	.332
INSOMNIA	6 (5.5)	5 (4.5)	11 (5.0)	.768
PRURITUS	6 (5.5)	6 (5.5)	12 (5.5)	1.00
EPISTAXIS	5 (4.6)	2 (1.8)	7 (3.2)	.280
HOSTILITY	5 (4.6)	5 (4.5)	10 (4.6)	1.00
INFECTION	5 (4.6)	5 (4.5)	10 (4.6)	1.00
PERSONALITY DISORDER	5 (4.6)	2 (1.8)	7 (3.2)	.280
SOMNOLENCE	5 (4.6)	4 (3.6)	9 (4.1)	.748
AGITATION	4 (3.7)	0	4 (1.8)	.060
ALLERGIC REACTION	4 (3.7)	2 (1.8)	6 (2.7)	.446
DYSMENORRHEA	4 (3.7)	4 (3.6)	8 (3.7)	1.00
DYSPEPSIA	4 (3.7)	5 (4.5)	9 (4.1)	1.00
ECCHYMOSIS	4 (3.7)	2 (1.8)	6 (2.7)	.446
FLU SYNDROME	4 (3.7)	3 (2.7)	7 (3.2)	.721
HYPERKINESIA	4 (3.7)	1 (0.9)	5 (2.3)	.212
PHOTOSENSITIVITY REACTION	4 (3.7)	1 (0.9)	5 (2.3)	.212
SINUSITIS	4 (3.7)	2 (1.8)	6 (2.7)	.446
AKATHISIA	3 (2.8)	0	3 (1.4)	.122
ASTHMA	3 (2.8)	0	3 (1.4)	.122
CHEST PAIN	3 (2.8)	2 (1.8)	5 (2.3)	.683
CONSTIPATION	3 (2.8)	6 (5.5)	9 (4.1)	.499
CONTACT DERMATITIS	3 (2.8)	0	3 (1.4)	.122
DEPRESSION	3 (2.8)	2 (1.8)	5 (2.3)	.683
MYALGIA	3 (2.8)	6 (5.5)	9 (4.1)	.499
NECK PAIN	3 (2.8)	1 (0.9)	4 (1.8)	.369
SPEECH DISORDER	3 (2.8)	2 (1.8)	5 (2.3)	.683
TREMOR	3 (2.8)	1 (0.9)	4 (1.8)	.369

Table 16

Adverse Events Leading to Discontinuation
Incidence by Decreasing Frequency (Ordered by Fluoxetine)
All Randomized Patients
Study Periods III-V
B1Y-MC-HCJE

Event Classification	Flx (N=109) n (%)	Placebo (N=110) n (%)	Total (N=219) n (%)	p-Value*
PATIENTS DISCONTINUED	11 (10.1)	11 (10.0)	22 (10.0)	1.00
HOSTILITY	1 (0.9)	1 (0.9)	2 (0.9)	1.00
RASH	1 (0.9)	1 (0.9)	2 (0.9)	1.00
ABDOMINAL PAIN	0	1 (0.9)	1 (0.5)	1.00
AGITATION	1 (0.9)	0	1 (0.5)	.498
ALOPECIA	0	1 (0.9)	1 (0.5)	1.00
ANXIETY	0	1 (0.9)	1 (0.5)	1.00
CONSTIPATION	1 (0.9)	0	1 (0.5)	.498
DEPRESSION	1 (0.9)	0	1 (0.5)	.498
DIZZINESS	0	1 (0.9)	1 (0.5)	1.00
ENDOMETRIAL HYPERPLASIA	1 (0.9)	0	1 (0.5)	.498
EUPHORIA	1 (0.9)	0	1 (0.5)	.498
HEADACHE	0	1 (0.9)	1 (0.5)	1.00
HYPERKINESIA	1 (0.9)	0	1 (0.5)	.498
INFECTION	0	1 (0.9)	1 (0.5)	1.00
INTENTIONAL INJURY	0	1 (0.9)	1 (0.5)	1.00
LYMPHOCYTOSIS	0	1 (0.9)	1 (0.5)	1.00
MANIC REACTION	1 (0.9)	0	1 (0.5)	.498
MIGRAINE	1 (0.9)	0	1 (0.5)	.498
NAUSEA	0	1 (0.9)	1 (0.5)	1.00
PERSONALITY DISORDER	1 (0.9)	0	1 (0.5)	.498

RMP.B1YP.JCLLIB2(AES3JEAB)
RMP.B1YO.HCJEREP(AES3JEAB)
* Frequencies are analyzed using a Fisher’s Exact test.
XAES0003

4.1.2. Serious Adverse Events

There were a total of 9 serious adverse events in this study. Six of these occurred after randomization to study drug. Of these 6 patients, 2 were on fluoxetine: 1 was hospitalized for suicidal ideation and 1 was hospitalized for swollen tonsils. The other 4 patients receiving placebo were hospitalized for the following reasons: appendicitis, self-mutilatoy behavior, kidney infection and aggressive behavior.

4.1.3. Subgroup Analysis

Subgroup analyses were performed for three stratification variables for solicited adverse events: age (<13 years, ≥13 years), gender and family history of depression. When analyzing the data using last of visits 5-10 as endpoint, there were 2 events that yielded a significant age group by treatment interaction: “Eating” and “Doing things with your hands”. Both of these events occurred more frequently in the placebo group for the older age group (obviously not a safety concern, but an interesting result). When using visits 5-15 as endpoint, similar results were noted for eating and doing things with your hands, however in addition to these two events, an interaction between age group and treatment was found for “Being Sad”. The younger children on fluoxetine were more likely to have trouble with being sad (51%) than those on placebo (30%) whereas in the older children, the percent of patients “sad” is roughly equal (see Table 17).

There were no interactions of interest between gender and treatment or between family history of depression and treatment for any solicited adverse events.

Similar subgroup analyses were performed for spontaneous adverse events. There were no subgroups that had any events such that statistically significantly differences between treatment groups were detected, other than headache. Headache, which was noted to be the only spontaneous adverse event occurring significantly more often in the fluoxetine group, occurred significantly more frequently in females on fluoxetine but not males. That is, there was a statistically significant difference between treatment groups for females but not for males. There were no other events for which this happened. Nor did this phenonemon happen for either the subgroup analysis for age group or family history. The overall incidence of TESS events however, was significantly higher for fluoxetine treated patients for females (not males), younger children (not older children) and patients without a history of depression (not those with a history). However, these differences were reasonably small (see Table 18).

Table 17

Treatment-Emergent Solicited Adverse Events
Side-Effects Checklist Subgroup Analysis by Age
All Randomized Patients
Study Periods III - IV, B1Y-MC-HCJE

SECL Event - Have you had trouble with:	AGE	Flx 20 N	Flx 20 n	Flx 20 (%)	Placebo N	Placebo n	Placebo (%)	p-Values: Homogeneity of Odds Ratio p-Value*	p-Values: Between Group Comparison p-Value**
01. EATING	8 - <13	61	19	(31.1)	61	14	(23.0)	.040	.415
	13 - <=18	48	12	(25.0)	49	21	(42.9)		.087
20. DOING THINGS WITH YOUR HANDS	8 - <13	61	12	(19.7)	61	8	(13.1)	.002	.464
	13 - <=18	48	1	(2.1)	49	11	(22.4)		.004

Study Periods III - V, B1Y-MC-HCJE

SECL Event - Have you had trouble with:	AGE	Flx N	Flx n	Flx (%)	Placebo N	Placebo n	Placebo (%)	p-Values: Homogeneity of Odds Ratio p-Value*	p-Values: Between Group Comparison p-Value**
31. BEING SAD	8 - <13	61	31	(50.8)	61	18	(29.5)	.064	.026
	13 - <=18	48	16	(33.3)	49	18	(36.7)		.832

Table 18

Treatment-Emergent Adverse Events
Subgroup Analysis
All Randomized Patients
Study Periods III-IV, B1Y-MC-HCJE

PATIENTS WITH >= 1 TESS

Gender	Flx 20 N	Flx 20 n (%)	Placebo N	Placebo n (%)	Total N	Total n (%)	p-Value*
Female	54	48 (88.9)	54	37 (68.5)	108	85 (78.7)	.017
Male	55	46 (83.6)	56	43 (76.8)	111	89 (80.2)	.476
Total	109	94 (86.2)	110	80 (72.7)	219	174 (79.5)	.019
AGE							
8 - < 13	61	53 (86.9)	61	44 (72.1)	122	97 (79.5)	.071
13 - < 18	48	41 (85.4)	49	36 (73.5)	97	77 (79.4)	.210
Total	109	94 (86.2)	110	80 (72.7)	219	174 (79.5)	.019
FAMILY HISTORY OF DEPRESSION							
No	41	37 (90.2)	39	26 (66.7)	80	63 (78.8)	.014
Yes	61	52 (85.2)	60	48 (80.0)	121	100 (82.6)	.481
Total	102	89 (87.3)	99	74 (74.7)	201	163 (81.1)	.030

Study Periods III-V, B1Y-MC-HCJE

Gender	Flx N	Flx n (%)	Placebo N	Placebo n (%)	Total N	Total n (%)	p-Value*
Female	54	52 (96.3)	54	41 (75.9)	108	93 (86.1)	.004
Male	55	49 (89.1)	56	46 (82.1)	111	95 (85.6)	.419
Total	109	101 (92.7)	110	87 (79.1)	219	188 (85.8)	.006
AGE							
8 - < 13	61	57 (93.4)	61	48 (78.7)	122	105 (86.1)	.034
13 - < 18	48	44 (91.7)	49	39 (79.6)	97	83 (85.6)	.147
Total	109	101 (92.7)	110	87 (79.1)	219	188 (85.8)	.006
FAMILY HISOTRY OF DEPRESSION							
NO	41	38 (92.7)	39	29 (74.4)	80	67 (83.8)	.035
YES	61	58 (95.1)	60	51 (85.0)	121	109 (90.1)	.075
Total	102	96 (94.1)	99	80 (80.8)	201	176 (87.6)	.005

4.2. Laboratory Analysis

Laboratory data was analyzed two ways. First, mean change from baseline to endpoint (last measurement from Visits 5 through Visit 15) was compared between treatment groups. Note that since laboratory analytes were not collected routinely at Visits 2 through Visit 14, baseline values will be those collected at Visit 1 and endpoint values will be those collected at Visit 15 or the visit of discontinuation if discontinued prior to Visit 15. Second, the incidence of treatment-emergent extreme values (using [redacted] Reference Ranges) was also compared between treatments for continuous laboratory analytes. Specifically, percentages of patients whose values changed from normal or low during baseline to high at any time during Study Period III through V were compared between treatment groups among patients with normal or low values during baseline. Similarly, percentages of patients whose values changed from normal or high during baseline to low at any time during Study Period III through V were compared between treatment groups for categorical laboratory analytes. For non-numeric laboratory analytes, the percentages of patients whose values changed from normal during baseline to abnormal at anytime during Study Period III through V were compared between treatment groups among patients with normal values during baseline.

The mean change analysis is given in Table 19. Statistically significant differences were detected for two labs, cholesterol and alkaline phosphatase. The fluoxetine patients experienced a slight increase in cholesterol while the placebo patients decreased, resulting in a significant difference. The alkaline phosphatase level decreased from baseline to endpoint for both the placebo and fluoxetine patients, however the decrease was quite dramatic for fluoxetine patients (roughly a 7 fold decrease over what the placebo group experienced). The categorical analysis for both of these labs did not detect a difference between the two treatment groups. There were no patients in the fluoxetine group that experienced an extreme low or high lab for alkaline phosphatase, while the placebo group had only 1 patient experience an extreme high and none experience an extreme low. For cholesterol extreme low values, there were 1/79 patients on fluoxetine and 3/74 patients on placebo (p=.339) that had such values. For cholesterol extreme high values, there were 8/78 patients on fluoxetine and 4/63 patients on placebo (p=.548). No labs had statistically significant differences between treatment groups when analyzing the treatment-emergent extreme values.

The analysis was also done for the subset of patients who entered Period V, i.e., who did not discontinue prior to visit 11. The results of the mean change from baseline analysis is the same as what is seen in Table 19. Again, the extreme value analysis did not reveal any statistically significant differences between groups.

Table 19

Laboratory Analysis
Change from Baseline to Endpoint
All Randomized Patients
Study Periods III-V, B1Y-MC-HCJE

Laboratory Test Group: Complete Blood Count

Lab Test	Lab Unit	Therapy	n	Baseline Mean	Baseline SD	Change to Endpoint Mean	Change to Endpoint SD	p-Values Therapy
HCT	1	Flx	88	0.401	0.029	-0.014	0.029	.523
		Placebo	71	0.403	0.031	-0.011	0.025	
HGB	mml/L-Fe	Flx	88	8.401	0.564	-0.212	0.400	.902
		Placebo	73	8.421	0.661	-0.204	0.451	
RBC	TI/L	Flx	88	4.714	0.319	-0.122	0.244	.451
		Placebo	73	4.778	0.348	-0.095	0.202	
MCHC	mml/L-Fe	Flx	88	21.051	0.956	0.134	1.218	.681
		Placebo	71	20.969	0.944	0.052	1.266	
MCH	fmol(Fe)	Flx	88	1.791	0.108	0.004	0.063	.330
		Placebo	73	1.767	0.107	-0.006	0.060	
WBC	GI/L	Flx	88	6.794	1.925	0.230	1.783	.827
		Placebo	73	6.767	1.879	0.161	2.202	
BANDS	GI/L	Flx	88	0.000	0.000	0.003	0.027	.494
		Placebo	73	0.000	0.000	0.009	0.074	
POLYS	GI/L	Flx	88	3.751	1.498	0.211	1.471	.889
		Placebo	73	3.678	1.423	0.174	1.895	
LYMPHS	GI/L	Flx	88	2.363	0.567	-0.012	0.530	.869
		Placebo	73	2.439	0.661	-0.027	0.643	
MONOS	GI/L	Flx	88	0.442	0.173	0.018	0.169	.511
		Placebo	73	0.455	0.163	-0.002	0.221	
EOSN	GI/L	Flx	88	0.194	0.205	0.006	0.171	.854
		Placebo	73	0.150	0.119	0.002	0.104	
BASO	GI/L	Flx	88	0.045	0.020	0.003	0.027	.640
		Placebo	73	0.045	0.020	0.005	0.031	
MCV	fL	Flx	88	85.170	4.305	-0.455	4.045	.945
		Placebo	71	84.394	4.856	-0.408	4.406	
PLTCT	GI/L	Flx	88	281.727	67.434	-1.239	44.353	.280
		Placebo	73	272.808	60.324	6.329	43.869	
ATLYMP	GI/L	Flx	88	0.000	0.000	0.000	0.000	.274
		Placebo	73	0.000	0.000	0.002	0.014	

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Table 19 (continued)

Laboratory Test Group: Blood Chemistry

Lab Test	Lab Unit	Therapy	n	Baseline Mean	Baseline SD	Change to Endpoint Mean	Change to Endpoint SD	p-Values Therapy
AST	U/L	Flx	86	25.035	8.879	-0.326	7.760	.621
		Placebo	75	25.613	6.476	-0.933	7.748	
ALT	U/L	Flx	86	19.453	14.829	-0.163	13.094	.921
		Placebo	75	20.480	8.916	-0.360	11.820	
CPK	U/L	Flx	86	126.465	79.854	15.395	80.020	.875
		Placebo	75	129.187	68.611	17.467	87.351	
ALKPH	U/L	Flx	84	221.429	93.843	-34.929	28.982	<.001
		Placebo	74	223.649	94.546	-5.081	39.230	
GGT	U/L	Flx	86	15.372	6.815	-0.895	4.574	.326
		Placebo	75	15.440	7.389	-0.067	6.079	
BUN	mmol/L	Flx	86	3.935	1.040	0.428	1.096	.232
		Placebo	75	4.217	0.948	0.219	1.106	
CREAT	umol/L	Flx	86	76.887	11.105	1.542	9.413	.618
		Placebo	75	75.317	11.007	2.239	8.104	
CALC	mmol/L	Flx	86	2.365	0.080	-0.030	0.092	.328
		Placebo	75	2.353	0.085	-0.016	0.095	
PHOS	mmol/L	Flx	83	1.486	0.206	0.000	0.187	.696
		Placebo	74	1.526	0.156	-0.012	0.189	
TPROT	g/L	Flx	86	73.709	4.270	-1.488	4.087	.136
		Placebo	75	72.507	4.394	-0.600	3.317	
ALBUM	g/L	Flx	86	42.942	2.578	-1.523	2.482	.403
		Placebo	75	42.547	2.835	-1.173	2.811	
NFGLU	mmol/L	Flx	84	4.944	0.606	0.057	0.947	.217
		Placebo	75	4.955	0.818	0.256	1.080	
UR AC	umol/L	Flx	86	272.501	71.856	5.602	46.212	.190
		Placebo	75	264.012	70.424	14.830	42.244	
CHOL	mmol/L	Flx	86	4.384	0.867	0.087	0.536	.014
		Placebo	75	4.286	0.915	-0.127	0.550	
T.BILI	umol/L	Flx	84	7.858	3.359	-0.346	2.652	.742
		Placebo	71	8.165	3.986	-0.169	3.996	

XLAS0006

Table 19 (continued)

Laboratory Test Group: Electrolytes

Lab Test	Lab Unit	Therapy	n	Baseline Mean	Baseline SD	Change to Endpoint Mean	Change to Endpoint SD	p-Values Therapy
SODIUM	mmol/L	Flx	86	139.593	1.990	-0.093	2.831	.340
		Placebo	75	139.253	2.302	0.333	2.801	
POTAS	mmol/L	Flx	83	4.193	0.331	-0.059	0.375	.419
		Placebo	74	4.184	0.307	-0.009	0.391	
CHLOR	mmol/L	Flx	86	102.512	2.340	0.651	3.044	.610
		Placebo	75	102.307	2.509	0.893	2.953	
BICARB	mmol/L	Flx	86	25.609	2.065	0.438	2.372	.386
		Placebo	74	25.809	1.969	0.768	2.407	

Laboratory Test Group: Thyroids

Lab Test	Lab Unit	Therapy	n	Baseline Mean	Baseline SD	Change to Endpoint Mean	Change to Endpoint SD	p-Values Therapy
T4-RIA	nmol/L	Flx	37	100.386	14.072	-2.574	13.282	.205
		Placebo	33	103.155	15.631	2.340	18.652	
TSH	mU/L	Flx	37	1.933	1.101	-0.401	1.014	.121
		Placebo	33	1.788	0.886	-0.051	0.832	
T3-TOT	nmol/L	Flx	37	1.947	0.354	-0.073	0.341	.264
		Placebo	33	1.900	0.370	0.027	0.395	
FTI	INDEX	Flx	37	2.651	0.277	-0.049	0.341	.492
		Placebo	33	2.748	0.356	0.015	0.430	
RT3U	1	Flx	37	0.341	0.027	0.005	0.017	.081
		Placebo	33	0.345	0.026	-0.002	0.020	

Laboratory Test Group: Urinalysis

Lab Test	Lab Unit	Therapy	n	Baseline Mean	Baseline SD	Change to Endpoint Mean	Change to Endpoint SD	p-Values Therapy
U-SPGR	NO UNITS	Flx	85	1.021	0.008	0.003	0.010	.588
		Placebo	75	1.024	0.007	0.003	0.008	
U-PH	U	Flx	85	5.882	0.878	0.082	1.126	.588
		Placebo	75	5.773	0.815	-0.013	1.097	

RMP.B1YP.JCLLIB2(LAS6JEAA)
RMP.B1Y0.HCJEREP(LAS6JEAA)
Note: n = Total number of patients in each treatment group having the variable in both baseline and postbaseline visits.

Note: Models:
FULL1 - Type III Sums of Squares from an analysis of variance (ANOVA): PROC GLM model=treatment.
Least-squares mean option in PROC GLM from the ANOVA using the mean square for error.

Table 19 (concluded)

Legend of Lab Test Code Abbreviations:

Abbrev.	Description
HCT	HEMATOCRIT
HGB	HEMOGLOBIN
RBC	ERYTHROCYTE COUNT
MCHC	MEAN CELL HEMOGLOBIN CONCENTRATION (MCHC)
MCH	MEAN CELL HEMOGLOBIN (MCH)
WBC	LEUKOCYTE COUNT
BANDS	BANDS
POLYS	NEUTROPHILS, SEGMENTED
LYMPHS	LYMPHOCYTES
MONOS	MONOCYTES
EOSN	EOSINOPHILS
BASO	BASOPHILS
MCV	MEAN CELL VOLUME (MCV)
PLTCT	PLATELET COUNT
ATLYMP	LYMPHOCYTES, ATYPICAL
U-SPGR	UA-SPECIFIC GRAVITY
U-PH	UA-PH
AST	AST/SGOT
ALT	ALT/SGPT
CPK	CREATINE PHOSPHOKINASE
ALKPH	ALKALINE PHOSPHATASE
GGT	GGT (GGPT/SGGT/YGGT)
T4-RIA	THYROXINE, TOTAL-T4
TSH	THYROID STIM. HORMONE
T3-TOT	T3, TOTAL (TRIIODOTHYRONINE)
FTI	FREE THYROXINE INDEX
RT3U	T3 % UPTAKE
BUN	UREA NITROGEN
CREAT	CREATININE
CALC	CALCIUM
PHOS	INORGANIC PHOSPHORUS
SODIUM	SODIUM
POTAS	POTASSIUM
CHLOR	CHLORIDE
TPROT	TOTAL PROTEIN
ALBUM	ALBUMIN
NFGLU	GLUCOSE, NON-FASTING
UR AC	URIC ACID
CHOL	CHOLESTEROL
BICARB	BICARBONATE, HCO3
T.BILI	BILIRUBIN, TOTAL

The mean change pattern observed for cholesterol is similar to what is reported in the CIB for adult patients, however, the alkaline phosphatase difference that was observed is not similar to what is reported for adults. For this reason, I investigated it further. Below in Table 20 is the alkaline phosphatase mean change to endpoint for all 3 pediatric studies. HCJW is an OCD trial 14 weeks in length and X065 is the [redacted] depression trial that is 8 weeks in length (from baseline to endpoint). The adult data given here is from the CIB for all depression trials pooled, and all OCD trials pooled.

As can be seen, the same pattern of decreased alkaline phosphatase is seen for all 3 pediatric studies while it is not seen for the adult population.

Table 20

Alkaline Phosphatase Change from Baseline to Endpoint for Different Studies

			-----Baseline------		Change to -----Endpoint-----		p-Values
Study	Therapy	n	Mean	SD	Mean	SD	Therapy
HCJE	Flx	84	221.429	93.843	-34.929	28.982	<.001
	Placebo	74	223.649	94.546	-5.081	39.230	
HCJW	Flx	69	209.957	83.774	-22.783	33.509	.002
	Placebo	28	187.571	81.854	1.857	31.570	
X065	Flx 20mg	33	194.8	72.0	-25.5	26.6	.006
	Placebo	33	168.5	72.6	-11.6	41.0	
Adult Patients Depression Trials	Flx	1534	68.6	26.7	0.0	12.7	<.001
	Placebo	895	75.9	34.5	-1.8	15.1	
OCD Trials	Flx	230	62.3	21.1	2.1	11.6	.002
	Placebo	80	64.2	18.4	-1.7	10.3	

Because alkaline phosphatase decreases as people get older, I was curious to see if the pattern was similar among children (<13 years old) and adolescents (≥13 years) in the HCJE study population. Subgroup analysis is given below in Table 21. As can be seen in the table, similar patterns are observed for both groups of patients.

Table 21
Age Subgroup Analysis for Alkaline Phosphatase

Strata	Therapy	Baseline N	Baseline Mean	Baseline SD	Change Mean	Change SD	Therapy p-Value[1]
8 - <13	Flx	48	254.0	68.5	-38.4	28.9	<.001
	Placebo	45	270.8	51.1	-3.7	46.6	
13 - <18	Flx	36	178.0	105.8	-30.3	28.8	.001
	Placebo	29	150.4	100.3	-7.2	24.2	

Note: There was no therapy by age group interaction (p=.301) nor a overall age group effect (p=.676).

4.3. Vital Sign Analysis

Vital signs were analyzed using a mean change to endpoint. Heart rate, blood pressure and temperature were measured at every visit. Height and weight were measured at baseline and Visit 15 (or discontinuation visit if it occurred prior to visit 15). Table 22 gives the analysis using last of visits 5-15 (Periods III-V) as endpoint.

There were no statistically significant differences seen between treatment groups for heart rate, blood pressure or temperature. There was a statistically significant difference detected for weight. The fluoxetine treated patients gained less weight than the placebo treated patients. There is also a trend seen for height. The fluoxetine group has a lower mean change in height (1.3) compared to the placebo group (2.3, p=0.064).

An additional analysis was done for this data for the subset of patients that entered Period V, i.e., those patients that did not discontinue prior to Visit 11. The pattern seen in Table 22 was also seen for that analysis, i.e., there was a significant difference in weight, and a trend in height.

Table 22

Vital Signs
Change from Baseline to Endpoint
All Randomized Patients
Study Periods III-V, B1Y-MC-HCJE

Variables Analyzed	Therapy	n	Baseline Mean	Baseline SD	Change to Endpoint Mean	Change to Endpoint SD	Therapy (Int*1) p-Values
HEIGHT	Flx	88	155.1	14.6	1.3	3.7	.064
	Placebo	75	153.3	12.4	2.3	3.4	
WEIGHT	Flx	91	56.5	19.0	1.2	2.7	.008
	Placebo	78	55.8	18.9	2.3	2.6	
SI_HR	Flx	109	79.5	13.1	-1.2	13.8	.390
	Placebo	105	79.8	11.3	0.3	11.3	
SI_SYSBP	Flx	109	109.2	10.4	0.3	10.4	.576
	Placebo	105	110.1	11.6	1.1	10.1	
SI_DIABP	Flx	109	65.8	9.0	0.3	8.8	.395
	Placebo	105	65.9	8.7	1.4	9.3	
TEMP	Flx	109	36.6	0.4	0.0	0.5	.649
	Placebo	105	36.6	0.5	-0.0	0.5	

RMP.B1YP.JCLLIB2(LAS6JEAC)
RMP.B1YO.HCJEREP(LAS6JEAC)
Note: n = Total number of patients in each treatment group having the variable in both baseline and postbaseline visits.

Note: Models:

FULL1 - *1 Type III Sums of Squares from an analysis of variance (ANOVA): PROC GLM model=treatment.
Least-squares mean option in PROC GLM from the ANOVA using the mean square for error.

4.4. ECG Analysis

An ECG was done at Visit 1 and Visit 15 (or discontinuation visit if earlier). The site then determined if the ECG was "acceptable" or "not acceptable". The ECGs were then collected and sent to an outside source [redacted] for interpretation. An ECG results worksheet was filled out by the [redacted] which recorded (among other things) if the ECG was considered normal or abnormal. There were 5 patients with ECGs considered abnormal that were randomized into the study. For all 5 of these patients, the ECGs were considered "acceptable" by the investigator. There were 2 patients who went from a normal ECG at baseline to an abnormal ECG during treatment. Both of these patients were on placebo and both were considered "acceptable" by the investigators. There was only 1 ECG considered unacceptable by an investigator, however, it was considered normal by [redacted] who noted "limb leads reversed, probably normal ECG".

Change from baseline to endpoint was analyzed for the following ECG parameters: Heart rate, RR interval, PR interval, QRS interval, QT interval and QTc interval. The results are presented in Table 23. There was a statistically significant difference detected between the groups for the QTC interval; the fluoxetine group had a greater mean change from endpoint than the placebo group. This data was also analyzed for those patients that entered Period V, i.e., that did not discontinue prior to visit 11. There were no statistically significant differences detected between the groups for that analysis.

Table 23

Electrocardiogram Measures
Change from Baseline to Endpoint
All Randomized Patients
Study Periods III-V, B1Y-MC-HCJE

Variables Analyzed	Therapy	n	Baseline Mean	Baseline SD	Change to Endpoint Mean	Change to Endpoint SD	p-Values Therapy
ECGHR	Flx	88	70.557	10.099	0.250	10.276	.908
	Placebo	73	73.658	12.160	0.452	11.846	
RR_INT	Flx	88	867.045	121.145	-5.114	123.707	.882
	Placebo	73	838.767	149.554	-8.219	141.797	
PR_INT	Flx	88	140.568	17.043	-0.909	14.435	.767
	Placebo	73	142.192	18.727	-0.274	12.244	
QRS_INT	Flx	88	81.477	6.166	-0.114	8.373	.670
	Placebo	73	81.781	7.700	0.411	6.960	
QT_INT	Flx	88	368.989	24.985	5.898	25.882	.070
	Placebo	73	365.959	22.801	-1.027	21.457	
QTC_INT	Flx	88	397.722	18.164	7.474	23.096	.049
	Placebo	73	402.200	18.550	0.589	20.323	

RMP.B1YP.JCLLIB2(LAS6JEAI)
RMP.B1YO.HCJEREP(LAS6JEAI)
Note: n = Total number of patients in each treatment group having the variable in both baseline and postbaseline visits.

Study B1Y-MC-HCJE
Unblinding record for interim results of the acute phase

Individual	Date of unblinding	Level of unblinding	Reason for unblinding
[redacted]	4/1/1999	Unblinded to a single patients therapy	Accidently unblinded by [redacted]
[redacted]	1/11/2000	Patient basis	PK analysis
[redacted]	1/11/2000	Patient basis	PK analysis
[redacted]	1/11/2000	Patient basis	PK analysis
[redacted]	1/11/2000	Patient basis	PK analysis
[redacted]	2/14/2000	Patient basis, summary analyses	Presentation to DMB
[redacted]	2/21/2000	Summary analyses	Statistical help for DMB preparation
Systems group:			
[redacted]	2/14/2000	Patient basis, summary analyses	Analysis for DMB/CSR
[redacted]	2/14/2000	Patient basis, summary analyses	Analysis for DMB/CSR
[redacted]	2/14/2000	Patient basis, summary analyses	Analysis for DMB/CSR
[redacted]	2/14/2000	Patient basis, summary analyses	Analysis for DMB/CSR
[redacted]	2/14/2000	Patient basis, summary analyses	Analysis for DMB/CSR
[redacted]	1/11/2000	Patient basis	Load analyst for data
[redacted]	3/24/2000	Patient basis, summary analyses	Working on ISS
[redacted]	3/20/2000	Patient basis, summary analyses	Additional Analysis for HCJE safety issues
Medical Writers:			
[redacted]	2/21/2000	Patient basis, summary analyses	Writing the CSR
[redacted]	2/21/2000	Patient basis, summary analyses	Writing the CSR
[redacted]	4/12/2000	Summary analyses	Writing the ISE
[redacted]	4/20/2000	Summary analyses	Writing the ISE
[redacted]	3/15/2000	Patient basis, summary analyses	Editorial review of CSR
DMB:			
[redacted]	2/29/20[redacted]	Sum[redacted]ry analyses	DMB assessment
[redacted]	2/29/20[redacted]	Sum[redacted]ry analyses	[redacted]B assessment
[redacted]	[redacted]/20[redacted]	Su[redacted] analyses	[redacted] assessm[redacted]t
Misc. others:			
[redacted]	[redacted]/20[redacted]	[redacted]ma[redacted]	[redacted]ting [redacted] (statistician)
[redacted]	[redacted]/20[redacted]	[redacted]ma[redacted]	[redacted]ng [redacted] (CRA)
[redacted]	[redacted]/20[redacted]	[redacted]	[redacted]ulti[redacted]Dr. Heiligenstein regarding safety

3/14/2000	Safety issues	Consulting with [redacted] regarding safety
3/30/2000	Summary analyses	LRL Senior Mngt Committee Designee
3/31/2000	ECG analysis	Consultant Cardiologist regarding ECG results
4/12/2000	Summary analyses	CSR peer review
4/12/2000	Summary analyses	CSR peer review
4/12/2000	Summary analyses	CSR peer review
4/7/2000	Summary analyses	AA: assisting with compiling report for reviewers
4/13/2000	Safety analysis	Statistical programmer for ISS
4/21/2000	Patient basis, summary analyses	Working on ISE (statistician)
4/24/2000	Summary analyses	Pediatric Project Leader
5/2/2000	Summary analyses, patient basis	Validating pt summaries/working on ISS
5/2/2000	Summary analyses	Collate CRFs/hand-off to CPC
5/5/2000	Safety analysis	Outside pediatric cardiologist consultant at [redacted]
5/5/2000	Safety analysis	Outside pediatric cardiologist consultant at [redacted]
5/10/2000	Summary analyses, patient basis	Clinical Team Leader

The DMB met on 4/27/2000 and agreed to unblind the following individuals in order to coordinate product team, regulatory and toxicology strategies across the fluoxetine and r-fluoxetine teams.

4/27/2000	Summary analyses	US regulatory director
4/27/2000	Summary analyses	r-fluoxetine team leader
4/27/2000	Summary analyses	r-fluoxetine medical director
4/27/2000	Summary analyses	toxicology director
4/27/2000	Summary analyses	fluoxetine toxicologist
4/27/2000	Summary analyses	r-fluoxetine toxicologist
4/27/2000	Summary analyses	legal
5/2/2000	Summary analyses	Re[redacted]latory VP
[redacted]	[redacted]fety analysis	To[redacted]statistician
[redacted]	[redacted]fety analysis	To[redacted]pediatric project
[redacted]	[redacted]fety analysis	To[redacted]pediatric project

Labeling Meeting

[redacted]	7/20/2000 Summary Analysis	Label development
	7/20/2000 Summary Analysis	Label development
	7/20/2000 Summary Analysis	Label development
	7/20/2000 Summary Analysis	Label development

Prozac Strategy Meeting

[redacted]	7/25/2000 Summary Analysis	Prozac Strategy development
	7/25/2000 Summary Analysis	Prozac Strategy development
	7/25/2000 Summary Analysis	Prozac Strategy development
	7/25/2000 Summary Analysis	Prozac Strategy development
	7/25/2000 Summary Analysis	Prozac Strategy development
	7/25/2000 Summary Analysis	Prozac Strategy development
	7/25/2000 Summary Analysis	Prozac Strategy development
[redacted]	6/13/2000 Summary Analysis	Peer review of ISE
	6/13/2000 Summary Analysis	Peer review of ISS

16.1.15
PK Dataset

Pharmacokinetic Dataset

Protocol	Patient Number	Investigator Number	Visit Number	Dose Date	Dose Time	Dose Amount (mg)	Dose Amount (mg/kg)	Time From First Dose (dy)	Sample Date	Sample Time	Fluoxetine Conc (ng/mL)	Fluoxetine Conc (ng/mL)/(mg/kg)
8031005	104	1	10	19980731	800	20	0.256351	58.208	19980731	1300	51.06	199.1797
8031005	110	1	8	19981124	800	20	0.469069	34.417	19981124	1800	181.72	387.406
8031005	114	1	10	19981229	1330	20	0.376859	62.224	19981229	1515	66.65	176.8568
8031005	118	1	10	19990119	730	20	0.415967	62.281	19990119	1430	109.58	263.4347
8031005	118	1	11	19990202	800	20	0.428082	76.26	19990202	1400	66.49	155.3207
8031005	124	1	15	19990420	700	20	0.773552	125.292	19990420	1500	291.16	376.3937
8031005	126	1	9	19990208	800	20	0.355584	39.983	19990208	950	120.14	337.8664
8031005	127	1	10	19990302	800	20	0.595844	61.271	19990302	1400	123.53	207.3194
8031005	127	1	11	19990319	700	20	0.595844	78.177	19990319	1145	82.1	137.7878
8031005	133	1	10	19990511	700	20	0.479266	62.292	19990511	1400	107.14	223.5503
8031005	133	1	11	19990525	700	20	0.464131	76.365	19990525	1545	138.85	299.1612
8031005	139	1	10	19990623	700	20	0.390199	63.417	19990623	1700	225.95	579.064
8031005	141	1	9	19990615	700	20	0.565288	48.417	19990615	1700	141.26	249.8904
8031005	142	1	10	19990701	1100	20	0.40084	58.09	19990702	1125	81.92	204.3706
8031005	150	1	10	19990720	800	20	0.612395	62.302	19990720	1515	435.01	710.342
8031005	150	1	15	19990927	700	20	0.587899	131.333	19990927	1600	401.11	682.2766
8031005	151	1	10	19990727	800	20	0.436559	62.229	19990727	1300	132.33	303.1206
8031005	151	1	11	19990809	700	20	0.404518	75.354	19990809	1600	78.81	194.8245
8031005	208	2	8	19990709	800	20	0.361414	40.174	19990709	1140	58.55	162.0028
8031005	302	3	9	19981003	1100	20	0.308339	53.938	19981005	1100	67.94	220.342
8031005	305	3	10	19981024	900	20	0.612395	60.146	19981024	1130	159.57	260.567
8031005	307	3	10	19981014	630	20	0.282644	63.177	19981014	1900	48.05	170.0019
8031005	319	3	10	19981202	1130	20	0.275578	62.302	19981202	1630	86.52	313.9585
8031005	326	3	10	19990112	630	20	0.218279	62.368	19990112	1840	78.67	360.4095
8031005	326	3	15	19990322	1730	20	0.207983	132.361	19990323	1830	45.17	217.1809

Pharmacokinetic Dataset (continued)

Protocol	Patient Number	Investigator Number	Visit Number	Dose Date	Dose Time	Dose Amount (mg)	Dose Amount (mg/kg)	Time From First Dose (dy)	Sample Date	Sample Time	Fluoxetine Conc (ng/mL)	Fluoxetine Conc (ng/mL)/(mg/kg)
8031005	334	3	10	19990329	730	20	0.246327	71.501	19990329	1941	46.07	187.0282
8031005	334	3	15	19990615	750	20	0.250525	149.51	19990615	1955	49.53	197.7046
8031005	346	3	10	19990523	2000	20	0.34994	63.65	19990524	1221	104.48	298.5654
8031005	346	3	15	19990806	2100	20	0.329048	138.596	19990807	1103	133.02	404.2569
8031005	353	3	10	19990707	800	20	0.34994	71.368	19990707	1735	115.85	331.0567
8031005	353	3	15	19990922	800	20	0.35274	148.421	19990922	1851	93.26	264.3877
8031005	354	3	10	19990908	745	20	0.19424	68.517	19990908	2000	69.81	359.401
8031005	354	3	15	19991117	645	20	0.19424	138.475	19991117	1900	77.87	400.896
8031005	355	3	10	19990826	1000	20	0.29395	65.066	19990826	1208	83.7	284.7426
8031005	355	3	15	19991103	715	20	0.295922	134.227	19991103	1600	104.23	352.2206
8031005	401	4	10	19980722	1325	20	0.279066	62	19980723	1325	125.99	451.47
8031005	401	4	12	19980813	1325	20	0.279066	84.076	19980814	1515	114.32	409.652
8031005	404	4	10	19980810	1544	20	0.397229	62	19980811	1544	93.03	234.1972
8031005	413	4	10	19981208	1300	20	0.196841	69.311	19981208	1620	38.33	194.7254
8031005	413	4	15	19990218	730	20	0.191706	141.207	19990218	1350	38.54	201.0367
8031005	415	4	10	19990119	700	20	0.218279	60.374	19990119	1605	116.73	534.7732
8031005	415	4	15	19990330	715	20	0.214041	130.328	19990330	1500	109.57	511.9112
8031005	416	4	10	19990225	700	20	0.304086	63.412	19990225	1700	62.52	205.5998
8031005	416	4	15	19990504	715	20	0.299949	131.339	19990504	1515	21.54	71.81229
8031005	419	4	10	19990409	630	20	.	62.417	19990409	1630	72.77	.
8031005	422	4	15	19990819	1100	20	0.544351	134.344	19990819	1645	208.15	382.3818
8031005	424	4	10	19990611	800	20	0.373665	55.271	19990611	1330	129.64	346.9419
8031005	424	4	15	19990825	600	20	0.34994	130.323	19990825	1445	75.5	215.7512
8031005	433	4	10	19990804	900	20	0.629892	69.125	19990804	1100	178.35	283.1437
8031005	810	8	10	19990514	700	20	0.50681	64.265	19990514	1540	119.67	236.1241
8031005	812	8	9	19990503	800	20	0.495421	48.115	19990503	1100	153.89	310.6248

Pharmacokinetic Dataset (continued)

Protocol	Patient Number	Investigator Number	Visit Number	Dose Date	Dose Time	Dose Amount (mg)	Dose Amount (mg/kg)	Time From First Dose (dy)	Sample Date	Sample Time	Fluoxetine Conc (ng/mL)	Fluoxetine Conc (ng/mL)/(mg/kg)
8031005	813	8	10	19990528	800	20	0.239633	65.271	19990528	1430	82	342.1901
8031005	814	8	10	19990625	800	20	0.207007	63.017	19990625	940	59.43	287.092
8031005	814	8	13	19990809	800	20	0.207007	108.01	19990809	930	11.82	57.09957
8031005	815	8	10	19990816	1100	20	0.380107	62.261	19990816	1700	139.14	366.0545
8031005	815	8	15	19991027	710	20	0.415967	134.032	19991027	1130	127.66	306.8997
8031005	901	9	10	19981221	800	20	0.272176	59.208	19981221	1245	44.2	162.3951
8031005	906	9	10	19990427	1330	20	0.314946	60.11	19990427	1545	46.46	147.5173
8031005	906	9	15	19990706	1155	20	0.290082	130.02	19990706	1335	15.57	53.67449
8031005	913	9	12	19990802	900	20	0.222689	80.167	19990802	1345	34.77	156.1369
8031005	915	9	15	19991110	745	20	0.279066	151.354	19991110	1800	59.96	214.8594
8031005	920	9	15	19991122	750	20	0.326611	128.385	19991122	1700	79.07	242.0925
8031005	1101	11	10	19980806	730	20	0.495421	63.229	19980806	1300	178.58	360.4612
8031005	1109	11	10	19980929	630	20	0.324209	61.398	19980929	1610	111.93	345.24
8031005	1109	11	11	19981013	700	20	0.319511	75.376	19981013	1539	104	325.4979
8031005	1129	11	10	19990302	730	20	0.383413	63.042	19990302	910	138.61	361.5165
8031005	1129	11	15	19990509	800	20	0.373665	132.354	19990510	1640	150.52	402.8209
8031005	1131	11	10	19990317	730	20	0.3644	68.066	19990317	927	59.88	164.3247
8031005	1137	11	10	19990518	720	20	0.52491	61.356	19990518	1600	160.35	305.4809
8031005	1137	11	15	19990802	700	20	0.489916	138.325	19990803	1515	121.9	248.8181
8031005	1141	11	10	19990609	1230	20	0.367437	61.097	19990609	1435	189.65	516.1428
8031005	1153	11	10	19990823	530	20	0.393683	67.092	19990823	1100	198.8	504.9753
8031005	1153	11	15	19991102	545	20	0.419928	138.283	19991102	1535	195.12	464.651
8031005	1156	11	10	19990921	800	20	0.565288	62.069	19990921	955	169.42	299.7057
8031005	1156	11	15	19991207	830	20	0.518735	139.074	19991207	1002	113.95	219.6691
8031005	1202	12	10	19980804	630	20	0.380107	60.385	19980804	1745	172.77	454.5295
8031005	1202	12	15	19981015	630	20	0.326611	132.427	19981015	1845	2.75	8.419808

Pharmacokinetic Dataset (continued)

Protocol	Patient Number	Investigator Number	Visit Number	Dose Date	Dose Time	Dose Amount (mg)	Dose Amount (mg/kg)	Time From First Dose (dy)	Sample Date	Sample Time	Fluoxetine Conc (ng/mL)	Fluoxetine Conc (ng/mL)/(mg/kg)
8031005	1204	12	10	19980904	700	20	0.288186	70.41	19980904	1650	28.63	99.34557
8031005	1205	12	15	19981230	1100	20	0.329048	146.167	19981230	1150	51.48	156.4513
8031005	1208	12	10	19981112	1415	20	0.361414	62.121	19981112	1450	131.85	364.8175
8031005	1208	12	15	19990128	1500	20	0.331522	139.173	19990128	1605	157.41	474.8098
8031005	1209	12	10	19981116	530	20	0.358475	58.396	19981116	1550	95.74	267.0756
8031005	1211	12	10	19981203	630	20	0.290082	69.319	19981203	1625	8.87	30.57757
8031005	1213	12	10	19990111	700	20	0.440925	67.424	19990111	1740	203	460.3963
8031005	1213	12	15	19990325	815	20	0.459296	140.389	19990325	1650	207.77	452.3659
8031005	1217	12	10	19990301	630	20	0.317212	73.448	19990301	1830	71.69	226.0004
8031005	1220	12	10	19990511	1545	20	0.376859	73.103	19990511	1620	22.26	59.06725
8031005	1225	12	10	19990817	645	20	0.22157	62.394	19990817	1730	71.65	323.3739
8031005	1225	12	15	19991028	1130	20	0.227281	134.328	19991028	1555	69.57	306.0973
8031005	1305	13	15	19990715	1330	20	0.31051	131.797	19990715	1445	81.23	261.6017
8031005	1503	15	10	19990226	745	20	0.29395	63.029	19990226	845	20.64	70.2161
8031005	1510	15	10	19990713	745	20	0.265617	60.085	19990713	910	37.01	139.3359
8031005	1510	15	15	19990928	630	20	0.244958	137.078	19990928	900	111.44	454.935
8031005	1515	15	10	19990812	830	20	0.227281	68.087	19990812	935	55.71	245.1154
8031005	1516	15	10	19990819	715	20	0.367437	62.01	19990819	815	217.09	590.8222
8031005	1516	15	15	19991028	750	20	0.34994	132.051	19991028	915	203.73	582.1854
8031005	1601	16	10	19990212	800	20	0.367437	64.271	19990212	1600	131.6	358.1565
8031005	1601	16	15	19990428	730	20	0.380107	139.104	19990428	1200	102.02	268.3979
8031005	1602	16	10	19990222	1130	20	0.495421	67.349	19990222	1645	210.3	424.4876
8031005	1603	16	8	19990221	730	20	0.445378	31.292	19990222	1430	218.09	489.6736

Pharmacokinetic Dataset (continued)

Protocol	Patient Number	Investigator Number	Visit Number	Dose Date	Dose Time	Dose Amount (mg)	Dose Amount (mg/kg)	Time From First Dose (dy)	Sample Date	Sample Time	Fluoxetine Conc (ng/mL)	Fluoxetine Conc (ng/mL)/(mg/kg)
8031005	1604	16	10	19990413	900	20	0.239633	62.198	19990413	1300	124.47	519.4195
8031005	1605	16	10	19990416	700	20	0.459296	62.375	19990416	1630	149.46	325.4108
8031005	1605	16	15	19990702	800	20	0.423966	139.333	19990702	1530	137.84	325.1205
8031005	1606	16	10	19990507	700	20	0.565288	66.264	19990507	1320	177.26	313.5748
8031005	1609	16	10	19990907	800	20	0.445378	68.25	19990907	1400	153.88	345.504
8031005	1609	16	15	19991117	800	20	0.423966	139.389	19991117	1720	132.89	313.445
8031005	1652	16	10	19990610	830	20	0.551156	64.094	19990610	1100	221.65	402.155
8031005	1652	16	11	19990621	900	20	0.512703	75.344	19990621	1700	170.23	332.0246
8031005	1654	16	10	19990614	900	20	0.40084	62.333	19990614	1700	94.99	236.9771
8031005	1658	16	10	19990708	1215	20	0.259367	64.071	19990708	1400	47.72	183.9861
8031005	1658	16	13	19990819	1200	20	0.251957	106.113	19990819	1500	88.4	350.8537
8031005	1659	16	10	19990714	900	20	0.216139	64.139	19990714	1105	38.31	177.2467
8031005	1667	16	11	19990913	730	20	0.629892	80.094	19990913	1030	217.02	344.5352
8031005	1701	17	10	19990616	1200	20	0.277311	62.212	19990616	1550	48	173.0908
8031005	1701	17	15	19990827	930	20	0.272176	134.021	19990827	1115	29.94	110.0025
8031005	1702	17	10	19990715	1030	20	0.612395	62.217	19990715	1400	246.18	401.9953
8031005	1702	17	15	19990924	830	20	0.551156	133.269	19990924	1515	232.51	421.859
8031005	1904	19	10	19990325	1450	20	0.440925	60.913	19990325	1520	99.25	225.0952
8031005	1905	19	10	19990330	630	20	0.239633	63.377	19990330	1525	33.26	138.7956
8031005	1905	19	15	19990615	545	20	0.22382	140.155	19990615	1005	23.67	105.7548
8031005	1906	19	10	19990316	730	20	0.479266	69.35	19990316	1550	244.18	509.4877
8031005	1906	19	15	19990604	730	20	0.474112	149.083	19990604	925	118.29	249.4978
8031005	1915	19	10	19990524	715	20	0.326611	61.295	19990524	1420	54.56	167.049
8031005	1919	19	10	19990708	745	20	0.397229	64.294	19990708	1440	136.29	343.1016

Pharmacokinetic Dataset (continued)

Protocol	Patient Number	Investigator Number	Visit Number	Dose Date	Dose Time	Dose Amount (mg)	Dose Amount (mg/kg)	Time From First Dose (dy)	Sample Date	Sample Time	Fluoxetine Conc (ng/mL)	Fluoxetine Conc (ng/mL)/(mg/kg)
8031005	1919	19	15	19990927	730	20	0.419928	145.217	19990927	1250	138.56	329.9612
8031005	1921	19	10	19990719	2100	20	0.580164	66.736	19990720	1440	128.74	221.9028
8031005	1924	19	10	19990816	715	20	0.24911	67.238	19990817	1420	70.83	284.3323
8031005	1924	19	15	19991024	1000	20	0.239633	136.151	19991025	1215	49.5	206.566
8031005	2202	22	10	19990615	1800	20	0.831933	74.059	19990616	1625	358.62	431.0683
8031005	2204	22	10	19990610	1200	20	0.383413	64.111	19990610	1640	24.21	63.14346
8031005	2205	22	10	19990714	1330	20	0.40084	67.258	19990714	1703	127.55	318.2064
8031005	2208	22	10	19990813	715	20	0.428082	62.065	19990813	930	97.08	226.7789
8031005	2208	22	15	19991021	1000	20	0.397229	131.341	19991021	1607	119.18	300.0282
8031005	2214	22	10	19990909	630	20	0.367437	62.351	19990909	1555	62.88	171.1313
8031005	2216	22	10	19990916	620	20	0.297922	68.401	19990916	1555	158.93	533.4618
8031005	2216	22	15	19991208	615	20	0.286315	151.394	19991208	1545	177.4	619.5981
8031005	2220	22	10	19990924	715	20	0.329048	63.311	19990924	1528	174.69	530.8949
8031005	2220	22	14	19991119	930	20	0.304086	119.177	19991119	1215	186.34	612.7874

Pharmacokinetic Dataset (continued)

Protocol	Patient Number	Investigator Number	Visit Number	Norfluoxetine Conc (ng/mL)	Norfluoxetine Conc (ng/mL)/(mg/kg)	Time From First Dose (hr)	Time From Recent Dose (hr)	Gender	Visit Date	Treatment Group	Dose Therapy Received	Weight (kg)
8031005	104	1	10	119.03	464.3235	1397	5	F	19980731	162620	162620	78.01788764
8031005	110	1	8	125.85	268.2976	826	10	M	19981124	162620	162620	42.63768278
8031005	114	1	10	166.03	440.5632	1493.383	1.75	F	19981229	162620	162620	53.07030729
8031005	118	1	10	220.32	529.658	1494.75	7	M	19990119	162620	162620	48.08079122
8031005	118	1	11	237.11	553.8891	1830.25	6	M	19990202	162620	162620	46.72001411
8031005	124	1	15	343.55	444.1202	3007	8	F	19990420	162620	162620	25.85476509
8031005	126	1	9	138.1	388.3749	959.583	1.833	F	19990208	162620	162620	56.24545388
8031005	127	1	10	183.78	308.4365	1470.5	6	F	19990302	162620	162620	33.56583538
8031005	127	1	11	167.09	280.4258	1876.25	4.75	F	19990319	162620	162620	33.56583538
8031005	133	1	10	192.65	401.969	1495	7	F	19990511	162620	162620	41.73049804
8031005	133	1	11	215.96	465.2996	1832.75	8.75	F	19990525	162620	162620	43.09127515
8031005	139	1	10	151.01	387.008	1522	10	M	19990623	162620	162620	51.25593781
8031005	141	1	9	191.53	338.8185	1162	10	M	19990615	162620	162620	35.38020486
8031005	142	1	10	184.35	459.9086	1394.167	24.417	M	19990702	162620	162620	49.8951607
8031005	150	1	10	198.02	323.3533	1495.25	7.25	F	19990720	162620	162620	32.65865064
8031005	150	1	15	186.56	317.3332	3152	9	F	19990927	162620	162620	34.01942775
8031005	151	1	10	212.34	486.3948	1493.5	5	M	19990727	162620	162620	45.81282937
8031005	151	1	11	192.87	476.7898	1808.5	9	M	19990809	162620	162620	49.44156833
8031005	208	2	8	80.07	221.5468	964.167	3.667	M	19990709	162620	162620	55.33826914
8031005	302	3	9	147.86	479.5374	1294.5	48	F	19981005	162620	162620	64.86370891
8031005	305	3	10	239.95	391.8222	1443.5	2.5	M	19981024	162620	162620	32.65865064
8031005	307	3	10	97.49	344.9216	1516.25	12.5	M	19981014	162620	162620	70.76040972
8031005	319	3	10	93.44	339.0694	1495.25	5	F	19981202	162620	162620	72.5747792
8031005	326	3	10	132.96	609.1274	1496.833	12.167	F	19990112	162620	162620	91.62565873
8031005	326	3	15	106.33	511.2431	3176.667	25	F	19990323	162620	162620	96.16158243

Pharmacokinetic Dataset (continued)

Protocol	Patient Number	Investigator Number	Visit Number	Norfluoxetine Conc (ng/mL)	Norfluoxetine Conc (ng/mL)/(mg/kg)	Time From First Dose (hr)	Time From Recent Dose (hr)	Gender	Visit Date	Treatment Group	Dose Therapy Received	Weight (kg)
8031005	334	3	10	89.5	363.3388	1716.017	12.183	M	19990329	162620	162620	81.19303422
8031005	334	3	15	94.13	375.7305	3588.25	12.083	M	19990615	162620	162620	79.83225712
8031005	346	3	10	141.68	404.8693	1527.6	16.35	F	19990524	162620	162620	57.15263862
8031005	346	3	15	160.77	488.5911	3326.3	14.05	F	19990807	162620	162620	60.78137758
8031005	353	3	10	115.3	329.485	1712.833	9.583	M	19990707	162620	162620	57.15263862
8031005	353	3	15	103.53	293.5026	3562.1	10.85	M	19990922	162620	162620	56.69904625
8031005	354	3	10	102.56	528.0069	1644.4	12.25	F	19990908	162620	162620	102.965468
8031005	354	3	15	105.23	541.7528	3323.4	12.25	F	19991117	162620	162620	102.965468
8031005	355	3	10	188.72	642.0146	1561.583	2.133	F	19990826	162620	162620	68.0388555
8031005	355	3	15	201.6	681.2595	3221.45	8.75	F	19991103	162620	162620	67.58526313
8031005	401	4	10	129.05	462.4352	1488	24	M	19980723	162620	162620	71.66759446
8031005	401	4	12	140.31	502.784	2017.833	25.833	M	19980814	162620	162620	71.66759446
8031005	404	4	10	174.66	439.6957	1488	24	M	19980811	162620	162620	50.34875307
8031005	413	4	10	134.47	683.1391	1663.467	3.333	F	19981208	162620	162620	101.6046909
8031005	413	4	15	126.29	658.7681	3388.967	6.333	F	19990218	162620	162620	104.3262451
8031005	415	4	10	79.54	364.3952	1448.967	9.083	F	19990119	162620	162620	91.62565873
8031005	415	4	15	74.02	345.8215	3127.883	7.75	F	19990330	162620	162620	93.44002821
8031005	416	4	10	131.37	432.0161	1521.883	10	F	19990225	162620	162620	65.77089365
8031005	416	4	15	105.7	352.3936	3152.133	8	F	19990504	162620	162620	66.67807839
8031005	419	4	10	199.6	.	1498	10	F	19990409	162620	162620	.
8031005	422	4	15	194.12	356.608	3224.25	5.75	F	19990819	162620	162620	36.74098197
8031005	424	4	10	152.24	407.4239	1326.5	5.5	F	19990611	162620	162620	53.52389966
8031005	424	4	15	128.03	365.8626	3127.75	8.75	F	19990825	162620	162620	57.15263862
8031005	433	4	10	226.04	358.8551	1659	2	F	19990804	162620	162620	31.7514659
8031005	810	8	10	143.17	282.4926	1542.367	8.667	M	19990514	162620	162620	39.46253619
8031005	812	8	9	128.9	260.1829	1154.75	3	M	19990503	162620	162620	40.36972093

Pharmacokinetic Dataset (continued)

Protocol	Patient Number	Investigator Number	Visit Number	Norfluoxetine Conc (ng/mL)	Norfluoxetine Conc (ng/mL)/(mg/kg)	Time From First Dose (hr)	Time From Recent Dose (hr)	Gender	Visit Date	Treatment Group	Dose Therapy Received	Weight (kg)
8031005	813	8	10	94.71	395.2295	1566.5	6.5	M	19990528	162620	162620	83.46099607
8031005	814	8	10	138.59	669.4949	1512.417	1.667	F	19990625	162620	162620	96.6151748
8031005	814	8	13	114.32	552.2523	2592.25	1.5	F	19990809	162620	162620	96.6151748
8031005	815	8	10	103.25	271.6338	1494.267	6	M	19990816	162620	162620	52.61671492
8031005	815	8	15	99.89	240.1395	3216.767	4.333	M	19991027	162620	162620	48.08079122
8031005	901	9	10	147.42	541.6356	1421	4.75	F	19981221	162620	162620	73.48196394
8031005	906	9	10	113.66	360.8872	1442.65	2.25	F	19990427	162620	162620	63.5029318
8031005	906	9	15	66.43	229.0043	3120.483	1.667	F	19990706	162620	162620	68.94604024
8031005	913	9	12	120.8	542.4602	1924	4.75	M	19990802	162620	162620	89.81128925
8031005	915	9	15	69.33	248.4357	3632.5	10.25	M	19991110	162620	162620	71.66759446
8031005	920	9	15	194.3	594.8977	3081.25	9.167	F	19991122	162620	162620	61.23496995
8031005	1101	11	10	239.52	483.4678	1517.5	5.5	F	19980806	162620	162620	40.36972093
8031005	1109	11	10	107	330.0338	1473.55	9.667	F	19980929	162620	162620	61.68856232
8031005	1109	11	11	101.58	317.9238	1809.033	8.65	F	19981013	162620	162620	62.59574706
8031005	1129	11	10	266.11	694.0564	1513	1.667	M	19990302	162620	162620	52.16312255
8031005	1129	11	15	231.69	620.0476	3176.5	32.667	M	19990510	162620	162620	53.52389966
8031005	1131	11	10	85.84	235.565	1633.583	1.95	M	19990317	162620	162620	54.88467677
8031005	1137	11	10	235.53	448.7054	1472.55	8.667	M	19990518	162620	162620	38.10175908
8031005	1137	11	15	231.64	472.8156	3319.8	32.25	M	19990803	162620	162620	40.8233133
8031005	1141	11	10	116.97	318.3402	1466.333	2.083	F	19990609	162620	162620	54.4310844
8031005	1153	11	10	143.84	365.3705	1610.2	5.5	F	19990823	162620	162620	50.80234544
8031005	1153	11	15	149.84	356.823	3318.783	9.833	F	19991102	162620	162620	47.62719885
8031005	1156	11	10	76.62	135.5416	1489.667	1.917	F	19990921	162620	162620	35.38020486
8031005	1156	11	15	47.13	90.85569	3337.783	1.533	F	19991207	162620	162620	38.55535145
8031005	1202	12	10	174.66	459.5018	1449.25	11.25	F	19980804	162620	162620	52.61671492
8031005	1202	12	15	65.71	201.1875	3178.25	12.25	F	19981015	162620	162620	61.23496995

Pharmacokinetic Dataset (continued)

Protocol	Patient Number	Investigator Number	Visit Number	Norfluoxetine Conc (ng/mL)	Norfluoxetine Conc (ng/mL)/(mg/kg)	Time From First Dose (hr)	Time From Recent Dose (hr)	Gender	Visit Date	Treatment Group	Dose Therapy Received	Weight (kg)
8031005	1204	12	10	42.79	148.4805	1689.833	9.833	M	19980904	162620	162620	69.39963261
8031005	1205	12	15	139.33	423.4335	3508	0.833	M	19981230	162620	162620	60.78137758
8031005	1208	12	10	82.69	228.7961	1490.9	0.583	M	19981112	162620	162620	55.33826914
8031005	1208	12	15	90.66	273.4659	3340.15	1.083	M	19990128	162620	162620	60.32778521
8031005	1209	12	10	179.52	500.7877	1401.5	10.333	F	19981116	162620	162620	55.79186151
8031005	1211	12	10	75.23	259.3405	1663.667	9.917	F	19981203	162620	162620	68.94604024
8031005	1213	12	10	260.1	589.8969	1618.167	10.667	M	19990111	162620	162620	45.359237
8031005	1213	12	15	255.69	556.6994	3369.333	8.583	M	19990325	162620	162620	43.54486752
8031005	1217	12	10	133.75	421.6425	1762.75	12	M	19990301	162620	162620	63.04933943
8031005	1220	12	10	93.05	246.9096	1754.467	0.583	F	19990511	162620	162620	53.07030729
8031005	1225	12	10	133.6	602.9694	1497.467	10.75	M	19990817	162620	162620	90.26488162
8031005	1225	12	15	133.88	589.0514	3223.883	4.417	M	19991028	162620	162620	87.99691977
8031005	1305	13	15	82.93	267.0765	3163.133	1.25	M	19990715	162620	162620	64.41011654
8031005	1503	15	10	41.77	142.0991	1512.7	1	M	19990226	162620	162620	68.0388555
8031005	1510	15	10	31.57	118.8553	1442.05	1.417	F	19990713	162620	162620	75.29633342
8031005	1510	15	15	61.29	250.2061	3289.883	2.5	F	19990928	162620	162620	81.64662659
8031005	1515	15	10	124.4	547.3408	1634.083	1.083	F	19990812	162620	162620	87.99691977
8031005	1516	15	10	209.07	568.9953	1488.233	1	F	19990819	162620	162620	54.4310844
8031005	1516	15	15	208.81	596.7021	3169.233	1.417	F	19991028	162620	162620	57.15263862
8031005	1601	16	10	208.25	566.7637	1542.5	8	M	19990212	162620	162620	54.4310844
8031005	1601	16	15	188	494.5971	3338.5	4.5	M	19990428	162620	162620	52.61671492
8031005	1602	16	10	145.98	294.6586	1616.383	5.25	F	19990222	162620	162620	40.36972093
8031005	1603	16	8	67.07	150.5911	751	31	M	19990222	162620	162620	44.90564463

Pharmacokinetic Dataset (continued)

Protocol	Patient Number	Investigator Number	Visit Number	Norfluoxetine Conc (ng/mL)	Norfluoxetine Conc (ng/mL)/(mg/kg)	Time From First Dose (hr)	Time From Recent Dose (hr)	Gender	Visit Date	Treatment Group	Dose Therapy Received	Weight (kg)
8031005	1604	16	10	173.66	724.6918	1492.75	4	M	19990413	162620	162620	83.46099607
8031005	1605	16	10	105.12	228.8718	1497	9.5	M	19990416	162620	162620	43.54486752
8031005	1605	16	15	90.67	213.8615	3344	7.5	M	19990702	162620	162620	47.17360648
8031005	1606	16	10	293.45	519.1161	1590.333	6.333	M	19990507	162620	162620	35.38020486
8031005	1609	16	10	183.21	411.3582	1638	6	F	19990907	162620	162620	44.90564463
8031005	1609	16	15	187.22	441.5921	3345.333	9.333	F	19991117	162620	162620	47.17360648
8031005	1652	16	10	104.96	190.4362	1538.25	2.5	M	19990610	162620	162620	36.2873896
8031005	1652	16	11	89.25	174.0774	1808.25	8	M	19990621	162620	162620	39.00894382
8031005	1654	16	10	126.24	314.9383	1496	8	M	19990614	162620	162620	49.8951607
8031005	1658	16	10	87.17	336.087	1537.7	1.75	F	19990708	162620	162620	77.1107029
8031005	1658	16	13	142.31	564.8189	2546.7	3	F	19990819	162620	162620	79.37866475
8031005	1659	16	10	82.27	380.6339	1539.333	2.083	M	19990714	162620	162620	92.53284347
8031005	1667	16	11	198.35	314.8952	1922.25	3	M	19990913	162620	162620	31.7514659
8031005	1701	17	10	106.7	384.7665	1493.083	3.833	M	19990616	162620	162620	72.12118683
8031005	1701	17	15	95.21	349.8109	3216.5	1.75	M	19990827	162620	162620	73.48196394
8031005	1702	17	10	229.68	375.0519	1493.2	3.5	M	19990715	162620	162620	32.65865064
8031005	1702	17	15	215.18	390.416	3198.45	6.75	M	19990924	162620	162620	36.2873896
8031005	1904	19	10	145.04	328.9452	1461.917	0.5	M	19990325	162620	162620	45.359237
8031005	1905	19	10	74.69	311.6851	1521.05	8.917	F	19990330	162620	162620	83.46099607
8031005	1905	19	15	70.54	315.1646	3363.717	4.333	F	19990615	162620	162620	89.35769688
8031005	1906	19	10	101.72	212.2413	1664.4	8.333	M	19990316	162620	162620	41.73049804
8031005	1906	19	15	58.75	123.9158	3577.983	1.917	M	19990604	162620	162620	42.18409041
8031005	1915	19	10	140.65	430.6349	1471.083	7.083	F	19990524	162620	162620	61.23496995
8031005	1919	19	10	210.98	531.129	1543.05	6.917	F	19990708	162620	162620	50.34875307

Pharmacokinetic Dataset (continued)

Protocol	Patient Number	Investigator Number	Visit Number	Norfluoxetine Conc (ng/mL)	Norfluoxetine Conc (ng/mL)/(mg/kg)	Time From First Dose (hr)	Time From Recent Dose (hr)	Gender	Visit Date	Treatment Group	Dose Therapy Received	Weight (kg)
8031005	1919	19	15	226.58	539.5685	3485.217	5.333	F	19990927	162620	162620	47.62719885
8031005	1921	19	10	148.99	256.8068	1601.667	17.667	F	19990720	162620	162620	34.47302012
8031005	1924	19	10	94.03	377.4639	1613.717	31.083	M	19990817	162620	162620	80.28584948
8031005	1924	19	15	73.46	306.5522	3267.633	26.25	M	19991025	162620	162620	83.46099607
8031005	2202	22	10	254.29	305.6616	1777.417	22.417	F	19990616	162620	162620	24.04039561
8031005	2204	22	10	118.57	309.2491	1538.667	4.667	M	19990610	162620	162620	52.16312255
8031005	2205	22	10	139.25	347.3951	1614.183	3.55	F	19990714	162620	162620	49.8951607
8031005	2208	22	10	161.27	376.7268	1489.567	2.25	M	19990813	162620	162620	46.72001411
8031005	2208	22	15	187.5	472.0196	3152.183	6.117	M	19991021	162620	162620	50.34875307
8031005	2214	22	10	144.48	393.2102	1496.417	9.417	M	19990909	162620	162620	54.4310844
8031005	2216	22	10	85.9	288.3305	1641.633	9.583	F	19990916	162620	162620	67.13167076
8031005	2216	22	15	105.01	366.7644	3633.467	9.5	F	19991208	162620	162620	69.85322498
8031005	2220	22	10	190.97	580.371	1519.467	8.217	F	19990924	162620	162620	60.78137758
8031005	2220	22	14	218.19	717.5276	2860.25	2.75	F	19991119	162620	162620	65.77089365

Pharmacokinetic Dataset (continued)

Protocol	Patient Number	Investigator Number	Visit Number	BMI (kg/cm^2)	Age (yrs)	Age Category	Height (cm)	Ethnic Origin	Origin Category	Smoking History (yrs)	Smoking Amount (smokes/day)	Alcohol Amount (drinks/wk)	Caffeine Amount (drinks/dy)
8031005	104	1	10	22.08327	11.36756	1	187.96	2	2	0	0	0	1.5
8031005	110	1	8	18.35793	11.36756	1	152.4	1	1	0	0	0	0.5
8031005	114	1	10	17.78961	14.19576	2	172.72	1	1	0	0	0	2.5
8031005	118	1	10	22.93794	11.44422	1	144.78	1	1	1	0.5	0	2
8031005	118	1	11	22.28876	11.44422	1	144.78	1	1	1	0.5	0	2
8031005	124	1	15	16.69095	8.260096	1	124.46	1	1	0	0	0	1.5
8031005	126	1	9	20.01392	15.37029	2	167.64	1	1	1	4	0.5	6.5
8031005	127	1	10	20.00275	9.322382	1	129.54	1	1	0	0	0	0.5
8031005	127	1	11	20.00275	9.322382	1	129.54	1	1	0	0	0	0.5
8031005	133	1	10	16.2969	12.38877	1	160.02	1	1	0	0	0	3.5
8031005	133	1	11	16.82832	12.38877	1	160.02	1	1	0	0	0	3.5
8031005	139	1	10	22.823	8.621492	1	149.86	1	1	0	0	0	3
8031005	141	1	9	15.23317	12.62697	1	152.4	1	1	0	0	0	2
8031005	142	1	10	20.7841	11.69884	1	154.94	1	1	0	0	0	3.5
8031005	150	1	10	16.1419	10.86653	1	142.24	1	1	0	0	0	1
8031005	150	1	15	16.81448	10.86653	1	142.24	1	1	0	0	0	1
8031005	151	1	10	22.6435	10.39014	1	142.24	1	1	0	0	0	3
8031005	151	1	11	24.43705	10.39014	1	142.24	1	1	0	0	0	3
8031005	208	2	8	23.05146	12.78303	1	154.94	2	2	0	0	0	1
8031005	302	3	9	24.54564	17.24846	2	162.56	1	1	2	3	3	1
8031005	305	3	10	15.58049	11.70705	1	144.78	1	1	0	0	0	2
8031005	307	3	10	25.1788	15.34565	2	167.64	1	1	2	15	0	7
8031005	319	3	10	22.95737	17.05133	2	177.8	1	1	1	0.5	1.5	0.5
8031005	326	3	10	32.60332	16.26831	2	167.64	1	1	0	0	0	0.5
8031005	326	3	15	34.21734	16.26831	2	167.64	1	1	0	0	0	0.5

Pharmacokinetic Dataset (continued)

Protocol	Patient Number	Investigator Number	Visit Number	BMI (kg/cm^2)	Age (yrs)	Age Category	Height (cm)	Ethnic Origin	Origin Category	Smoking History (yrs)	Smoking Amount (smokes/day)	Alcohol Amount (drinks/wk)	Caffeine Amount (drinks/dy)
8031005	334	3	10	25.68356	13.74127	2	177.8	1	1	0	0	0	1
8031005	334	3	15	25.25311	13.74127	2	177.8	1	1	0	0	0	1
8031005	346	3	10	23.80725	11.69336	1	154.94	1	1	0	0	0	0
8031005	346	3	15	25.31882	11.69336	1	154.94	1	1	0	0	0	0
8031005	353	3	10	20.33672	16.01916	2	167.64	2	2	0	0	0	0.5
8031005	353	3	15	20.17532	16.01916	2	167.64	2	2	0	0	0	0.5
8031005	354	3	10	35.55286	16.59959	2	170.18	2	2	0	0	0	0.5
8031005	354	3	15	35.55286	16.59959	2	170.18	2	2	0	0	0	0.5
8031005	355	3	10	39.00164	12.10404	1	132.08	1	1	0	0	0	1
8031005	355	3	15	38.74163	12.10404	1	132.08	1	1	0	0	0	1
8031005	401	4	10	28.89828	12.78029	1	157.48	1	1	0	0	0	3
8031005	401	4	12	28.89828	12.78029	1	157.48	1	1	0	0	0	3
8031005	404	4	10	17.91568	15.63587	2	167.64	1	1	1	30	1	5
8031005	413	4	10	37.27517	12.21081	1	165.1	1	1	0	0	0	0
8031005	413	4	15	38.27361	12.21081	1	165.1	1	1	0	0	0	0
8031005	415	4	10	32.60332	13.35797	2	167.64	1	1	1	0	0	0.5
8031005	415	4	15	33.24893	13.35797	2	167.64	1	1	1	0	0	0.5
8031005	416	4	10	24.12902	15.55647	2	165.1	1	1	0	0	0	2
8031005	416	4	15	24.46183	15.55647	2	165.1	1	1	0	0	0	2
8031005	419	4	10	.	13.26489	2	.	1	1	0	0	0	0.5
8031005	422	4	15	21.06089	8.610541	1	132.08	1	1	0	0	0	0
8031005	424	4	10	28.45069	8.911704	1	137.16	1	1	0	0	0	1
8031005	424	4	15	30.37955	8.911704	1	137.16	1	1	0	0	0	1
8031005	433	4	10	15.1477	9.749487	1	144.78	1	1	0	0	0	1
8031005	810	8	10	20.22051	9.242984	1	139.7	1	1	0	0	0	0
8031005	812	8	9	20.68535	10.25051	1	139.7	1	1	0	0	0	0

Pharmacokinetic Dataset (continued)

Protocol	Patient Number	Investigator Number	Visit Number	BMI (kg/cm^2)	Age (yrs)	Age Category	Height (cm)	Ethnic Origin	Origin Category	Smoking History (yrs)	Smoking Amount (smokes/day)	Alcohol Amount (drinks/wk)	Caffeine Amount (drinks/dy)
8031005	813	8	10	27.97682	13.58248	2	172.72	1	1	0	0	0	0
8031005	814	8	10	36.56099	15.33196	2	162.56	1	1	0	0	0	0
8031005	814	8	13	36.56099	15.33196	2	162.56	1	1	0	0	0	0
8031005	815	8	10	24.24378	10.07255	1	147.32	1	1	0	0	0	1
8031005	815	8	15	22.1538	10.07255	1	147.32	1	1	0	0	0	1
8031005	901	9	10	24.63176	15.18686	2	172.72	1	1	0	0	0	4
8031005	906	9	10	25.60607	12.34497	1	157.48	1	1	0	0	0	2
8031005	906	9	15	27.80088	12.34497	1	157.48	1	1	0	0	0	2
8031005	913	9	12	25.42143	16.81862	2	187.96	1	1	0	0	0	2.5
8031005	915	9	15	27.12036	14.59001	2	162.56	1	1	0	0	0	1.5
8031005	920	9	15	21.14377	14.46954	2	170.18	1	1	0	0	0	2.5
8031005	1101	11	10	19.95319	10.33265	1	142.24	1	1	0	0	0	0.5
8031005	1109	11	10	24.87447	10.57358	1	157.48	1	1	0	0	0	2
8031005	1109	11	11	25.24027	10.57358	1	157.48	1	1	0	0	0	2
8031005	1129	11	10	24.03478	10.45311	1	147.32	1	1	0	0	0	0.5
8031005	1129	11	15	24.66177	10.45311	1	147.32	1	1	0	0	0	0.5
8031005	1131	11	10	18.3978	14.40931	2	172.72	1	1	0	0	0	2
8031005	1137	11	10	18.83222	11.18412	1	142.24	1	1	0	0	0	0
8031005	1137	11	15	20.17738	11.18412	1	142.24	1	1	0	0	0	0
8031005	1141	11	10	19.36831	17.27858	2	167.64	1	1	0	0	0	1
8031005	1153	11	10	19.83971	13.41273	2	160.02	1	1	0	0	0	1
8031005	1153	11	15	18.59972	13.41273	2	160.02	1	1	0	0	0	1
8031005	1156	11	10	21.08398	8.832307	1	129.54	1	1	0	0	0	2
8031005	1156	11	15	22.97613	8.832307	1	129.54	1	1	0	0	0	2
8031005	1202	12	10	19.30321	13.87817	2	165.1	1	1	0	0	0	3
8031005	1202	12	15	22.46495	13.87817	2	165.1	1	1	0	0	0	3

Pharmacokinetic Dataset (continued)

Protocol	Patient Number	Investigator Number	Visit Number	BMI (kg/cm^2)	Age (yrs)	Age Category	Height (cm)	Ethnic Origin	Origin Category	Smoking History (yrs)	Smoking Amount (smokes/day)	Alcohol Amount (drinks/wk)	Caffeine Amount (drinks/dy)
8031005	1204	12	10	27.10246	13.51951	2	160.02	1	1	0	0	0	2
8031005	1205	12	15	20.98715	16.11499	2	170.18	1	1	0	0	0	0.5
8031005	1208	12	10	18.54985	15.1102	2	172.72	1	1	3	3	0	12
8031005	1208	12	15	20.22237	15.1102	2	172.72	1	1	3	3	0	12
8031005	1209	12	10	24.02154	12.4052	1	152.4	1	1	1	1	1	1
8031005	1211	12	10	27.80088	15.05544	2	157.48	3	2	5	0.5	0.5	2
8031005	1213	12	10	18.89464	11.27995	1	154.94	1	1	0	0	0	0
8031005	1213	12	15	18.13886	11.27995	1	154.94	1	1	0	0	0	0
8031005	1217	12	10	20.5265	15.80287	2	175.26	3	2	0	0	0	4
8031005	1220	12	10	20.0828	17.03765	2	162.56	1	1	0	0	0	1.5
8031005	1225	12	10	30.25754	17.51677	2	172.72	1	1	2	0	0	3
8031005	1225	12	15	29.4973	17.51677	2	172.72	1	1	2	0	0	3
8031005	1305	13	15	21.5908	15.91513	2	172.72	1	1	0	0	0	0
8031005	1503	15	10	22.80719	15.01985	2	172.72	1	1	0	0	0	3
8031005	1510	15	10	28.49354	13.37988	2	162.56	1	1	0	0	0	3
8031005	1510	15	15	30.89661	13.37988	2	162.56	1	1	0	0	0	3
8031005	1515	15	10	33.29968	12.72005	1	162.56	1	1	0	0	0	0
8031005	1516	15	10	25.07977	11.01985	1	147.32	1	1	0	0	0	0
8031005	1516	15	15	26.33376	11.01985	1	147.32	1	1	0	0	0	0
8031005	1601	16	10	24.23681	12.39151	1	149.86	1	1	0	0	0	2
8031005	1601	16	15	23.42892	12.39151	1	149.86	1	1	0	0	0	2
8031005	1602	16	10	21.45857	9.598905	1	137.16	1	1	0	0	0	0
8031005	1603	16	8	21.42317	11.46612	1	144.78	1	1	0	0	0	0.5

Pharmacokinetic Dataset (continued)

Protocol	Patient Number	Investigator Number	Visit Number	BMI (kg/cm^2)	Age (yrs)	Age Category	Height (cm)	Ethnic Origin	Origin Category	Smoking History (yrs)	Smoking Amount (smokes/day)	Alcohol Amount (drinks/wk)	Caffeine Amount (drinks/dy)
8031005	1604	16	10	34.76614	9.7577	1	154.94	1	1	0	0	0	2.5
8031005	1605	16	10	18.74852	11.154	1	152.4	1	1	0	0	0	0.5
8031005	1605	16	15	20.3109	11.154	1	152.4	1	1	0	0	0	0.5
8031005	1606	16	10	16.30185	12.564	1	147.32	1	1	0	0	0	7
8031005	1609	16	10	20.69081	9.626283	1	147.32	1	1	0	0	0	2
8031005	1609	16	15	21.7358	9.626283	1	147.32	1	1	0	0	0	2
8031005	1652	16	10	19.2886	9.169062	1	137.16	1	1	0	0	0	1
8031005	1652	16	11	20.73525	9.169062	1	137.16	1	1	0	0	0	1
8031005	1654	16	10	22.98979	11.58658	1	147.32	1	1	0	0	0	3
8031005	1658	16	10	33.20051	12.76386	1	152.4	1	1	0	0	0	1
8031005	1658	16	13	34.17699	12.76386	1	152.4	1	1	0	0	0	1
8031005	1659	16	10	31.01778	15.17864	2	172.72	1	1	0	0	0	4
8031005	1667	16	11	15.69352	9.678303	1	142.24	1	1	0	0	0	2.5
8031005	1701	17	10	39.79639	14.06982	2	134.62	1	1	0	0	0	3
8031005	1701	17	15	40.54727	14.06982	2	134.62	1	1	0	0	0	3
8031005	1702	17	10	15.58049	10.77892	1	144.78	1	1	0	0	0	0.5
8031005	1702	17	15	17.31165	10.77892	1	144.78	1	1	0	0	0	0.5
8031005	1904	19	10	18.29005	11.42779	1	157.48	1	1	0	0	0	0.5
8031005	1905	19	10	29.69807	14.40931	2	167.64	1	1	1	0	0	2.5
8031005	1905	19	15	31.79631	14.40931	2	167.64	1	1	1	0	0	2.5
8031005	1906	19	10	21.38261	11.19781	1	139.7	1	1	0	0	0	0
8031005	1906	19	15	21.61503	11.19781	1	139.7	1	1	0	0	0	0
8031005	1915	19	10	19.37028	17.1937	2	177.8	1	1	0	0	0	0
8031005	1919	19	10	21.67798	15.16222	2	152.4	1	1	0	0	0	0

Pharmacokinetic Dataset (continued)

Protocol	Patient Number	Investigator Number	Visit Number	BMI (kg/cm^2)	Age (yrs)	Age Category	Height (cm)	Ethnic Origin	Origin Category	Smoking History (yrs)	Smoking Amount (smokes/day)	Alcohol Amount (drinks/wk)	Caffeine Amount (drinks/dy)
8031005	1919	19	15	20.5062	15.16222	2	152.4	1	1	0	0	0	0
8031005	1921	19	10	15.88385	13.66188	2	147.32	13	2	0	0	0	1
8031005	1924	19	10	27.72183	14.89665	2	170.18	99	2	0	0	0	0.5
8031005	1924	19	15	28.81818	14.89665	2	170.18	99	2	0	0	0	0.5
8031005	2202	22	10	15.51965	8.561259	1	124.46	1	1	0	0	0	0.5
8031005	2204	22	10	23.22695	11.21424	1	149.86	1	1	0	0	0	0.5
8031005	2205	22	10	22.21708	10.97604	1	149.86	1	1	0	0	0	2
8031005	2208	22	10	25.78005	10.15469	1	134.62	1	1	0	0	0	0
8031005	2208	22	15	27.78239	10.15469	1	134.62	1	1	0	0	0	0
8031005	2214	22	10	19.36831	13.27036	2	167.64	1	1	1	0	0	4
8031005	2216	22	10	26.21675	15.09925	2	160.02	1	1	1	0.5	0	0
8031005	2216	22	15	27.2796	15.09925	2	160.02	1	1	1	0.5	0	0
8031005	2220	22	10	31.14424	10.10267	1	139.7	99	2	0	0	0	0.5
8031005	2220	22	14	33.70086	10.10267	1	139.7	99	2	0	0	0	0.5

16.1.16.
LC/MS Method and Validation for the Determination of Fluoxetine and Norfluoxetine in Human Plasma

HPLC/MS/MS Method Validation for the Determination of Fluoxetine and Norfluoxetine in Human Plasma

Job Number: 132019 (Lot: 001)

Analytical Site:

Study Sponsor:

Project Protocol Date: September 12, 1997

Analysis Performed By:

Instrumental Analysis Performed By:

Analyst Notebook Numbers:

Dates of Analyses: October 1, 1997 through October 13, 1997

Validation Report Date: January 6, 1998

HPLC/MS/MS Method Validation for the Determination of Fluoxetine and Norfluoxetine in Human Plasma

ORS Job Number: 132019 (Lot: 001)

THIS STUDY WAS CONDUCTED IN COMPLIANCE WITH GOOD LABORATORY PRACTICES AS DESCRIBED IN THE CODE OF FEDERAL REGULATIONS, TITLE 21:PART 58.

[redacted]

1/6/98
Date

HPLC/MS/MS Method Validation for the Determination of Fluoxetine and Norfluoxetine in Human Plasma

ORS Job Number: 132019 (Lot: 001)

Pharmaceutical and Chemical Analysis Section
Study Personnel

[redacted] 01/06/98
Date

Reviewed by:

[redacted] 1/6/98
Date

Approved by:

[redacted] 1/6/98
Date

QUALITY ASSURANCE DEPARTMENT

The accompanying Final Report entitled: **HPLC/MS/MS Method Validation for the Determination of Fluoxetine and Norfluoxetine in Human Plasma,** [redacted] **Job Number: 132019 (Lot: 001)** has been reviewed by the Quality Assurance Department and meets the acceptability requirements of the [redacted] The data in this report were obtained subject to applicable GLP compliance requirements.

This report was audited for compliance by the [redacted] on December 4, 5, and 8, 1997. The audit results were reported to the [redacted] Study Director on December [illegible], 1997 and to [redacted] management on January 6, 1998.

January 6, 1998
Date

[redacted] Job Number: 132019 (Lot: 001)

Analysis Description: Validation of an HPLC/MS/MS Method for the Quantitation of Fluoxetine and Norfluoxetine in Human Plasma using Atmospheric Pressure Chemical Ionization, Performed at [redacted]

VI. Origin and Purpose: An HPLC/MS/MS method for the analysis of Fluoxetine and Norfluoxetine in human plasma was developed and validated in the Bioanalytical Mass Spectrometry Department of [redacted] The detailed analytical method (Appendix A: Bioanalytical Method) and the validation results are provided in this report.

VII. Summary of the HPLC/MS/MS Method and Validation Results:

Method Summary: 2.0 ml of 0.1 M potassium phosphate buffer (pH 6.0) and 50 µl of a 2.00 µg/ml internal standard solution are added to 1.0 ml of human plasma. The samples are then loaded onto an Isolute Column and the analytes eluted with 2% ammonium hydroxide in methylene chloride/methanol (80/20). The eluant is evaporated and then reconstituted in 100 µl of 80/20 methanol/0.05% TFA. A 40 µl aliquot was analyzed by HPLC/MS/MS.

Analytical Reference Standards: Fluoxetine HCl, lot no. 001PD5, potency 99.80%, expiry: 10/28/2000, Norfluoxetine HCl, lot no. U096FK20, potency 87.60% as a freebase, expiry: 10/28/97, R-isomer, Fluoxetine internal standard - SN141999-[$^2H_5$] (also referenced as d_5-Fluoxetine), used at 100% purity, lot no. 067, expiry: 6/3/98; Norfluoxetine internal standard - 215299-[$^2H_4$] HCl (also referenced as d_4-Norfluoxetine) used at 100% purity, lot no. 253A, expiry: 6/3/98. All analytical reference standards were supplied by the sponsor.

Validation Summary: The following validation parameters were determined:

1. Specificity: No significant interfering peaks were observed.

2. Intra-Day Precision and Accuracy: Precision (%RSD) of 1.83 to 8.30% and accuracy (%RE) between -9.25 to -2.72% were obtained for Fluoxetine. Precision of 2.53 to 8.49% and accuracy (%RE) between -6.50 to 5.90% were obtained for Norfluoxetine.

3. Inter-Day Precision and Accuracy: Precision of 4.38 to 5.75% and accuracy between -6.64 and -5.23% were obtained for Fluoxetine. Precision of 4.91 to 7.68% and accuracy between -0.31 and 3.17% were obtained for Norfluoxetine.

4. Limits of Quantitation: The Lower Limit of Quantitation for Fluoxetine and Norfluoxetine was 1.00 ng/ml. The Upper Limit of Quantitation for Fluoxetine and Norfluoxetine was 500 ng/ml.

5. Range: The validated concentration range for this assay was 1.00 to 500 ng/ml for Fluoxetine and Norfluoxetine.

6. Extraction Efficiency: Ratios of the peak area of processed samples to the mean peak area of five unprocesssed analytical solutions provided an overall recovery ranging from 80.25 to 114.58% for Fluoxetine and 71.70 to 102.82% for Norfluoxetine. The recovery of d_5-Fluoxetine was determined to be 125.22% and 147.86% for d_4-Norfluoxetine.

7. Dilution Integrity: As per Lilly SOP, dilution integrity will be evaluated when needed on a run by run basis.

8. Stability:

   a. Processed Sample: The processed samples were stable for up to 36 hours at room temperature. The accuracy of quality control samples stored for this time ranged from -9.25 to -4.35% for Fluoxetine and 2.94 to 3.75% for Norfluoxetine. The processed samples were stable for up to 21 hours at 4°C. The accuracy of quality control samples stored for this time ranged from -10.17 to -7.00% for Fluoxetine and -0.82 to 8.20% for Norfloxetine.

   b. Bench Top: Unprocessed samples were stable for up to 5 hours on the wet lab bench at room temperature. The accuracy of quality control samples stored for this time ranged from -2.92 to -2.60% for Fluoxetine and -0.60 to 7.10% for Norfluoxetine.

   c. Freeze/Thaw: Three cycles of freeze/thaw samples at -20°C and room temperature, respectively, were performed prior to extraction. The samples were shown to be stable during these periods. The accuracy of the freeze/thaw samples for these cycles ranged from -7.40 to -1.30% for Fluoxetine and -8.80 to 6.89% for Norfluoxetine.

   d. Long Term Storage Stability: Long term storage stability at -20°C and -70°C at 1, 3, 6, 9 and 12 month intervals is ongoing.

VIII. **Conclusion:** The HPLC/MS/MS method for Fluoxetine and Norfluoxetine has been validated for the concentration range of 1.00 to 500 ng/ml in human plasma. The method has been demonstrated to be precise, accurate and sufficiently robust for analysis of clinical samples.

Written By:

[redacted]

11/10/97

Date

IX. Validation: The HPLC/MS/MS method for the determination of Fluoxetine and Norfluoxetine in human plasma was validated for the concentration range of 1.00 to 500 ng/ml. Calibration standards, validation samples and stability samples were prepared by spiking control human plasma with known amounts of drug. The following assay validation parameters were determined:

1. Specificity: No significant interfering peaks due to endogenous compounds or reagents were observed at the retention times of Fluoxetine, Norfluoxetine or internal standards (d_5-Fluoxetine and d_4-Norfluoxetine) in the mass chromatograms of the control human plasma (Figure 1). In addition to the plasma blanks analyzed with the validation samples, plasma blanks from six (6) different lots of plasma were analyzed on one validation day (day 2) and displayed no significant interfering peaks.

2. Intra-Day Precision and Accuracy: On three validation days five replicates of validation samples at three concentrations representing the entire standard curve range were analyzed. The intra-day precision of the assay for Fluoxetine ranged from 1.83 to 8.30% and the accuracy was between -9.25 and -2.72%. The intra-day precision of the assay for Norfluoxetine ranged from 2.53 to 8.49% and the accuracy was between -6.50 and 5.90% (Tables 3a and 3b).

3. Inter-Day Precision and Accuracy: The inter-day precision of the assay for Fluoxetine ranged from 4.38 to 5.75% and the accuracy was between -6.64 and -5.23%. The inter-day precision of the assay for Norfluoxetine ranged from 4.91 to 7.68% and the accuracy was between -0.31 and 3.17% (Tables 3a and 3b).

4. Limits of Quantitation: The lowest calibration standard concentration (1.00 ng/ml) was defined as the lower limit of quantitation (LOQ) of the assay for Fluoxetine and Norfluoxetine. Validation samples at this concentration were analyzed in replicates of five on each validation day. The highest calibration standard concentration (500 ng/ml) was defined as the upper limit of quantitation of the assay. Validation samples at this concentration were analyzed in replicates of five on each validation day.

5. Range: A line was fitted through the calibration standards (range 1.00 to 500 ng/ml) by weighted regression of ($1/x^2$). Correlation coefficients of at least 0.991606 for the Fluoxetine and Norfluoxetine calibration curves were obtained (Figures 4 - 9).

6. Extraction Efficiency: Human plasma samples (n=5) at two concentrations (1.00 ng/ml and 500 ng/ml) were processed and injected onto the HPLC/MS/MS system (called processed samples). Replicates of five non-extracted spiked samples were prepared by extracting matrix blanks and fortifying with the analytes of interest (called unprocessed samples).

   The ratio of the peak area of processed samples to the mean peak areas of the processed analytical solutions provided the extraction efficiency. Overall recoveries of 80.25 and 114.58% for Fluoxetine and 71.70 and 102.82% for Norfluoxetine were observed (Tables 4a and 4b). The recovery of the internal standard was determined at the working concentration (100 ng/ml). The recovery for d_5-Fluoxetine was found to be 125.22% (Table 5a) and 147.86% for d_4-Norfluoxetine (Table 5b).

7. Dilution Integrity: As per Lilly SOP, dilution integrity will be evaluated when needed on a run by run basis.

8. Stability: Stability was determined for the following conditions:

   a. Processed Sample Stability (Ambient Temperature): Quality control samples at three concentrations (n=5) and duplicate calibration standards were processed and, due to instrumental problems, were stored at ambient temperature for 36 hours. When the problem had been corrected, the samples were analyzed and quantitated against the calibration standards stored at ambient temperature for 36 hours. The processed samples were stable for at least 36 hours at ambient temperature for Fluoxetine (%RE for quality control samples ranged from -9.25 to -4.35%) and Norfluoxetine (%RE for quality control samples ranged from 2.94 to 3.75%) (Tables 8a and 8b).

   An examination of 48 hour ambient temperature stability was also performed. The results failed to meet acceptance criteria and the run was rejected. The raw data for this run is located in the validation study binder [redacted] Job # 132019 (Lot: 001)).

   Processed Sample Stability (4°C): Quality control samples at three concentrations (n=5) and duplicate calibration standards were processed and stored at approximately 4°C for at least 21 hours. The samples were then analyzed and quantitated against the calibration standards stored at approximately 4°C for 21 hours. The processed samples were stable for at least 21 hours at approximately 4°C for Fluoxetine (%RE ranged from -10.17 to -7.00%) and for Norfluoxetine (%RE ranged from -0.82 to 8.20%) (Tables 9a and 9b).

b. Bench Top Stability: Stability samples at two concentrations in replicates of five were prepared for HPLC/MS/MS analysis. The samples were stored for up to 5 hours on a wet lab bench at room temperature prior to extraction. The samples were shown to be stable for that time. The accuracy of the bench top samples ranged from -2.92 to -2.60% for Fluoxetine and -0.60 to 7.10% for Norfluoxetine (Tables 6a and 6b).

c. Freeze/Thaw Stability: Quality control samples at two concentrations (1.00 and 500 ng/ml) were processed through three freeze (-20°C)/thaw (ambient temperature) cycles prior to extraction. The samples were shown to be stable through three freeze/thaw cycles for both Fluoxetine and Norfluoxetine. The accuracy of the freeze/thaw samples for these cycles ranged from -7.40 to -1.30% for Fluoxetine and -8.80 to 6.89% for Norfluoxetine (Tables 7a and 7b).

9. System Suitability: System suitability samples consisting of a mid-level quality control sample, extracted matrix blank and extracted low calibration standard will be analyzed at the beginning of each specimen run. The repeatability portion of system suitability was established using the 250 ng/ml quality control samples. The apex scan number for each component of interest was recorded and the relative retention was determined according to the following:

Relative Retention = (scan # of drug / scan # of internal standard)

The acceptable relative retention range for specimen analysis was determined as 0.85 to 1.15 for both fluoxetine and norfluoxetine (Appendix C).

Printouts of all chromatograms, results tables and sample queues are kept in raw data binders. These documents, notebooks and an exact copy of the final report will be archived at [redacted] according to [redacted] Standard Operating Procedures AR-1 and AR-2. Exact copies of all hardcopy raw data, representing 100% of the data, are provided to the sponsor.

Validation of Fluoxetine and Norfluoxetine in Human Plasma

Table 1a: Standard Curve Parameters, Fluoxetine

Validation Run	Date	Slope $(ng/ml)^{-1}$	Intercept	Correlation Coefficient
30	10/1/1997	0.015695	0.000179	0.996332
31	10/3/1997	0.014838	0.003258	0.991606
32	10/3/1997	0.012962	-0.002234	0.997926
	Mean	0.014498	0.000401	0.995288
	SD	0.00140	-	0.00329
	%RSD	9.64	-	0.330
	n	3	3	3

Validation of Fluoxetine and Norfluoxetine in Human Plasma

Table 1b: Standard Curve Parameters, Norfluoxetine

Validation Run	Date	Slope $(ng/ml)^{-1}$	Intercept	Correlation Coefficient
30	10/1/1997	0.015394	-0.001267	0.995347
31	10/3/1997	0.015285	-0.001357	0.995999
32	10/3/1997	0.011884	-0.002893	0.994022
	Mean	0.014188	-0.001839	0.995123
	SD	0.00200	-	0.00101
	%RSD	14.1	-	0.101
	n	3	3	3

Validation of Fluoxetine and Norfluoxetine in Human Plasma

Table 2a: Standard Readback Concentrations, Fluoxetine

Validation		Nominal Concentrations (ng/ml)						
Run	Date	1.00	2.00	5.00	25.00	100.00	300.00	500.00
30	10/1/1997	1.07	1.90	4.15	27.18	97.64	315.73	474.04
		0.96	2.10	4.80	26.67	108.10	293.49	492.91
31	10/3/1997	1.07	2.22	5.52	21.80	97.04	308.88	481.38
		0.96	1.66	4.44	31.28	93.82	305.81	498.89
32	10/3/1997	1.06	1.86	4.27	25.82	96.26	314.63	517.85
		1.01	2.01	4.92	25.30	100.68	313.05	510.47
	Mean	1.02	1.96	4.68	26.34	98.92	308.60	495.92
	SD	0.05	0.20	0.51	3.07	5.01	8.28	16.74
	%RSD	5.16	10.04	10.82	11.66	5.07	2.68	3.37
	%RE	2.17	-2.08	-6.33	5.37	-1.08	2.87	-0.82
	N	6	6	6	6	6	6	6

Validation of Fluoxetine and Norfluoxetine in Human Plasma

Table 2b: Standard Readback Concentrations, Norfluoxetine

Validation		Nominal Concentrations (ng/ml)						
Run	Date	1.00	2.00	5.00	25.00	100.00	300.00	500.00
30	10/1/1997	1.05	1.74	4.49	23.53	96.55	325.29	522.56
		1.10	1.84	4.61	24.95	101.75	318.38	566.60
31	10/3/1997	0.95	2.33	5.01	24.43	97.12	322.05	495.84
		1.03	1.87	4.41	27.65	91.48	298.03	510.52
32	10/4/1997	1.14	1.90	4.68	25.68	93.68	285.03	579.90
		1.00	1.69	4.42	25.78	97.97	329.17	533.76
	Mean	1.05	1.90	4.60	25.34	96.43	312.99	534.86
	SD	0.07	0.23	0.23	1.41	3.56	17.49	32.57
	%RSD	6.54	12.01	4.91	5.55	3.69	5.59	6.09
	%RE	4.50	-5.25	-7.93	1.35	-3.58	4.33	6.97
	N	6	6	6	6	6	6	6

Validation of Fluoxetine and Norfluoxetine in Human Plasma

Table 3a: Quality Control Sample Concentrations, Fluoxetine

Validation Run	Date	Nominal Concentrations (ng/ml) 1.00	250.00	500.00
30	10/1/1997	1.09	220.70	449.14
		0.88	217.38	471.35
		0.96	243.94	466.26
		0.92	235.30	464.12
		0.94	239.75	458.68
	Mean	0.96	231.41	461.91
	SD	0.08	11.76	8.46
	%RSD	8.30	5.08	1.83
	%RE	-4.20	-7.43	-7.62
	N	5	5	5
31	10/3/1997	0.89	230.54	471.85
		(a)	247.53	456.70
		0.87	236.50	451.26
		0.94	237.01	462.24
		0.93	244.10	524.20
	Mean	0.91	239.14	473.25
	SD	0.03	6.72	29.48
	%RSD	3.64	2.81	6.23
	%RE	-9.25	-4.35	-5.35
	N	4	5	5
32	10/3/1997	0.98	247.29	484.99
		0.91	223.08	495.79
		0.92	233.80	530.00
		0.92	246.07	468.68
		0.92	221.47	452.42

…continued

(Continued) Validation of Fluoxetine and Norfluoxetine in Human Plasma

Table 3a: Quality Control Sample Concentrations, Fluoxetine

	Mean	0.93	234.34	486.38
	SD	0.03	12.23	29.41
	%RSD	3.04	5.22	6.05
	%RE	-7.00	-6.26	-2.72
	N	5	5	5
Inter-Day Statistics:	Mean	0.93	234.96	473.85
	SD	0.05	10.29	24.96
	%RSD	5.75	4.38	5.27
	%RE	-6.64	-6.01	-5.23
	N	14	15	15

(a) File Not Used, no signal detected.

Validation of Fluoxetine and Norfluoxetine in Human Plasma

Table 3b: Quality Control Sample Concentrations, Norfluoxetine

Validation Run	Date	Nominal Concentrations (ng/ml) 1.00	250.00	500.00
30	10/1/1997	1.12	249.15	495.80
		0.97	235.10	559.85
		0.94	273.62	557.70
		1.08	269.91	534.48
		0.96	255.05	499.79
	Mean	1.01	256.57	529.52
	SD	0.08	15.71	30.66
	%RSD	7.94	6.12	5.79
	%RE	1.40	2.63	5.90
	n	5	5	5
31	10/3/1997	1.04	269.71	523.43
		(a)	267.41	471.19
		1.05	244.72	566.49
		1.06	245.32	486.27
		1.00	263.45	526.18
	Mean	1.04	258.12	514.71
	SD	0.03	12.17	37.39
	%RSD	2.53	4.71	7.26
	%RE	3.75	3.25	2.94
	n	4	5	5

…continued

(Continued) Validation of Fluoxetine and Norfluoxetine in Human Plasma

Table 3b: Quality Control Sample Concentrations, Norfluoxetine

32	10/3/1997	1.05	263.28	520.30
		(a)	253.34	501.80
		0.90	233.65	511.63
		0.87	262.23	495.64
		0.92	253.66	487.28
	Mean	0.94	253.23	503.33
	SD	0.08	11.89	13.00
	%RSD	8.49	4.70	2.58
	%RE	-6.50	1.29	0.67
	N	4	5	5
Inter-Day	Mean	1.00	255.97	515.86
Statistics:	SD	0.08	12.56	28.97
	%RSD	7.68	4.91	5.62
	%RE	-0.31	2.39	3.17
	N	13	15	15

(a) File Not Used, no signal detected.

Validation of Fluoxetine and Norfluoxetine in Human Plasma

Table 4a: Extraction Efficiency, Fluoxetine

Validation Run	Fluoxetine Concentration (ng/ml)	Sample Replicate	Unprocessed Samples	Peak Area Mean Unextracted Sample (A)	Processed Samples (B)	Percent Extraction Efficiency (B)/(A)x100	Mean Extraction Efficiency	Standard Deviation
31	1.00	A	15747	14055	13185	93.81	80.25	11.68
		B	14948		*	-		
		C	11573		11631	82.75		
		D	15045		9207	65.51		
		E	12962		11095	78.94		
	500.00	A	3495765	4633908	6121124	132.09	114.58	20.42
		B	5566776		5025819	108.46		
		C	5291410		5379848	116.10		
		D	4918848		6163408	133.01		
		E	3896743		3857748	83.25		
					Overall Statistics			
					Mean	99.32		
					SD	24.23		
					%RSD	24.39		
					n	9		

* File Not Used, no signal detected.

Validation of Fluoxetine and Norfluoxetine in Human Plasma

Table 4b: Extraction Efficiency, Norfluoxetine

Validation Run	Norfluoxetine Concentration (ng/ml)	Sample Replicate	Unprocessed Smples	Peak Area Mean Unextracted Sample (A)	Processed Samples (B)	Percent Extraction Efficiency (B)/(A)x100	Mean Extraction Efficiency	Standard Deviation
31	1.00	A	2663	2847	2300	80.80	71.70	9.84
		B	3047		*	-		
		C	2859		2246	78.90		
		D	3027		1713	60.18		
		E	2637		1905	66.92		
	500.00	A	856150	1107025	1198486	108.26	102.82	14.91
		B	1206233		1216300	109.87		
		C	1293862		1225537	110.71		
		D	1251059		1207503	109.08		
		E	927822		843649	76.21		
					Overall Statistics			
					Mean	88.99		
					SD	20.41		
					%RSD	22.93		
					N	9		

* File Not Used, no signal detected.

Table 5a: Extraction Efficiency, D5-Fluoxetine

Validation Run	D5-Fluoxetine Concentration (ng/ml)	Sample Replicate	Unprocessed Samples	Peak Area Mean Unextracted Sample (A)	Processed Samples (B)	Percent Extraction Efficiency (B)/(A)x100	Mean Extraction Efficiency	Standard Deviation
31	100.00	A	477262	578557	797692	137.88	125.22	24.23
		B	543579		*	-		
		C	521913		722312	124.85		
		D	582343		536775	92.78		
		E	753896		651043	112.53		
		A	371583		873899	151.05		
		B	745335		741318	128.13		
		C	661998		803094	138.81		
		D	651834		898219	155.25		
		E	475828		495783	85.69		
					Overall Statistics			
					Mean	125.22		
					SD	24.23		
					%RSD	19.35		
					n	9		

* File Not Used, no signal detected.

Validation of Fluoxetine and Norfluoxetine in Human Plasma

Table 5b: Extraction Efficiency, D4-Norfluoxetine

D4-Norfluoxetine Concentration (ng/ml)	Sample Replicate	Unprocessed Samples	Peak Area Mean Unextracted Sample (A)	Processed Samples (B)	Percent Extraction Efficiency (B)/(A)x100	Mean Extraction Efficiency	Standard Deviation
100.00	A	76885	96927	158406	163.43	147.86	22.17
	B	104283		*	-		
	C	118448		152275	157.10		
	D	76993		115146	118.80		
	E	103949		136306	140.63		
	A	78003		149820	154.57		
	B	138277		168907	174.26		
	C	94261		141556	146.04		
	D	84910		162485	167.64		
	E	93265		104913	108.24		
				Overall Statistics			
				Mean	147.86		
				Mean	147.86		
				SD	22.17		
				%RSD	14.99		
				N	9		

* File Not Used, no signal detected.

Validation of Fluoxetine and Norfluoxetine in Human Plasma

Table 6a: Bench Top Stability, Fluoxetine

Validation Run	Date	Nominal Concentrations (ng/ml) 1.00	500.00
32	10/3/1997	0.95	475.60
		0.97	470.11
		0.99	471.30
		0.96	517.42
		1.00	492.45
	Mean	0.97	485.38
	SD	0.02	20.02
	%RSD	2.13	4.13
	%RE	-2.60	-2.92
	N	5	5

Validation of Fluoxetine and Norfluoxetine in Human Plasma

Table 6b: Bench Top Stability, Norfluoxetine

Validation Run	Date	Nominal Concentrations (ng/ml) 1.00	500.00
32	10/3/1997	1.08	556.26
		0.97	520.20
		0.96	555.90
		1.07	568.22
		0.89	476.80
	Mean	0.99	535.48
	SD	0.08	37.41
	%RSD	8.07	6.99
	%RE	-0.60	7.10
	N	5	5

Validation of Fluoxetine and Norfluoxetine in Human Plasma

Table 7a: Freeze (-20°C)/Thaw (Room Temperature) Stability, Fluoxetine

Validation Run	Date	Nominal Concentrations (ng/ml) 1.00	500.00
32	10/3/1997	0.91	494.45
		0.94	495.51
		0.92	485.32
		0.96	493.05
		0.90	499.23
	Mean	0.93	493.51
	SD	0.02	5.12
	%RSD	2.60	1.04
	%RE	-7.40	-1.30
	N	5	5

Validation of Fluoxetine and Norfluoxetine in Human Plasma

Table 7b: Freeze (-20°C)/Thaw (Room Temperature) Stability, Norfluoxetine

Validation Run	Date	Nominal Concentrations (ng/ml) 1.00	500.00
32	10/3/1997	0.96	552.67
		0.86	538.10
		0.99	489.89
		0.84	512.79
		0.91	578.84
	Mean	0.91	534.46
	SD	0.06	34.53
	%RSD	7.00	6.46
	%RE	-8.80	6.89
	N	5	5

Validation of Fluoxetine and Norfluoxetine in Human Plasma

Table 8a: 36 Hour Storage Stability (Room Temperature), Fluoxetine

		Standard Curve Parameters		
Validation Run	**Date**	**Slope**	**Intercept**	**Correlation Coefficient**
31	10/3/1997	0.014838	0.003258	0.991606

		Standard Readback Concentrations						
Validation		**Nominal Concentrations (ng/ml)**						
Run	**Date**	**1.00**	**2.00**	**5.00**	**25.00**	**100.00**	**300.00**	**500.00**
31	10/3/1997	1.07	2.22	5.52	21.80	97.04	308.88	481.38
		0.96	1.66	4.44	31.28	93.82	305.81	498.89
	Mean	1.02	1.94	4.98	26.54	95.43	307.35	490.14
	%RE	1.50	-3.00	-0.40	6.16	-4.57	2.45	-1.97

		Quality Control Sample Concentrations				
Validation		**Storage**	**Time**	**Nominal Concentrations (ng/ml)**		
Run	**Date**	**Temp.**	**(hours)**	**1.00**	**250.00**	**500.00**
31	10/3/1997	Ambient	36	0.89	230.54	471.85
				*	247.53	456.70
				0.87	236.50	451.26
				0.94	237.01	462.24
				0.93	244.10	524.20
		Mean		0.91	239.14	473.25
		SD		0.03	6.72	29.48
		%RSD		3.64	2.81	6.23
		%RE		-9.25	-4.35	-5.35
		N		4	5	5

* File Not Used, no signal detected.

Validation of Fluoxetine and Norfluoxtine in Human Plasma

Table 8b: 36 Hour Storage Stability (Room Temperature), Norfluoxetine

		Standard Curve Parameters		
Validation Run	**Date**	**Slope**	**Intercept**	**Correlation Coefficient**
31	10/3/1997	0.015285	-0.001357	0.995999

		Standard Readback Concentrations						
Validation		**Nominal Concentrations (ng/ml)**						
Run	**Date**	**1.00**	**2.00**	**5.00**	**25.00**	**100.00**	**300.00**	**500.00**
31	10/3/1997	0.95	2.33	5.01	24.43	97.12	322.05	495.84
		1.03	1.87	4.41	27.65	91.48	298.03	510.52
	Mean	0.99	2.10	4.71	26.04	94.30	310.04	503.18
	%RE	-1.00	5.00	-5.80	4.16	-5.70	3.35	0.64

		Quality Control Sample Concentrations				
Validation		**Storage**	**Time**	**Nominal Concentrations (ng/ml)**		
Run	**Date**	**Temp.**	**(hours)**	**1.00**	**250.00**	**500.00**
31	10/3/1997	Ambient	36	1.04	269.71	523.43
				*	267.41	471.19
				1.05	244.72	566.49
				1.06	245.32	486.27
				1.00	263.45	526.18
		Mean		1.04	258.12	514.71
		SD		0.03	12.17	37.39
		%RSD		2.53	4.71	7.26
		%RE		3.75	3.25	2.94
		n		4	5	5

* File Not Used, no signal detected.

Validation of Fluoxetine and Norfluoxetine in Human Plasma

Table 9a: 21 Hour Storage Stability (4°C), Fluoxetine

Standard Curve Parameters				
Validation Run	**Date**	**Slope**	**Intercept**	**Correlation Coefficient**
34	10/4/1997	0.016113	-0.000866	0.997420

Standard Readback Concentrations								
Validation		**Nominal Concentrations (ng/ml)**						
Run	**Date**	**1.00**	**2.00**	**5.00**	**25.00**	**100.00**	**300.00**	**500.00**
34	10/4/1997	0.86	2.12	5.01	24.05	95.31	298.51	532.60
		1.11	1.99	5.09	24.03	96.10	315.36	502.04
	Mean	0.99	2.06	5.05	24.04	95.71	306.94	517.32
	%RE	-1.50	2.75	1.00	-3.84	-4.30	2.31	3.46

Quality Control Sample Concentrations						
				Nominal		
Validation		Storage	Time	Concentrations (ng/ml)		
Run	Date	Temp.	(hours)	1.00	250.00	500.00
34	10/4/1997	4°C	21	0.89	239.55	458.69
				0.90	235.65	449.71
				0.97	212.94	456.46
				0.91	223.67	442.54
				0.98	232.08	438.37
		Mean		0.93	228.78	449.15
		SD		0.04	10.62	8.73
		%RSD		4.50	4.64	1.94
		%RE		-7.00	-8.49	-10.17
		n		5	5	5

Validation of Fluoxetine and Norfluoxetine in Human Plasma

Table 9b: 21 Hour Storage Stability (4°C), Norfluoxetine

	Standard Curve Parameters			
Validation Run	**Date**	**Slope**	**Intercept**	**Correlation Coefficient**
34	10/4/1997	0.013869	-0.003831	0.994883

	Standard Readback Concentrations							
Validation		**Nominal Concentrations (ng/ml)**						
Run	**Date**	**1.00**	**2.00**	**5.00**	**25.00**	**100.00**	**300.00**	**500.00**
34	10/4/1997	0.98	1.84	4.34	24.55	100.48	313.36	538.83
		1.08	2.15	4.36	23.56	92.94	330.06	563.74
	Mean	1.03	2.00	4.35	24.06	96.71	321.71	551.29
	%RE	3.00	-0.25	-13.00	-3.78	-3.29	7.24	10.26

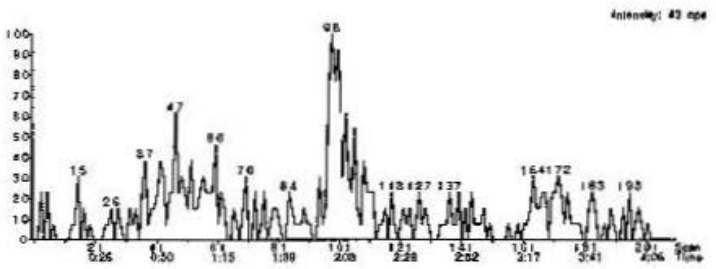
	Quality Control Sample Concentrations					
				Nominal		
Validation		Storage	Time	Concentrations (ng/ml)		
Run	Date	Temp.	(hours)	1.00	250.00	500.00
34	10/4/1997	4°C	21	1.11	252.91	537.58
				1.09	241.77	535.50
				1.12	239.41	518.44
				1.02	252.85	504.69
				1.07	252.82	563.27
		Mean		1.08	247.95	531.90
		SD		0.04	6.77	22.08
		%RSD		3.66	2.73	4.15
		%RE		8.20	-0.82	6.38
		n		5	5	5

Figure 1: **Representative Chromatogram of Fluoxetine and Norfluoxetine in Human Plasma, Human Plasma Blank**

MacQuan, version 1.4-noFPU
Printed: Fri, Oct 17, 1997 15:02
Calibration File: 30FluValcal Path: Macintosh HD:DATA 10/97:Lilly:Fluox/Norfluox:Validation:30FluVal:
Comments: Validation Day 1[redacted]

30pba pb Wed, Oct 1, 1997 17:16
plasma blank

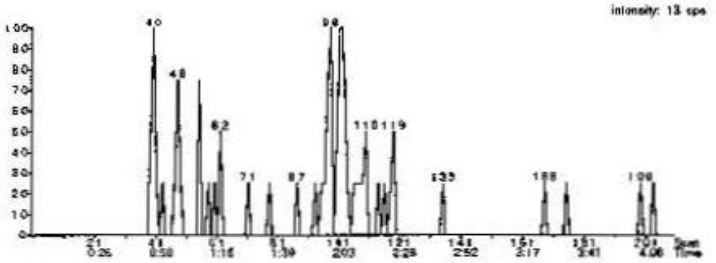
4:15 in 1 period
Fluoxetine
Internal Standard: d5-Fluoxetine
Use Area
Absolute Retention Time
1: 4:14 MRM, 209 scans
310.1->44.0
Noise Thres. 10.0
Quant Thres. 2.0
Min. Width 5
Mult. Width 2
Base Width 100
RT Win. (secs) 20
Smooth 0
Expected RT 2:04
Area 0
Height 0
Start Time 0:00.0
End Time 0:00.0
Integration Width 0:00.0
Retention Time 0:00.0
Integration Type



30pba pb Wed, Oct 1, 1997 17:16
plasma blank

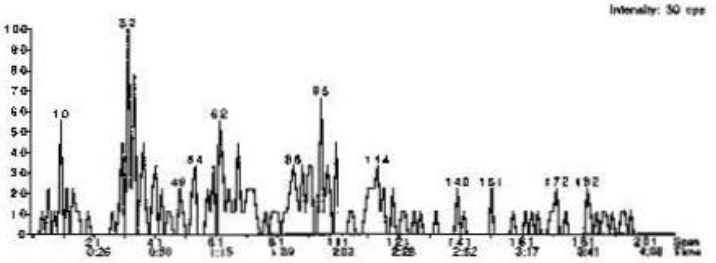
4:15 in 1 period
d5 Fluoxetine
use as Internal Standard

1: 4:14 MRM, 209 scans
315.1->44.0
Noise Thres. 10.0
Quant Thres. 2.0
Min. Width 5
Mult. Width 2
Base Width 100
RT Win. (secs) 20
Smooth 0
Expected RT 1:50
Area 0
Height 0
Start Time 0:00.0
End Time 0:00.0
Integration Width 0:00.0
Retention Time 0:00.0
Integration Type



30pba pb Wed, Oct 1, 1997 17:16
plasma blank

4:15 in 1 period
Norfluoxetine
Internal Standard: d4-Norfluoxetine
Use Area
Absolute Retention Time
1: 4:14 MRM, 209 scans
296.1->134.0
Noise Thres. 10.0
Quant Thres. 2.0
Min. Width 5
Mult. Width 4
Base Width 100
RT Win. (secs) 20
Smooth 0
Expected RT 1:48
Area 0
Height 0
Start Time 0:00.0
End Time 0:00.0
Integration Width 0:00.0
Retention Time 0:00.0
Integration Type



30pba pb Wed, Oct 1, 1997 17:16
plasma blank

4:15 in 1 period
d4-Norfluoxetine
use as Internal Standard

1: 4:14 MRM, 209 scans
300.1->134.0
Noise Thres. 10.0
Quant Thres. 2.0
Min. Width 5
Mult. Width 2
Base Width 40
RT Win. (secs) 20
Smooth 0
Expected RT 1:49
Area 0
Height 0
Start Time 0:00.0
End Time 0:00.0
Integration Width 0:00.0
Retention Time 0:00.0
Integration Type

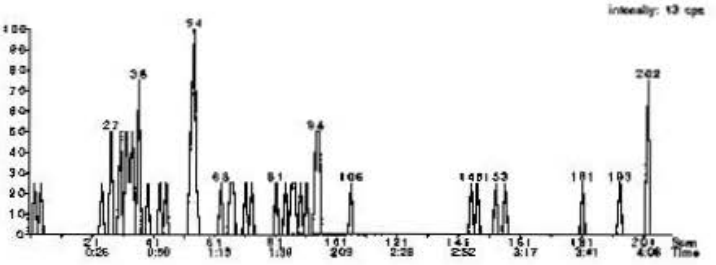


Figure 2: Representative Chromatogram of Fluoxetine and Norfluoxetine in Human Plasma, 1.00 ng/ml Plasma Calibration Standard

MacQuan, version 1.4-noFPU
Printed: Fri, Oct 17, 1997 15:02
Calibration File: 30FluValcal Path: Macintosh HD:DATA 10/97:Lilly:Fluox/Norfluox:Validation:30FluVal:
Comments: Validation Day 1 [redacted]

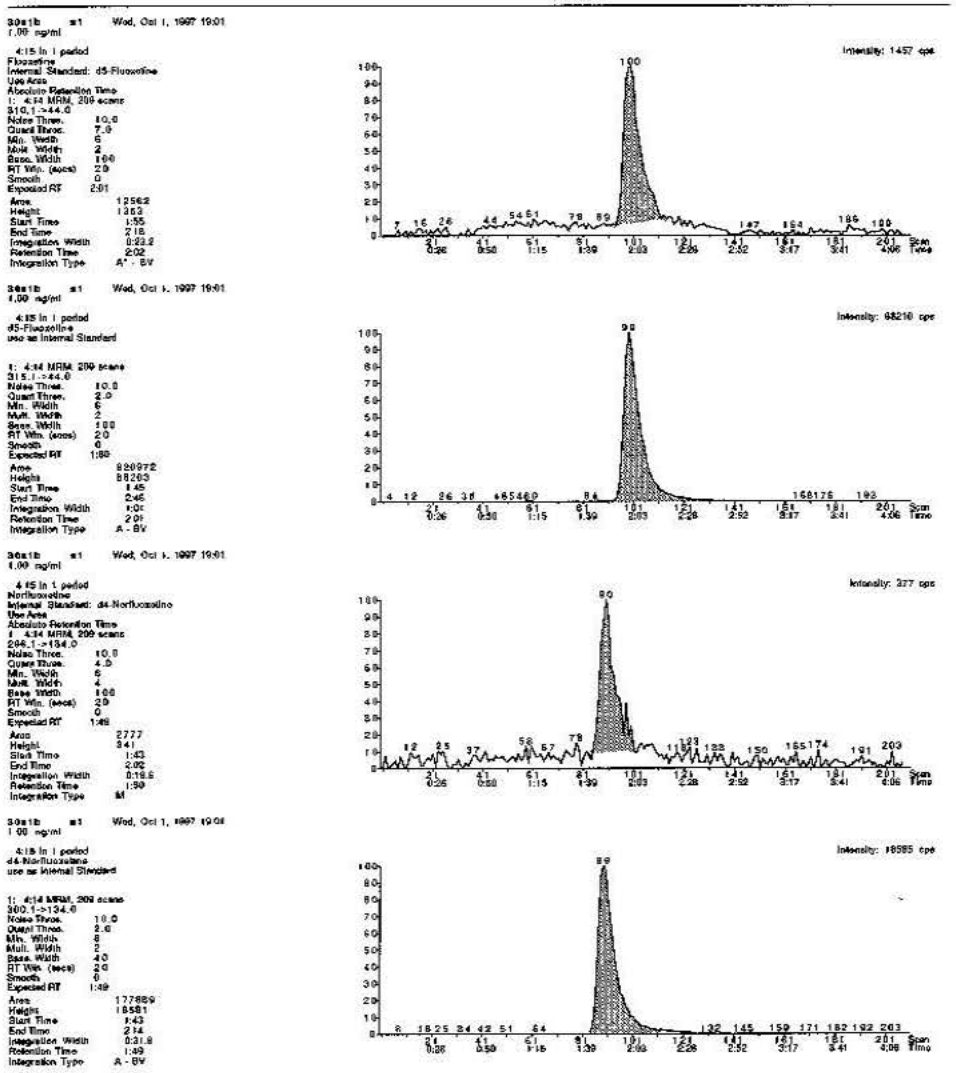


Figure 3: Representative Chromatogram of Fluoxetine and Norfluoxetine in Human Plasma, 500 ng/ml Plasma Calibration Standard

MacQuan, version 1.4-noFPU
Printed: Fri, Oct 17, 1997 15:02
Calibration File: 30FluValcal Path: Macintosh HD:DATA 10/97:Lilly:Fluox/Norfluox:Validation:30FluVal:
Comments: Validation Day 1 [redacted]

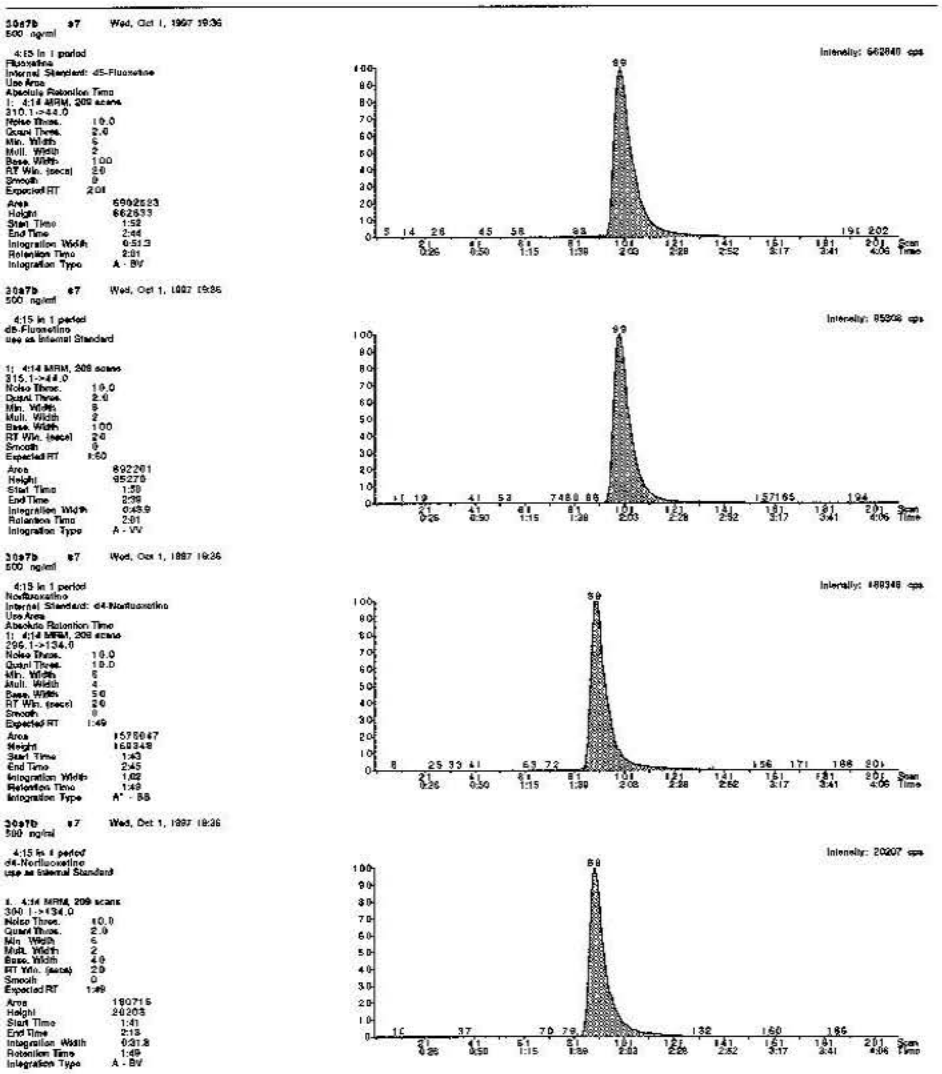


Figure 4: Standard Curve of Fluoxetine in Human Plasma, Run 30, 10/1/97

MacQuan, version 1.4-noFPU

Page 1 of 1

Printed: Fri, Oct 17, 1997 16:01

Calibration File: 30FluValcal Path: Macintosh HD:DATA 1997:Lilly:Fluox/Norfluox:Validation:30FluVal:

Comments: Validation Day 1 [redacted]

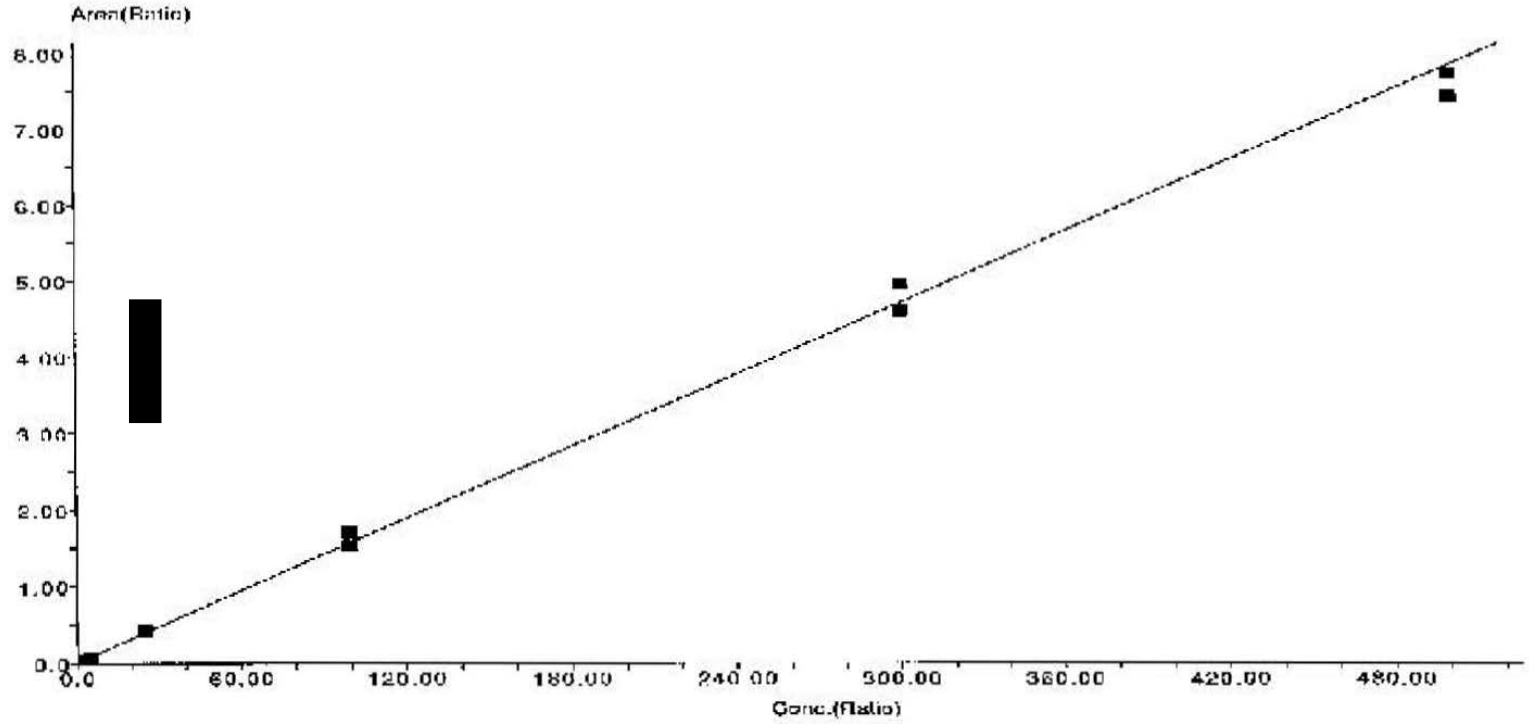
Fluoxetine 310.1->44.0 Internal Standard: d5 Fluoxetine

Weighted (1/x^x)

Intercept = 0.000178

Slope = 0.015895

Correlation Coeff. = 0.990332



[redacted]

Figure 5: Standard Curve of Norfluoxetine in Human Plasma, Run 30, 10/1/97

MacQuan, version 1.4-noFPU
Printed: Wed, Oct 22, 1997 16:46
Calibration File: 30FluValcal Path: Macintosh HD:DATA 10/97:Lilly:Fluox/Norfluox:Validation:30FluVal:
Comments: Validation Day 1 [redacted]

Page 1 of 1

Norfluoxetine 296.1->134.0 Internal Standard: d4-Norfluoxetine
Weighted (1/x*x)
Intercept = 0.001267
Slope 0.015394
Correlation Coeff. = 0.995347

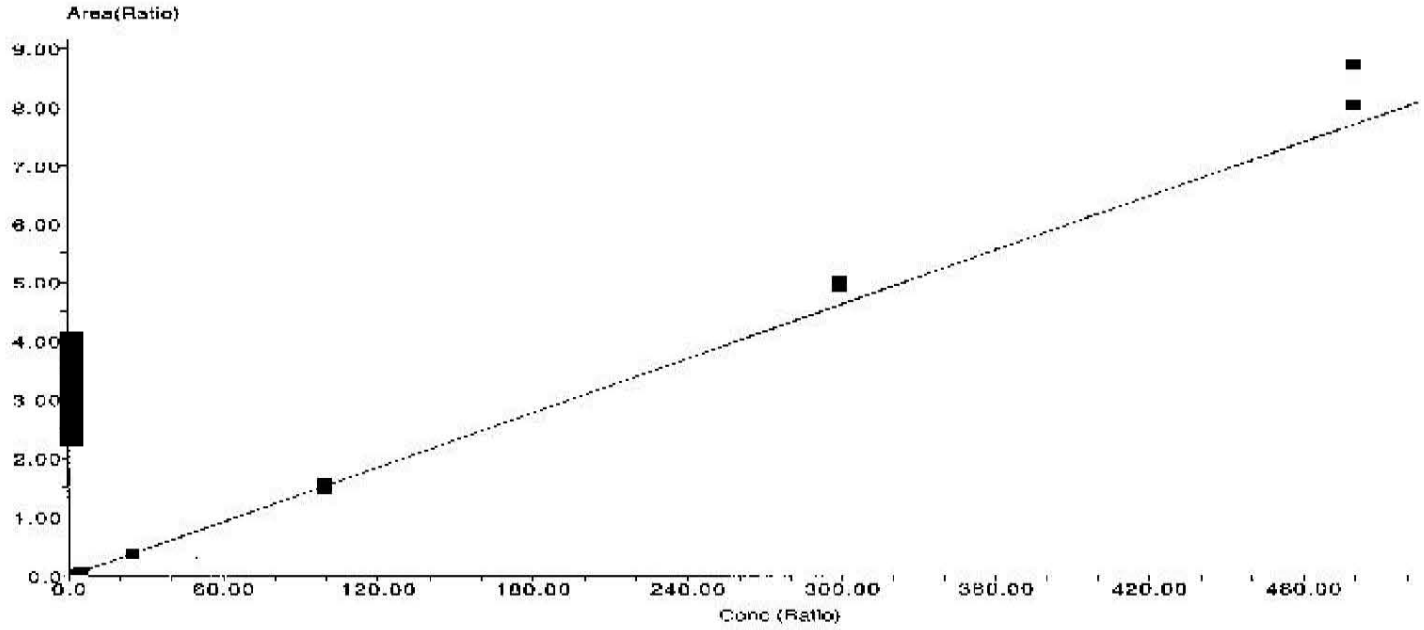


Figure 6: Standard Curve of Fluoxetine in Human Plasma, Run 31, 10/3/97

MacQuan, version 1.4-noFPU
Printed: Tue, Oct 21, 1997 09:12
Calibration File: 31FluValcal Path: Macintosh HD:DATA 10/97:Lilly:Fluox/Norfluox:Validation:31FluVal:
Comments: Validation Day 2

Page 1 of 1

Fluoxetine 310.1->44.0 Internal Standard: d5-Fluoxetine
Weighted (1/x*x)
Intercept = 0.003258
Slope = 0.014838
Correlation Coeff. = 0.991606

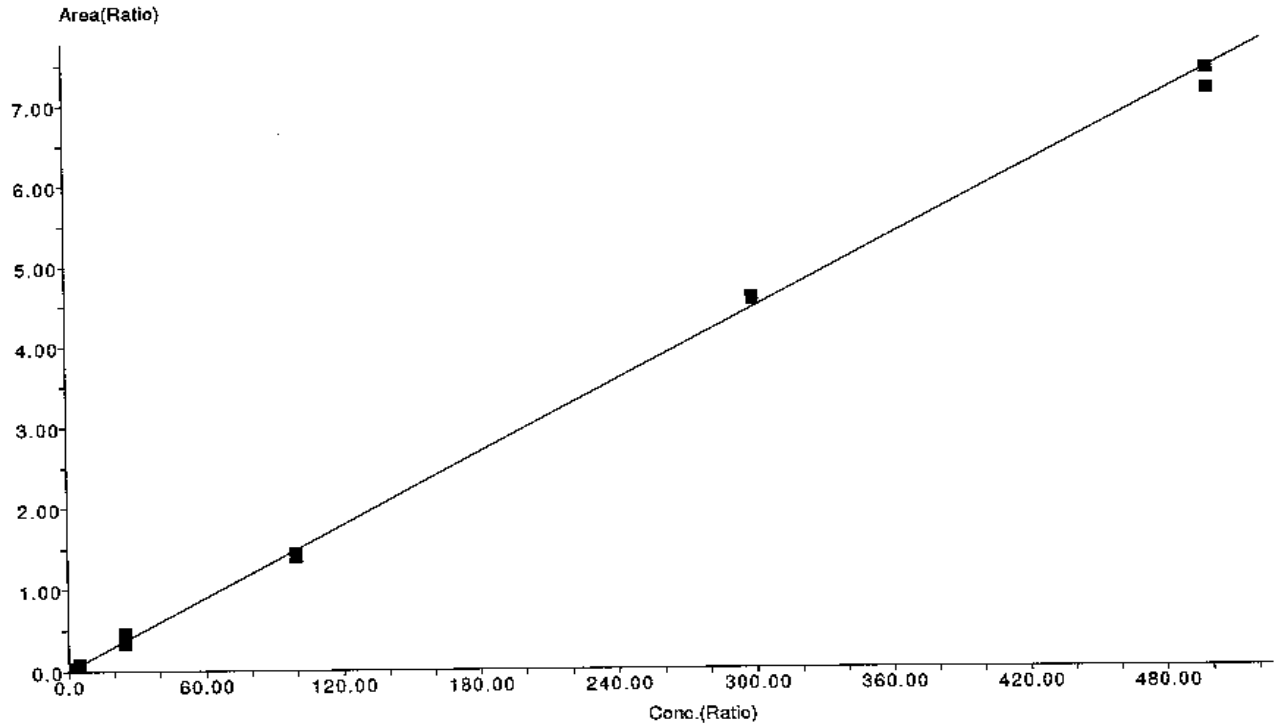


Figure 7: Standard Curve of Norfluoxetine in Human Plasma, Run 31, 10/3/97

MacQuan, version 1.4-noFPU
Printed: Wed, Oct 22, 1997 16:48
Calibration File: 31FluValcal Path: Macintosh HD:DATA 10/97:Lilly:Fluox/Norfluox:Validation:31FluVal:
Comments: Validation Day 2

Page 1 of 1

Norfluoxetine 296.1->134.0 Internal Standard: d4-Norfluoxetine
Weighted (1/x*x)
Intercept = -0.001357
Slope = 0.015285
Correlation Coeff. = 0.995999

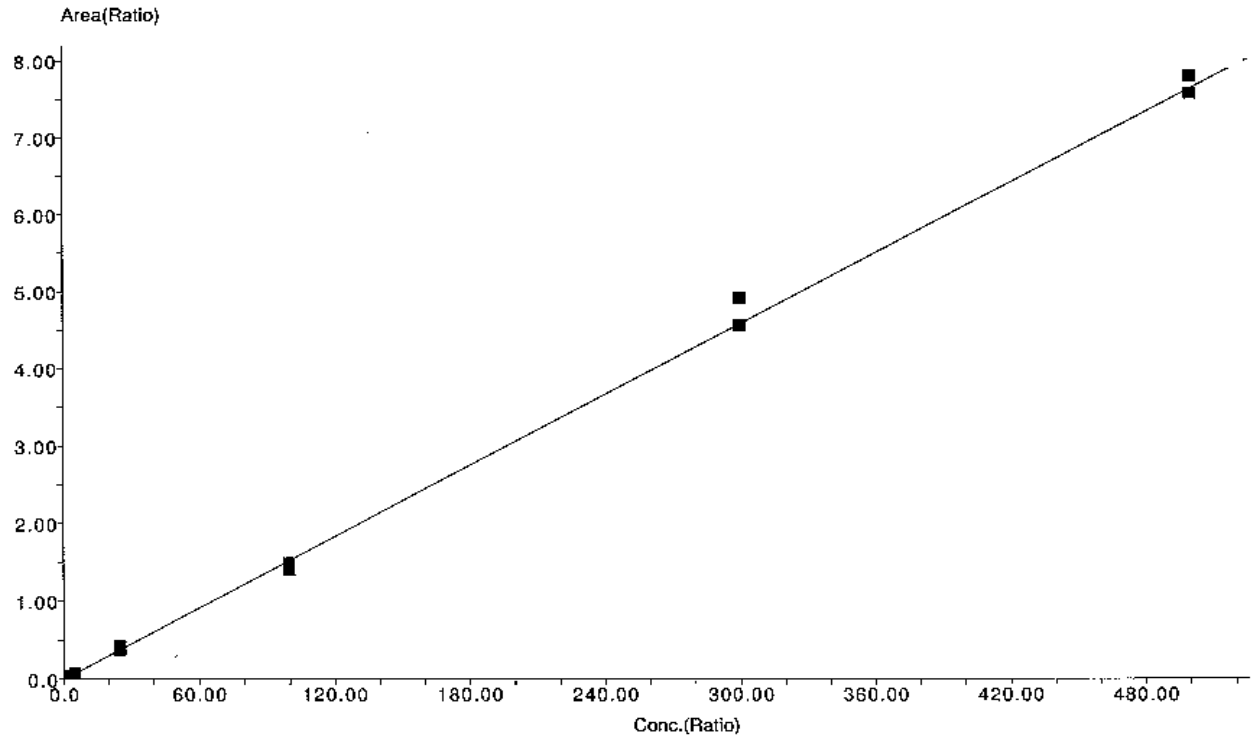


Figure 8: Standard Curve of Fluoxetine in Human Plasma, Run 32, 10/3/97

MacQuan, version 1.4-noFPU
Printed: Tue, Oct 21, 1997 09:23
Calibration File: 32FluValCal Path: Macintosh HD:DATA 10/97:Lilly:Fluox/Norfluox:Validation:32FluVal:
Comments: Validation Day 3

Page 1 of 1

Fluoxetine 310.1->44.0 Internal Standard: d5-Fluoxetine
Weighted (1/x*x)
Intercept = -0.002234
Slope = 0.012962
Correlation Coeff. = 0.997926

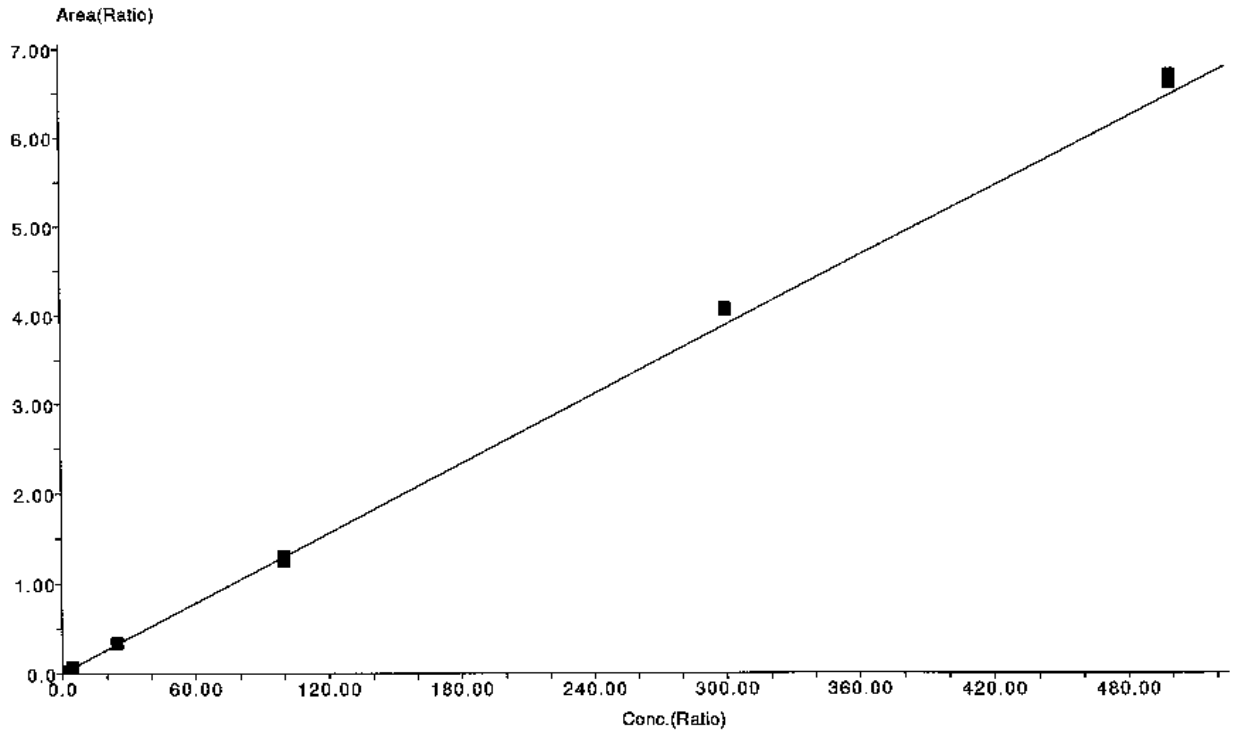
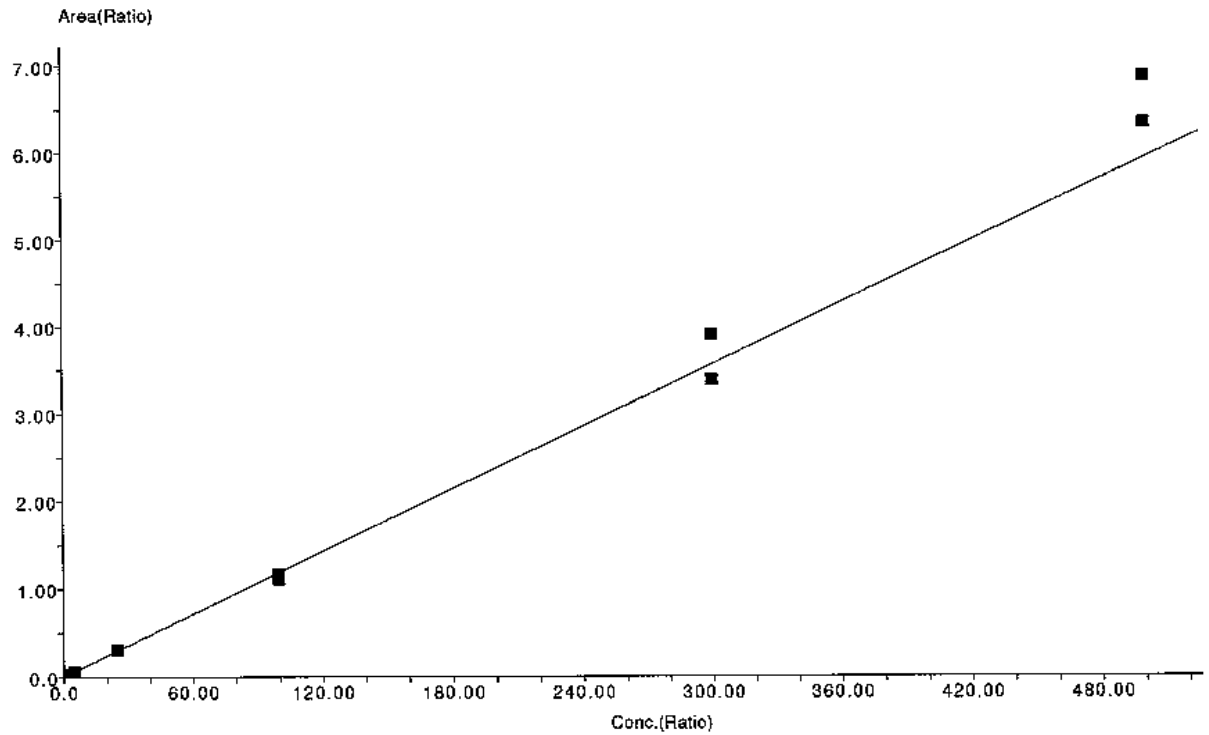


Figure 9: Standard Curve of Norfluoxetine in Human Plasma, Run 32, 10/3/97

MacQuan, version 1.4-noFPU
Printed: Tue, Oct 21, 1997 09:23
Calibration File: 32FluValCal Path: Macintosh HD:DATA 10/97:Lilly:Fluox/Norfluox:Validation:32FluVal:
Comments: Validation Day 3

Page 1 of 1

Norfluoxetine 296.1->134.0 Internal Standard: d4-Norfluoxetine
Weighted (1/x*x)
Intercept = -0.002893
Slope = 0.011884
Correlation Coeff. = 0.994022



XII. Appendix A: Bioanalytical Method

[redacted]

Bioanalytical Method

Method No.: M2.FluoxLCMS.1 **Rev. No.: New**

Test Compound: Fluoxetine and Norfluoxetine

Matrix: Human Heparinized Plasma

Title: Determination of Fluoxetine and Norfluoxetine in Human Plasma by APCI HPLC/MS/MS

References: None

Written By: [redacted] **Date:** 01/06/98

Approved By [redacted] **Date:** 1/6/98

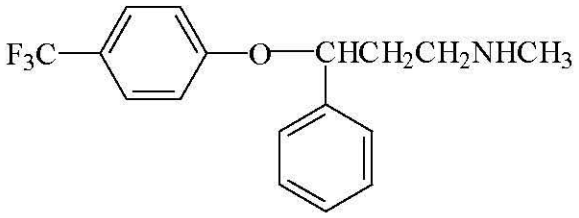
Method Summary: 2.0 ml of 0.1 M potassium phosphate buffer (pH 6.0) and 50 µl of a 2.00 µg/ml internal standard solution are added to 1.0 ml of human plasma. The samples are then loaded onto an Isolute Column and the analytes eluted with 2% ammonium hydroxide in methylene chloride/methanol(80/20). The eluant is evaporated and then reconstituted with 100µl of 80:20 methanol:0.05% TFA solution. Forty microliters are injected onto the HPLC/MS/MS system.

Introduction: The assay performed at [redacted] is an HPLC/MS/MS method employing atmospheric pressure chemical ionization (APCI) validated at [redacted] Refer to the report entitled, "HPLC/MS/MS Method Validation for the Determination of Fluoxetine and Norfluoxetine in Human Plasma"; [redacted] Job Number: 132019 (Lot: 001).

Compounds: Fluoxetine

Empirical Formula = $C_{17}H_{18}F_3NO$
Mol. Wt. = 309.33
HCl Salt = 345.79

Structure

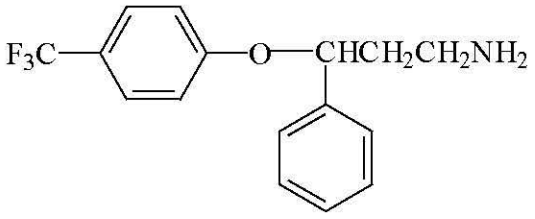


MS/MS Transition : m/z 310 → m/z 44

Compounds: Norfluoxetine

Empirical Formula = $C_{16}H_{16}F_3NO$
Mol. Wt. = 295.30
HCl Salt = 331.76

Structure



MS/MS Transition : m/z 296 → m/z 134

Internal Standards:

d_5-Fluoxetine	Empirical Formula = $C_{17}H_{13}F_3NOD_5$ Mol. Wt. = 314.33 MS/MS Transition m/z 315 → m/z 44
d_4-Norfluoxetine	Empirical Formula = $C_{16}H_{12}F_3NOD_4$ Mol. Wt. = 299.30 MS/MS Transition m/z 300 → m/z 134

Assay Parameters:

Plasma Volume:	1.0 ml
Assay Range:	1.00 - 500 ng/ml
Lower Limit of Quantitation:	1.00 ng/ml for Fluoxetine and Norfluoxetine
Approximate Retention Times:	Fluoxetine: ~ 2.1 minutes Norfluoxetine: ~ 1.8 minutes d_5-Fluoxetine: ~ 2.1 minutes d_4-Norfluoxetine: ~ 1.8 minutes
Total Run Time:	Approximately 4.25 minutes

Instrumentation and Settings:

Mass Spectrometer: PE Sciex API-300

Ionization Mode:	APCI (Heated Nebulizer)	
Heated Nebulizer Temp.:	450°C	
Nebulizer Gas Setting:	10	
Curtain Gas Flow Setting:	6	
Discharge Current:	3.5 μA	
Collision Gas Setting:	3	
Multiplier Voltage:	2000 v	
Scan Mode:	Multiple Reaction Monitoring (MRM)	
Transitions Monitored:	Fluoxetine:	m/z 310 → m/z 44
	d_5-Fluoxetine:	m/z 315 → m/z 44
	Norfluoxetine:	m/z 296 → m/z 134
	d_4-Norfluoxetine:	m/z 300 → m/z 134

Note: Mass Spectrometer settings optimized as needed.

Liquid Chromatograph/Autosampler:

Instrument:	Waters 2690 Separations Module (Alliance)
Column:	Waters Nova-Pak CN HP (3.9 x 75 mm)
Mobile Phase:	80:20 methanol:0.05% TFA
Flow Rate:	1 ml/min.
Injection Volume:	40 µl
Autosampler vials:	Polypropylene
Wash Solvent:	60:40 ACN:H_2O

Note: Equivalent equipment may be substituted.

Data Acquisition: Apple Power Macintosh 8500/150 with System Software 7.5.3 Revision 2 and Sample Control 1.2.

Data Reduction: Weighted (1/x2) linear regression using PE Sciex MacQuan (version 1.4-noFPU), of concentration (x-axis) vs. peak area ratio (y-axis). Peak area ratios (ratio of peaks areas of the drug and its respective internal standard) were calculated using PE Sciex MacQuan (version 1.4-noFPU).

Chemicals and Supplies

Chemical/Solvents	Grade	Supplier
Ammonium Hydroxide*	ACS	Fisher
Trifluoroacetic Acid (TFA)**	Reagent	Pierce
Potassium Hydroxide*	Reagent	Fisher
Potassium Phosphate Monobasic*	Reagent	Mallinckrodt
Methylene Chloride*	Optima	Fisher
Hexanes, (≥85% n-hexane)*	Optima	Fisher
Ethyl Acetate*	Optima	Fisher
Acetonitrile*	HPLC	Fisher
Hexamethyldisilazane	Reagent	Pierce
Methanol*	Optima	Fisher
Water*	HPLC	Millipore and Burdick & Jackson Bottled Water
Isolute SPE Column, HCX 130 mg, 3 ml part no. 902-0013-B		Jones

*Equivalent substitutions can be made and should be documented in the lab notebook. **1 ml sealed ampules are suggested, to be opened fresh just prior to use. This helps to ensure that the reagent is moisture free.

Reagents (Volumes may be scaled as needed):

1. A 1.0 M potassium hydroxide solution is prepared by adding 5.6 grams of potassium hydroxide to 60 ml of water in a 100 ml volumetric flask. The potassium hydroxide is dissolved and the solution is brought to 100 ml with water. The solution is stored at room temperature and given a three month expiry period.

2. A 0.1 M phosphate buffer solution is prepared by adding 27.22 grams of potassium phosphate monobasic to 1975 ml of water in a 2 liter bottle. The solution is adjusted to pH 6.0 with 1.0 M potassium hydroxide, and stored at room temperature with a **2 day** expiry period.

3. A 2% (v/v) ammonium hydroxide in methylene chloride/methanol (80/20) solution is prepared **fresh daily, just prior to performing elution** by adding to a 1000 ml reagent bottle (1st) 784 mls of methylene chloride, (2nd) 196 mls of methanol and (lastly) 20 ml of concentrated ammonium hydroxide and mixing well. Note: The elution solvent should initially look cloudy, then clear.

4. A hexanes/ethyl acetate (50/50) solution is prepared **fresh daily** by adding 500 ml of hexanes and 500 ml of ethyl acetate to a 1 liter bottle and mixing well.

5. To prepare HPLC Mobile Phase, 80:20 Methanol: 0.05% TFA, measure 200 ml of water and remove 0.100 ml of it and replace with 0.100 ml of TFA. Mix well and add 800 ml of methanol.

Stock Solutions

Preparation of Fluoxetine and Norfluoxetine Calibration Standards:

An approximately 194 μg/ml solution of Fluoxetine is prepared by weighing 2.171 mg of Fluoxetine-HCl (purity 99.80%, conversion factor 0.89456) and dissolving it in 10.00 ml of methanol.

An approximately 240 μg/ml solution of Norfluoxetine is prepared by weighing 2.742 mg of Norfluoxetine (0.8760 conversion for free base)^ and dissolving it in 10.00 ml of methanol.

A 50.0 μg/ml solution of combined Fluoxetine and Norfluoxetine is prepared by combining 2.577 ml of the 194 μg/ml Fluoxetine stock solution with 2.083 ml of the 240 μg/ml Norfluoxetine stock solution and diluting to 10.00 ml with methanol. The 50.0 μg/ml solution is stored at 4°C. Standard spiking solutions are prepared by transferring the volumes of stock solutions listed in Table A to a 10 ml volumetric flask and diluting to a final volume of 10.0 ml with methanol. These solutions are stored at 4°C.

Table A

Standard Spiking Solutions

Standard Spiking Solution Prepared	Stock Solution Used (ng/ml)	Volume of Stock Solution (μl)	Final Volume (ml)	Final Concentration of Fluoxetine and Norfluoxetine (ng/ml)
S1	500	400	10.0	20.0
S2	500	800	10.0	40.0
S3	2000	500	10.0	100
S4	10000	500	10.0	500
S5	50000	400	10.0	2000
S6	50000	1200	10.0	6000
S7	50000	2000	10.0	10000

^ Note: Purity and free base conversion will vary depending upon the drug standard lot (refer to the certificate of analysis). Weighing may be adjusted as needed for changes in drug purity.

Preparation of Standard Curve in Human Plasma

Standard curve samples are prepared according to the scheme in Table B. All plasma standards are prepared daily in 13 x 100 mm silanized borosilicate tubes and mixed vigorously on a multi-tube vortexer for approximately 30 seconds.

Table B

Preparation of Standard Curve in Human Plasma

Standard Spiking Solution Used	Volume of Spiking Solution (μl)	Volume of Plasma (ml)	Final Concentration of Fluoxetine and Norfluoxetine (ng/ml)
S1	50.0	1.00	1.00
S2	50.0	1.00	2.00
S3	50.0	1.00	5.00
S4	50.0	1.00	25.0
S5	50.0	1.00	100
S6	50.0	1.00	300
S7	50.0	1.00	500

Internal Standard (R-isomer, d_5-Fluoxetine):

An approximately 199 μg/ml internal standard stock solution is prepared by weighing 1.990 mg of d_5-Fluoxetine (purity: 100%) and dissolving it in 10.00 ml of methanol. The solution is stored at 4°C.

Internal Standard (215229, d4-Norfluoxetine):

An approximately 200 μg/ml internal standard stock solution is prepared by weighing 2.330 mg of d_4- Norfluoxetine (purity: 100%) and dissolving it in 11.650 ml of methanol. The solution is stored at 4°C.

A 2.00 μg/ml working internal standard solution of combined d_5-Fluoxetine and d_4-Norfluoxetine is prepared by combining 100.5 μl of the 199 μg/ml d_5-Fluoxetine stock solution with 100 μl of the 200 μg/ml d_4-Norfluoxetine stock solution and diluting to 10.00 ml with methanol. The 2.00 μg/ml internal standard stock solution is stored at 4°C.

Method For the Preparation of Quality Control Validation Samples (V1-V3):

An approximately 296 µg/ml solution of Fluoxetine is prepared by weighing 3.312 mg of Fluoxetine-HCl (purity 99.80%, conversion factor 0.89456) and dissolving it in 10.00 ml of methanol.

An approximately 237 µg/ml solution of Norfluoxetine is prepared by weighing 2.702 mg of Norfluoxetine (0.8760 conversion to free base) and dissolving it in 10.00 ml of methanol.

A 50.0 µg/ml solution of combined Fluoxetine and Norfluoxetine (stock solution SQV1) is prepared by combining 1.689 ml of the 296 µg/ml Fluoxetine QC stock solution with 2.110 ml of the 237 µg/ml Norfluoxetine QC stock solution and diluting to 10.00 ml with methanol. The 50.0 µg/ml QC solution is stored at 4°C.

Quality control spiking solutions are prepared by transferring the volumes of stock solution listed in Table C to a 10 ml volumetric flask and diluting to a final volume of 10.0 ml with methanol. These solutions are stored at 4°C.

Table C

Quality Control Spiking Solutions

Stock Solution Used (µg/ml)	Volume of Stock Solution (ml)	Final Volume (ml)	Final Concentration of Fluoxetine and Norfluoxetine (µg/ml)
50.0 (SQV1)	0.400	10.0	2.00
2.00	1.00	10.0	0.200

Quality Control Samples are prepared according to the scheme in Table D. Each solution is mixed and approximately 5.50 ml aliquots are transferred to approximately 10 ml polypropylene conical tubes and frozen at -20°C until use.

Table D

Preparation of Quality Control Samples in Human Plasma

Quality Control Spiking Solution Used (µg/ml)	Volume of Spiking Solution (µl)	Final Volume in Plasma (ml)	Final Concentration of Fluoxetine and Norfluoxetine (ng/ml)	Quality Control Sample ID
0.200	500	100	1.00	vq1
50.0	500	100	250	q2
50.0	1000	100	500	vq3

Note: Adjustable pipettes were used in this method. Smaller or larger volumes of solutions and quality control samples may be prepared as needed. Unless otherwise specified all volumetric glassware is class A. All glassware used for the preparation of standards and quality control samples must be silanized.

Preparation of Blank Samples

The plasma blank is prepared by aliquoting 1 ml of blank control plasma into a 13x100 mm silanized test tube to which no analyte or internal standard is added.

Silanizing Procedure

All glassware is placed into a vacuum oven and heated to 200°C. The oven is then evacuated to -100 kPa., approximately 2.5 to 3 ml of hexamethyldisilazane is injected into the oven and allowed to stand for 1 hour. The glassware is then allowed to cool to room temperature. Refer to [redacted] Standard Operating Procedure EQ-17 for complete procedure.

Sample Preparation Procedure

Note : The use of silanized glassware is recommended, but not required.

1. A 1.0 ml aliquot of calibration standard, zero point, quality control sample or specimen is placed into a glass tube and a 50 µl volume of the working internal standard solution (2.00 µg/ml) is added.

2. To each sample 2.0 ml of 0.1M phosphate buffer is added and the samples are covered with parafilm and vortexed for approximately 30 seconds at medium speed to mix.

3. SPE columns are conditioned with 2.0 ml of methanol and 2.0 ml of 0.1 M phosphate buffer.

4. The samples are applied to the preconditioned SPE columns and are allowed to pass through by gravity. After the samples have passed through, aspirate under high vacuum for approximately 1 minute.

5. The SPE columns are washed with 3 ml of methanol, vacuum is applied to start the methanol dripping, then turned off. Allow the methanol to drip by gravity until at least 2/3 has gone through, then apply full vacuum to pull the remainder through and dry the columns for approximately 1 minute. Wash columns with 3 ml of acetonitrile again allowing approximately 2/3 to drip through before drying columns with full vacuum for approximately 1 minute. Finally wash with 50/50 hexane/ethyl acetate exactly as in acetonitrile wash, but allow the columns to dry for 1 minute before proceeding with elution step. (Note: the final drying step is a good time to prepare elution solvent.)

6. The SPE columns are removed from the manifold and placed in appropriately labeled silanized 10 ml snap cap conicals. The analytes are eluted with a 2 ml aliquot of 2% (v/v) ammonium hydroxide in methylene chloride/methanol (80/20). The elution solvent receives a final push through the column with air. The eluant is taken to dryness under a stream of dry nitrogen in a 40°C water bath.

7. The samples are reconstituted in 0.100 ml of 80:20 methanol:0.05% TFA, vortexed, and centrifuged for 5 minutes at 3000 RPM. A 90.0 µl aliquot of sample is transferred to appropriately labeled polypropylene GC vials.

XIII. Appendix B

As per client request, a cross-validation between the Fluoxetine/Norfluoxetine GC/MS method and the LC/MS/MS method was performed. Residual plasma samples from two previous Eli Lilly studies (B1Y-SP-0004, [redacted] Job #123742 and B1Y-MC-HCIT, [redacted] Job # 126926) were pooled for the cross-validation. Using results from both studies above (Bioanalytical reports entitled "Fluoxetine Versus Sertraline and Paroxetine in Major Depression: Comparison of Discontinuation-Emergent Signs and Symptoms" from study B1Y-MC-HCIT and "Bioequivalence Study between Two 20 mg Oral Formulations of Fluoxetine in Sachets and Capsules in Healthy Volunteers" from B1Y-SP-0004), sample pools at approximate Fluoxetine concentrations of <1.00 (BLQ), 1.00, 2.50, 10.0, 50.0, 100 and 250 ng/ml were prepared. The amount of Norfluoxetine in these sample pools will be somewhat different than the respective Fluoxetine levels, therefore another set of sample pools at the same approximate concentrations for Norfluoxetine was prepared. Sufficient sample pools were prepared to allow for five replicates per method.

Polypropylene conical test tubes were labeled with the naming scheme outlined in Table B1. The collective sample pools were placed into the conical test tube and vortexed thoroughly.

Table B1
Sample Pool Identification Key

V1 = Fluoxetine and Norfluoxetine at < 1.00 ng/ml
V2 = Fluoxetine at approximately 1.00 ng/ml
V3 = Fluoxetine at approximately 2.50 ng/ml
V4 = Fluoxetine at approximately 10.0 ng/ml
V5 = Fluoxetine at approximately 50.0 ng/ml
V6 = Fluoxetine at approximately 100 ng/ml
V7 = Fluoxetine at approximately 250 ng/ml
V8 = Norfluoxetine at approximately 1.00 ng/ml
V9 = Norfluoxetine at approximately 2.50 ng/ml
V10 = Norfluoxetine at approximately 10.0 ng/ml
V11 = Norfluoxetine at approximately 50.0 ng/ml
V12 = Norfluoxetine at approximately 100 ng/ml
V13 = Norfluoxetine at approximately 250 ng/ml

The cross-validation was performed as follows. For each method a duplicate standard curve and validation quality control samples in replicates of five (both GC/MS and HPLC/MS/MS preparations) at 1.00, 250, and 500 ng/ml (Fluoxetine and Norfluoxetine) were extracted according to their respective methods (M2.Fluoxetine.1 Rev.5 and M2.FluoxLCMS.1 Rev New.). The sample pools (V1 through V13) were extracted in replicates of five.

Standard curve parameters and standard readback concentrations are located in Tables B1a and B1b for the HPLC/MS/MS analysis and Tables B3a, B3b, and B3c for the GC/MS analyses. All results are within normal acceptance criteria. Results for the GC/MS and HPLC/MS/MS quality control sample preparations by each method are located in Tables B2a and B2b (for HPLC/MS/MS analysis) and Tables B4a, B4b, and B4c (for GC/MS analyses).

A comparison of the sample pool results by each method are given in Tables B5 and B6. The results showed an accuracy (%RE of means) from -5.26 to 4.85% for Fluoxetine and from -24.29 to 5.54% for Norfluoxetine. The largest error occurs at the two lowest Norfluoxetine concentrations. Based on the acceptable results of the 1.00 ng/ml validation QC samples from each preparation as analyzed by each method, it is hypothesized that the pools were not sufficiently mixed prior to extraction.

XIV. Method Deviation

During the extraction of the cross-validation portion for analysis by HPLC/MS/MS a deviation from the method was performed using non-silanized glassware for the standard curve preparation, the GC/MS quality control samples, and sample pool samples V1-V8. As insufficient sample remained to re-aliquot into silanized glassware, a comparison between using silanized and un-silanized glassware was performed concurrent with specimen analysis. For this determination, a second duplicate standard curve, the HPLC/MS/MS quality control samples (in replicates of five), and the V9-V13 samples were extracted in silanized glassware.

Based on the acceptable results of the silanized curve and silanized QC readbacks against the un-silanized curve (refer to Run 35 data), it is the opinion of the [redacted] Study Director that the use of silanized or un-silanized glassware for the extraction of Fluoxetine/Norfluoxetine Human Plasma samples is equivalent.

[redacted] Date

Validation of Fluoxetine and Norfluoxetine in Human Plasma

Table B1a: Run 35 (LC Validation Run) Standard Curve Readbacks and Parameters

Fluoxetine

Standard Curve Parameters			
Date	Slope	Intercept	Correlation Coefficient
10/10/1997	0.013015	-0.001701	0.997125

Standard Readback Concentrations							
	Nominal Concentrations (ng/ml)						
Date	1.00	2.00	5.00	25.00	100.00	300.00	500.00
10/10/1997	0.98	2.14	4.32	24.89	93.54	301.26	508.86
	1.03	1.99	4.46	26.54	102.92	319.44	528.12
Mean	1.01	2.07	4.39	25.72	98.23	310.35	518.49
%RE	0.50	3.25	-12.20	2.86	-1.77	3.45	3.70

Validation of Fluoxetine and Norfluoxetine in Human Plasma

Table B1b: Run 35 (LC Validation Run) Standard Curve Readbacks and Parameters

Norfluoxetine

Standard Curve Parameters			
Date	Slope	Intercept	Correlation Coefficient
10/10/1997	0.012003	-0.000643	0.993379

Standard Readback Concentrations							
	Nominal Concentrations (ng/ml)						
Date	**1.00**	**2.00**	**5.00**	**25.00**	**100.00**	**300.00**	**500.00**
10/10/1997	1.02	1.69	4.45	24.82	86.80	325.44	563.91
	1.10	2.05	4.30	25.40	103.00	307.44	560.82
Mean	1.06	1.87	4.38	25.11	94.90	316.44	562.37
%RE	6.00	-6.50	-12.50	0.44	-5.10	5.48	12.47

Validation of Fluoxetine and Norfluoxetine in Human Plasma

Table B2a: Run 35 (LC Validation Run) Quality Control Sample Concentrations

Fluoxetine

Analysis Date	Type	Nominal Concentrations (ng/ml) 1.00	250.00	500.00
10/10/1997	GC/MS	0.96	236.73	443.05
		0.85	240.79	417.09
		0.99	216.78	425.68
		0.94	253.14	432.14
		0.89	249.86	462.13
	Mean	0.93	239.46	436.02
	SD	0.06	14.31	17.40
	%RSD	6.04	5.98	3.99
	%RE	-7.40	-4.22	-12.80
	n	5	5	5
	LC/MS/MS	0.97	224.13	464.67
		0.96	240.13	464.77
		0.96	235.28	527.88
		0.93	246.22	494.22
		0.89	239.41	471.08
	Mean	0.94	237.03	484.52
	SD	0.03	8.20	27.11
	%RSD	3.47	3.46	5.59
	%RE	-5.80	-5.19	-3.10
	n	5	5	5
Inter-method %RE (a)		-1.70	1.02	-10.01

(a) Calculated using the means of each extraction type, with LC/MS/MS as nominal.

Validation of Fluoxetine and Norfluoxetine in Human Plasma

Table B2b: Run 35 (LC Validation Run) Quality Control Sample Concentrations

Norfluoxetine

Analysis Date	Type	Nominal Concentrations (ng/ml) 1.00	250.00	500.00
10/10/1997	GC/MS	0.96	250.65	489.27
		0.83	263.94	448.71
		0.90	254.26	446.59
		0.90	256.70	472.10
		0.83	269.53	478.42
	Mean	0.88	259.02	467.02
	SD	0.06	7.63	18.73
	%RSD	6.23	2.95	4.01
	%RE	-11.60	3.61	-6.60
	n	5	5	5
	LC/MS/MS	1.04	244.70	517.55
		0.85	282.99	537.27
		0.91	258.35	530.88
		0.90	275.52	521.75
		0.88	256.91	498.52
	Mean	0.92	263.69	521.19
	SD	0.07	15.39	14.83
	%RSD	7.97	5.84	2.85
	%RE	-8.40	5.48	4.24
	n	5	5	5
Inter-method %RE (a)		-3.49	-1.77	-10.39

(a) Calculated using the means of each extraction type, with LC/MS/MS as nominal.

Validation of Fluoxetine and Norfluoxetine in Human Plasma

Table B3a: Run 4 (GC Validation Run 1) Standard Curve Readbacks and Parameters, Fluoxetine

Standard Curve Parameters				
Analysis Date	A	B	C	Coefficient of Determination
10/9/1997	0.018884	0.913323	-5.724498	0.9996

Standard Readback Concentrations											
Analysis	**Nominal Concentrations (ng/ml)**										
Date	**1.00**	**2.00**	**5.00**	**25.00**	**75.00**	**100.00**	**125.00**	**200.00**	**300.00**	**400.00**	**500.00**
10/9/1997	0.97	2.08	4.71	26.82	71.14	100.13	129.96	202.40	312.69	393.73	505.47
	1.08	1.87	4.86	26.91	71.34	96.16	122.80	203.31	310.75	393.50	480.28
Mean	1.03	1.98	4.79	26.87	71.24	98.15	126.38	202.86	311.72	393.62	492.88
%RE	2.50	-1.25	-4.30	7.46	-5.01	-1.86	1.10	1.43	3.91	-1.60	-1.43

Validation of Fluoxetine and Norfluoxetine in Human Plasma

Table B3b: Run 4 (GC Validation Run 1) Standard Curve Readbacks and Parameters, Norfluoxetine

Standard Curve Parameters				
Analysis Date	A	B	C	Coefficient of Determination
10/9/1997	0.025869	0.868376	-5.486782	0.9991

Standard Readback Concentrations											
Analysis	Nominal Concentrations (ng/ml)										
Date	1.00	2.00	5.00	25.00	75.00	100.00	125.00	200.00	300.00	400.00	500.00
10/9/1997	1.01	2.12	4.68	26.64	68.17	97.85	123.66	200.42	327.70	406.26	509.98
	1.03	1.89	4.71	27.86	70.74	99.74	125.39	210.41	328.01	372.54	452.02
Mean	1.02	2.01	4.70	27.25	69.46	98.80	124.53	205.42	327.86	389.40	481.00
%RE	2.00	0.25	-6.10	9.00	-7.39	-1.21	-0.38	2.71	9.29	-2.65	-3.80

Validation of Fluoxetine and Norfluoxetine in Human Plasma

Table B3c: Run 5 (GC Validation Run 2) Standard Curve Readbacks and Parameters, Norfluoxetine

Standard Curve Parameters				
Analysis Date	A	B	C	Coefficient of Determination
10/13/1997	0.015325	0.925606	-4.900297	0.9993

Standard Readback Concentrations											
Analysis	Nominal Concentrations (ng/ml)										
Date	1.00	2.00	5.00	25.00	75.00	100.00	125.00	200.00	300.00	400.00	500.00
10/13/1997	1.07	1.93	5.24	25.00	70.51	97.84	124.01	213.19	306.69	380.12	481.00
	0.95	2.00	4.84	26.02	75.40	103.32	111.65	204.96	337.27	417.85	474.13
Mean	1.01	1.97	5.04	25.51	72.96	100.58	117.83	209.08	321.98	398.99	477.57
%RE	1.00	-1.75	0.80	2.04	-2.73	0.58	-5.74	4.54	7.33	-0.25	-4.49

Validation of Fluoxetine and Norfluoxetine in Human Plasma

Table B4a: Run 4 (GC Validation Run 1) Quality Control Sample Concentrations Fluoxetine

Analysis Date	Type	Nominal Concentrations (ng/ml) 1.00	250.00	500.00
10/9/1997	GC/MS	0.88	227.56	464.29
		0.84	228.52	433.56
		0.95	228.78	446.47
		0.77	232.66	454.96
		0.86	238.46	439.64
	Mean	0.86	231.20	447.78
	SD	0.07	4.50	12.19
	%RSD	7.58	1.95	2.72
	%RE	-14.00	-7.52	-10.44
	N	5	5	5
	LC/MS/MS	1.01	221.62	478.19
		0.82	228.72	475.10
		0.87	233.82	482.19
		0.97	226.66	492.00
		0.85	219.98	489.40

…continued

(Continued) Validation of Fluoxetine and Norfluoxetine in Human Plasma

Table B4a: Run 4 (GC Validation Run 1) Quality Control Sample Concentrations Fluoxetine

Analysis		Nominal Concentrations (ng/ml)		
Date	Type	1.00	250.00	500.00
	Mean	0.90	226.16	483.38
	SD	0.08	5.57	7.20
	%RSD	9.04	2.46	1.49
	%RE	-9.60	-9.54	-3.32
	N	5	5	5
Inter-method %RE (a)		5.12	-2.18	7.95

(a) Calculated using the means of each extraction type, with GC/MS as nominal.

Validation of Fluoxetine and Norfluoxetine in Human Plasma

Table B4b: Run 4 (GC Validation Run 1) Quality Control Sample Concentrations Norfluoxetine

Analysis Date	Type	Nominal Concentrations (ng/ml) 1.00	250.00	500.00
10/9/1997	GC/MS	1.14	256.67	499.25
		0.97	246.53	471.38
		0.94	266.58	488.20
		0.97	241.81	478.15
		0.91	248.77	494.59
	Mean	0.99	252.07	486.31
	SD	0.09	9.73	11.50
	%RSD	9.09	3.86	2.36
	%RE	-1.40	0.83	-2.74
	N	5	5	5
	LC/MS/MS	1.21	271.47	540.18
		1.09	258.88	509.65
		0.94	276.95	540.46
		1.04	267.39	549.91
		1.08	260.90	576.88

…continued

(Continued) Validation of Fluoxetine and Norfluoxetine in Human Plasma

Table B4b: Run 4 (GC Validation Run 1) Quality Control Sample Concentrations Norfluoxetine

Analysis Date	Type	Nominal Concentrations (ng/ml) 1.00	250.00	500.00
	Mean	1.07	267.12	543.42
	SD	0.10	7.45	24.09
	%RSD	9.08	2.79	4.43
	%RE	7.20	6.85	8.68
	N	5	5	5
Inter-method %RE (a)		8.72	5.97	11.74

(a) Calculated using the means of each extraction type, with GC/MS as nominal.

Validation of Fluoxetine and Norfluoxetine in Human Plasma

Table B4c: Run 5 (GC Validation Run 2) Quality Control Sample Concentrations
Norfluoxetine

Analysis Date	Type	Nominal Concentrations (ng/ml) 1.00	250.00	500.00
10/13/97	GC/MS	1.00	273.30	452.57
		1.03	260.15	503.25
		0.91	252.31	514.01
		0.99	215.53	482.00
		1.07	233.00	458.03
	Mean	1.00	246.86	481.97
	SD	0.06	22.80	27.00
	%RSD	5.92	9.24	5.60
	%RE	0.00	-1.26	-3.61
	n	5	5	5
	LC/MS/MS	0.98	260.50	525.79
		0.88	259.18	529.30
		0.80	273.78	480.85
		0.94	245.69	497.45
		1.04	260.68	555.29
	Mean	0.93	259.97	517.74
	SD	0.09	9.95	29.07
	%RSD	9.95	3.83	5.62
	%RE	-7.20	3.99	3.55
	n	5	5	5
Inter-method %RE (a)		-7.20	5.31	7.42

(a) Calculated using the means of each extraction type, with GC/MS as nominal.

Validation of Fluoxetine and Norfluoxetine in Human Plasma

Table B5: HPLC/MS/MS vs. GC/MS Comparison, Fluoxetine

GC/MS			HPLC/MS/MS			%RE
Filename	Result	Mean	Filename	Result	Mean	of Means
4CV1A	<1.00	<1.00	35v1a	<1.00	<1.00	0.00
4CV1B	<1.00		35v1b	<1.00		
4CV1C	<1.00		35v1c	<1.00		
4CV1D	<1.00		35v1d	<1.00		
4CV1E	<1.00		35v1e	<1.00		
4CV2A	1.39	1.36	35v2a	1.44	1.36	0.59
4CV2B	1.24		35v2b	1.36		
4CV2C	1.41		35v2c	1.29		
4CV2D	1.45		35v2d	1.49		
4CV2E	1.29		35v2e	1.24		
4CV3A	3.02	3.07	35v3a	3.20	2.91	-5.15
4CV3B	2.95		35v3b	2.91		
4CV3C	3.17		35v3c	2.90		
4CV3D	3.15		35v3d	3.09		
4CV3E	3.06		35v3e	2.46		
4CV4A	11.19	11.23	35v4a	11.21	11.38	1.30
4CV4B	11.77		35v4b	11.92		
4CV4C	11.86		35v4c	10.97		
4CV4D	10.37		35v4d	11.76		
4CV4E	10.96		35v4e	11.02		
4CV5A	53.41	57.13	35v5a	53.01	54.12	-5.26
4CV5B	56.84		35v5b	55.28		
4CV5C	61.89		35v5c	52.38		
4CV5D	55.28		35v5d	58.25		
4CV5E	58.22		35v5e	51.69		

…continued

(Continued) Validation of Fluoxetine and Norfluoxetine in Human Plasma

Table B5: HPLC/MS/MS vs. GC/MS Comparison, Fluoxetine

GC/MS			HPLC/MS/MS			%RE
Filename	Result	Mean	Filename	Result	Mean	of Means
4CV6A	104.79	104.75	35v6a	104.95	109.83	4.85
4CV6B	100.06		35v6b	107.22		
4CV6C	107.30		35v6c	109.57		
4CV6D	99.89		35v6d	114.36		
4CV6E	111.69		35v6e	113.05		
4CV7A	223.29	226.01	35v7a	231.76	223.01	-1.32
4CV7B	224.25		35v7b	230.16		
4CV7C	233.10		35v7c	217.44		
4CV7D	231.48		35v7d	213.22		
4CV7E	217.91		35v7e	222.49		

Validation of Fluoxetine and Norfluoxetine in Human Plasma

Table B6: HPLC/MS/MS vs. GC/MS Comparison, Norfluoxetine

GC/MS			HPLC/MS/MS			%RE
Filename	Result	Mean	Filename	Result	Mean	of Means
4CV1A	<1.00	<1.00	35v1a	<1.00	<1.00	0.00
4CV1B	<1.00		35v1b	<1.00		
4CV1C	<1.00		35v1c	<1.00		
4CV1D	<1.00		35v1d	<1.00		
4CV1E	<1.00		35v1e	<1.00		
5CV8A	1.96	1.75	35v8a	1.51	1.33	-24.29
5CV8B	1.70		35v8b	1.25		
5CV8C	1.69		35v8c	1.21		
5CV8D	1.67		35v8d	1.37		
5CV8E	1.75		35v8e	1.30		
5CV9A	3.49	3.46	35v9a	2.95	2.64	-23.69
5CV9B	3.35		35v9b	2.66		
5CV9C	3.26		35v9c	2.53		
5CV9D	3.40		35v9d	2.52		
5CV9E	3.81		35v9e	2.55		
5CV10A	12.01	11.57	35v10a	10.52	10.94	-5.43
5CV10B	11.11		35v10b	10.92		
5CV10C	10.95		35v10c	11.52		
5CV10D	11.85		35v10d	11.01		
5CV10E	11.93		35v10e	10.74		
5CV11A	65.46	64.57	35v11a	70.48	66.42	2.87
5CV11B	66.48		35v11b	62.45		
5CV11C	66.99		35v11c	68.85		
5CV11D	58.93		35v11d	63.50		
5CV11E	64.99		35v11e	66.84		

…continued

(Continued) Validation of Fluoxetine and Norfluoxetine in Human Plasma

Table B6: HPLC/MS/MS vs. GC/MS Comparison, Norfluoxetine

GC/MS			HPLC/MS/MS			%RE
Filename	Result	Mean	Filename	Result	Mean	of Means
5CV12A	118.47	110.15	35v12a	106.94	107.46	-2.45
5CV12B	103.30		35v12b	108.92		
5CV12C	110.14		35v12c	107.71		
5CV12D	103.49		35v12d	100.92		
5CV12E	115.36		35v12e	112.80		
5CV13A	284.98	269.33	35v13a	266.62	284.24	5.54
5CV13B	270.09		35v13b	262.61		
5CV13C	265.45		35v13c	315.58		
5CV13D	264.28		35v13d	284.13		
5CV13E	261.85		35v13e	292.26		

XIV. Appendix C: System Suitability Criteria Assessment

Validation of Fluoxetine and Norfluoxetine in Human Plasma

Appendix C: System Suitability Criteria Assessment

The apex scan number for each component of interest for the 250 ng/ml Quality Control samples are used in the table below to calculate the acceptable relative retention ranges.

Run #	Scan # of Fluoxetine	Relative Retention Fluoxetine	Scan # of d_5-Fluoxetine	Scan # of Norfluoxetine	Relative Retention Norfluoxetine	Scan # of d_4-Norfluoxetine
Run 30	99	1.00	99	89	1.00	89
(validation day 1)	99	1.01	98	89	1.00	89
	99	1.00	99	89	0.99	90
	99	1.00	99	89	1.00	89
	100	1.01	99	90	1.01	89
Run 31	101	1.00	101	93	1.02	91
(validation day 2)	102	1.00	102	91	1.00	91
	101	1.00	101	91	1.00	91
	101	1.00	101	91	1.00	91
	102	0.99	103	92	1.01	91
Run 32	101	1.00	101	92	1.01	91
(validation day 3)	100	1.00	100	91	1.01	90
	101	1.00	101	90	0.99	91
	101	1.00	101	91	1.00	91
	101	1.00	101	92	1.01	91

…continued

(Continued) Validation of Fluoxetine and Norfluoxetine in Human Plasma

Appendix C: System Suitability Criteria Assessment

The apex scan number for each component of interest for the 250 ng/ml Quality Control samples are used in the table below to calculate the acceptable relative retention ranges.

Run #	Scan # of Fluoxetine	Relative Retention Fluoxetine	Scan # of d_5-Fluoxetine	Scan # of Norfluoxetine	Relative Retention Norfluoxetine	Scan # of d_4-Norfluoxetine
	Mean Relative Retention:	1.00			1.00	
	Acceptable Range:					
	-15%	0.85			0.85	
	+15%	1.15			1.15	

Sample Calculation:

Relative Retention: = (scan # of drug "Fluoxetine" / scan # of internal standard "d_5-Fluoxetine")

= 99 / 99

= 1.00

XV. Method Deviation

1. During the extraction of the cross-validation portion for analysis by HPLC/MS/MS a deviation from the method was performed using non-silanized glassware for the standard curve preparation, the GC/MS quality control samples, the HPLC/MS/MS quality control samples and sample pools V1-V8. As insufficient sample remained to re-aliquot into silanized glassware, a comparison between using silanized and un-silanized glassware was performed concurrent with specimen analysis. For this determination, a second duplicate standard curve, one replicate of the GC/MS quality control samples, HPLC/MS/MS quality control samples (in replicates of five) and the V9-V13 samples were extracted in silanized glassware.

   Based on the acceptable results of the silanized curve and silanized QC readbacks against the un-silanized curve (refer to Run 35 data), it is the opinion of the [redacted] Study Director that the use of silanized or un-silanized glassware for the extraction of Fluoxetine/Norfluoxetine Human Plasma samples is equivalent.

2. The ambient extract storage stability was determined by analyzing an entire validation run approximately 36 hours after extraction. The validation IPP indicated the run would be initially analyzed and re-analyzed approximately 24 hours later with results from each analysis being compared. Due to instrumental issues, this analysis design was not performed. An entire validation run was stored at ambient temperature for approximately 36 hours prior to completion of analysis.

   Based on the acceptable results of the validation run in accordance with Lilly SOP DD906-004-03, it is the opinion of the [redacted] Study Director that ambient storage stability for up to 36 hours has been successfully demonstrated.

3. On 10/10/97 (the cross-validation portion analyzed by HPLC/MS/MS) a 0.2M phosphate buffer solution was inadvertently prepared and used in the sample extraction in addition to the required 0.1M phosphate buffer solution.

Based on the acceptable results obtained for the cross-validation samples, it is the opinion of the [redacted] Study Director that the use of the 0.2M phosphate buffer solution did not affect the integrity of the results obtained.

[redacted] _____

1/6/98
_____
Date

XV. Method Deviation

1. During the extraction of the cross-validation portion for analysis by HPLC/MS/MS a deviation from the method was performed using non-silanized glassware for the standard curve preparation, the GC/MS quality control samples, the HPLC/MS/MS quality control samples and sample pools V1-V8. As insufficient sample remained to re-aliquot into silanized glassware, a comparison between using silanized and un-silanized glassware was performed concurrent with specimen analysis. For this determination, a second duplicate standard curve, one replicate of the GC/MS quality control samples, HPLC/MS/MS quality control samples (in replicates of five) and the V9-V13 samples were extracted in silanized glassware.

   Based on the acceptable results of the silanized curve and silanized QC readbacks against the un-silanized curve (refer to Run 35 data), it is the opinion of the [redacted] Study Director that the use of silanized or un-silanized glassware for the extraction of Fluoxetine/Norfluoxetine Human Plasma samples is equivalent.

2. The ambient extract storage stability was determined by analyzing an entire validation run approximately 36 hours after extraction. The validation IPP indicated the run would be initially analyzed and re-analyzed approximately 24 hours later with results from each analysis being compared. Due to instrumental issues, this analysis design was not performed. An entire validation run was stored at ambient temperature for approximately 36 hours prior to completion of analysis.

   Based on the acceptable results of the validation run in accordance with Lilly SOP DD906-004-03, it is the opinion of the [redacted] Study Director that ambient storage stability for up to 36 hours has been successfully demonstrated.

3. On 10/10/97 (the cross-validation portion analyzed by HPLC/MS/MS) a 0.2M phosphate buffer solution was inadvertently prepared and used in the sample extraction in addition to the required 0.1M phosphate buffer solution.

   Based on the acceptable results obtained for the cross-validation samples, it is the opinion of the [redacted] Study Director that the use of the 0.2M phosphate buffer solution did not affect the integrity of the results obtained.

XVI. Amendments

No amendments have been issued for this report as of the report date.

HPLC/MS/MS Method Validation for the Determination of Fluoxetine and Norfluoxetine in Human Plasma

Table 10: Filename System Used for Validation

Run	Sample Identifier	Replicate	Re-injections (may or may not be used)

Runs: 30, 31, 32, 34

Sample Identifier:

pb	=	Blank Plasma
s0	=	0 ng/ml Plasma Calibration Standard
s1	=	1.00 ng/ml Plasma Calibration Standard
s2	=	2.00 ng/ml Plasma Calibration Standard
s3	=	5.00 ng/ml Plasma Calibration Standard
s4	=	25.0 ng/ml Plasma Calibration Standard
s5	=	100 ng/ml Plasma Calibration Standard
s6	=	300 ng/ml Plasma Calibration Standard
s7	=	500 ng/ml Plasma Calibration Standard
vq1	=	1.00 ng/ml Validation Quality Control Sample
q2	=	250 ng/ml Validation Quality Control Sample
vq3	=	500 ng/ml Validation Quality Control Sample
btvq1	=	Bench top Stability 1.00 ng/ml Quality Control Sample
btvq3	=	Bench top Stability 500 ng/ml Quality Control Sample
ftvql	=	Freeze (-20°C)/Thaw (ambient temperature) 1.00 ng/ml Quality Control Sample
ftvq3	=	Freeze (-20°C)/Thaw (ambient temperature) 500 ng/ml Quality Control Sample
a1	=	analytical standard 1.00 ng/ml equivalent
a3	=	analytical standard 500 ng/ml equivalent
pb2a-pb7a	=	plasma blank (specificity)

Replicate: a-e

Validation of Fluoxetine and Norfluoxetine in Human Plasma

Table 10b: 48 Hour Storage Stability (Room Temperature), Norfluoxetine

Standard Curve Parameters			
Date	Slope	Intercept	Correlation Coefficient
10/4/1997	0.017734	-0.003989	0.990858

Standard Readback Concentrations							
	Nominal Concentrations (ng/ml)						
Date	1.00	2.00	5.00	25.00	100.00	300.00	500.00
10/4/1997	0.89	2.49	4.64	23.24	83.90	293.64	541.33
	1.00	*	5.23	21.49	95.56	341.39	552.47
Mean	0.95	-	4.94	22.37	89.73	317.52	546.90
%RE	-5.50	-	-1.30	-10.54	-10.27	5.84	9.38

Quality Control Sample Concentrations					
			Nominal Concentrations (ng/ml)		
Date	Storage Temp.	Time (hours)	1.00	250.00	500.00
10/4/1997	Ambient	48	*	*	782.43
			0.94	587.12	920.47
			1.05	318.90	644.47
			1.04	344.29	535.78
			1.02	329.50	531.64
	Mean		1.01	394.95	682.96
	SD		0.05	128.53	167.59
	%RSD		4.93	32.54	24.54
	%RE		1.25	57.98	36.59
	n		4	4	5

* File Not Used, no signal detected.

HPLC/MS/MS Method Validation for the Determination of Fluoxetine and Norfluoxetine in Human Plasma

Table 11: Filenaming Key for HPLC/MS/MS and GC/MS Cross-Validation

HPLC/MS/MS Analysis:

Run	Sample Identifier	Replicate

Runs: 35 (10/10/97)

Sample Identifier:

Note: An additional "s" prior to these identifiers indicates silylated glassware employed

pb	=	plasma blank
s0	=	0.00 ng/ml Plasma Calibration Standard
s1	=	1.00 ng/ml Plasma Calibration Standard
s2	=	2.00 ng/ml Plasma Calibration Standard
s3	=	5.00 ng/ml Plasma Calibration Standard
s4	=	25.0 ng/ml Plasma Calibration Standard
s5	=	100 ng/ml Plasma Calibration Standard
s6	=	300 ng/ml Plasma Calibration Standard
s7	=	500 ng/ml Plasma Calibration Standard
vq1	=	1.00 ng/ml LC/MS/MS Validation Quality Control Sample
q2	=	250 ng/ml LC/MS/MS Validation Quality Control Sample
vq3	=	500 ng/ml LC/MS/MS Validation Quality Control Sample
vq4	=	1.00 ng/ml GC/MS Validation Quality Control Sample
q5	=	250 ng/ml GC/MS Validation Quality Control Sample
vq6	=	500 ng/ml GC/MS Validation Quality Control Sample
v1-v13	=	Refer to Appendix B in the text for detailed description.

Replicate: a-e

Note: Concentrations of "v" samples (v1-v13) are approximations.

HPLC/MS/MS Method Validation for the Determination of Fluoxetine and Norfluoxetine in Human Plasma

Table 11: Filenaming Key for HPLC/MS/MS and GC/MS Cross-Validation

GC/MS Analysis: Runs 4, 5

Sample Identifier:

A1	=	Analytical Standard
HEX	=	Solvent Blank
PB	=	Plasma Blank
RB	=	Reagent Blank
DB	=	Derivative Blank
S0	=	0.00 ng/ml Plasma Calibration Standard
S1	=	1.00 ng/ml Plasma Calibration Standard
S2	=	2.00 ng/ml Plasma Calibration Standard
S3	=	5.00 ng/ml Plasma Calibration Standard
S4	=	25.0 ng/ml Plasma Calibration Standard
S5	=	75.0 ng/ml Plasma Calibration Standard
S6	=	100 ng/ml Plasma Calibration Standard
S7	=	125 ng/ml Plasma Calibration Standard
S8	=	200 ng/ml Plasma Calibration Standard
S9	=	300 ng/ml Plasma Calibration Standard
S10	=	400 ng/ml Plasma Calibration Standard
S11	=	500 ng/ml Plasma Calibration Standard
QV1A-QV1E	=	1.00 ng/ml GC/MS Quality Control Sample
QV2A-QV2E	=	250 ng/ml GC/MS Quality Control Sample
QV3A-QV3E	=	500 ng/ml GC/MS Quality Control Sample
QV1F-QV1J	=	1.00 ng/ml LC/MS/MS Quality Control Sample
QV2F-QV2J	=	250 ng/ml LC/MS/MS Quality Control Sample
QV3F-QV3J	=	500 ng/ml LC/MS/MS Quality Control Sample

... continued

HPLC/MS/MS Method Validation for the Determination of Fluoxetine and Norfluoxetine in Human Plasma

Table 11: Filenaming Key for HPLC/MS/MS and GC/MS Cross-Validation

CV1	= < 1.00 ng/ml Fluoxetine and Norfluoxetine Validation Sample
CV2	= 1.00 ng/ml Fluoxetine Validation Sample
CV3	= 2.50 ng/ml Fluoxetine Validation Sample
CV4	= 10.0 ng/ml Fluoxetine Validation Sample
CV5	= 50.0 ng/ml Fluoxetine Validation Sample
CV6	= 100 ng/ml Fluoxetine Validation Sample
CV7	= 250 ng/ml Fluxoetine Validation Sample
CV8	= 1.00 ng/ml Norfluoxetine Validation Sample
CV9	= 2.50 ng/ml Norfluoxetine Validation Sample
CV10	= 10.0 ng/ml Nofluoxetine Validation Sample
CV11	= 50.0 ng/ml Norfluoxetine Validation Sample
CV12	= 100 ng/ml Norfluoxetine Validation Sample
CV13	= 250 ng/ml Norfluoxetine Validation Sample

Replicates: A-E, as appropriate

Note: Concentrations of "CV" samples (CV1-CV13) are approximations.

Addendum III to the Report Entitled, "HPLC/MS/MS Method Validation for the Determination of Fluoxetine and Norfluoxetine in Human Plasma [redacted] Job Number: 132019 (Lot: 001)"

Instrument (PE Sciex API-III+) Cross-Validation
[redacted] Job Number: 132019 (Lot: 004)

Analytical Site:	[redacted]
Study Sponsor:	[redacted]
[redacted] **Project Protocol Date:**	September 10, 1998
Analysis Performed By:	[redacted]
Instrumental Analysis Performed By:	[redacted]
Analyst Notebook Numbers:	[redacted]
Date of Analysis:	September 9, 1998
Cross-Validation Report Date:	October 7, 1998

Addendum III to the Report Entitled, "HPLC/MS/MS Method Validation for the Determination of Fluoxetine and Norfluoxetine in Human Plasma
[redacted] Job Number: 132019 (Lot: 001)"

Instrument (PE Sciex API-III+) Cross-Validation
[redacted] Job Number: 132019 (Lot: 004)

THIS STUDY WAS CONDUCTED IN COMPLIANCE WITH GOOD LABORATORY PRACTICES AS DESCRIBED IN THE CODE OF FEDERAL REGULATIONS, TITLE 21:PART 58.

[redacted]

98-Oct-7
Date

Addendum III to the Report Entitled, "HPLC/MS/MS Method Validation for the Determination of Fluoxetine and Norfluoxetine in Human Plasma [redacted] Job Number: 132019 (Lot: 001)"

Instrument (PE Sciex API-III+) Cross-Validation [redacted] Job Number: 132019 (Lot: 004)

[redacted]

[redacted]

10/7/98
Date

10/7/98
Date

10-7-98
Date

10/7/98
Date

10-7-98
Date

[redacted]

[redacted]

QUALITY ASSURANCE DEPARTMENT

The accompanying Final Report entitled: **Addendum III to the Report Entitled, "HPLC/MS/MS Method Validation for the Determination of Fluoxetine and Norfluoxetine in Human Plasma,** [redacted] ***Job Number: 132019 (Lot: 001)", Instrument (PE Sciex API-III+)*** **Cross-Validation,** [redacted] **Job Number: 132019 (Lot: 004)** has been reviewed by the Quality Assurance Department and meets the acceptability requirements of the [redacted] Quality Assurance System. The data in this report were obtained subject to applicable GLP compliance requirements.

The draft report was audited for compliance by the [redacted] Quality Assurance Department on September 25, 1998. The audit results were reported to the [redacted] Study Director on September 25, 1998 and to [redacted] management on October 2, 1998.

The final report was audited for compliance by the [redacted] Quality Assurance Department on October 7, 1998. The audit results were reported to the [redacted] Study Director and to ORS management on October 7, 1998.

[redacted] _____

October 7, 1998
Date

Addendum III, [redacted] Job Number: 132019-004

Analysis Description: Addendum to Validation of an HPLC/MS/MS Method for the Quantitation of Fluoxetine and Norfluoxetine in Human Plasma using Atmospheric Pressure Chemical Ionization, Performed at [redacted]

VI.	**Origin and Purpose:** An HPLC/MS/MS method for the analysis of Fluoxetine and Norfluoxetine in human plasma was validated in the Bioanalytical Mass Spectrometry Department of [redacted] A one day instrument (PE Sciex API-III+) cross-validation was performed in accordance with Eli Lilly and Company SOP DD906-004-03 and the [redacted] Individual Project Protocol (assigned [redacted] Job Number: 132019-004).
VII.	**Summary of the HPLC/MS/MS Method and Cross-Validation Results:** Method Summary: 2.0 ml of 0.1 M potassium phosphate buffer (pH 6.0) and 50 µl of a 2.00 µg/ml internal standard solution are added to 1.0 ml of human plasma. The samples are then loaded onto Isolute Columns and the analytes eluted with 2% ammonium hydroxide in methylene chloride/methanol (80/20). The eluant is evaporated and then reconstituted in 100 µl of 80:20 methanol:0.05% TFA solution. Forty microliters are injected onto the HPLC/MS/MS system. The bioanalytical method for the determination of Fluoxetine and Norfluoxetine concentrations (M2.FluoxLCMS.3, Rev. New) can be found in Appendix A of this report. Analytical Reference Standards: Fluoxetine HCl, lot no. 001PD5, potency 99.80%, expiry: 10/28/2000, Norfluoxetine HCl, lot no. U096FK20, potency 87.60% as a freebase, expiry: 10/28/2001, R-isomer, Fluoxetine internal standard - SN141999-[$^2H_5$] (also referenced as d_5-Fluoxetine), used at 100% purity, lot no. 067, expiry: None as per client's request and Norfluoxetine internal standard - 215299-[$^2H_4$] HCl (also referenced as d_4-Norfluoxetine) used at 100% purity, lot no. 253A, expiry: None as per client's request. All analytical reference standards were supplied by the sponsor. Cross-Validation Summary: The following cross-validation parameters were determined:

1.	Specificity: No significant interfering peaks were observed in any of the plasma blanks in the Fluoxetine, Norfluoxetine, d_5-Fluoxetine or d_4-Norfluoxetine transitions.

2.	Intra-Day Precision and Accuracy: Intra-day precision (%RSD) of ≤5.53% for Fluoxetine and ≤3.16% for Norfluoxetine and intra-day accuracy (%RE) between -0.39 and 13.40% for Fluoxetine and between -1.55 and 12.00% for Norfluoxetine were obtained for quality control samples at 1.00, 250.00 and 500.00 ng/ml.
3.	Range: The cross-validated concentration range for this assay was 1.00 to 500.00 ng/ml for Fluoxetine and Norfluoxetine in human plasma.

VIII.	**Conclusion:** The HPLC/MS/MS method for Fluoxetine and Norfluoxetine has been cross-validated on a PE Sciex API-III+ for the concentration range of 1.00 to 500.00 ng/ml in human plasma. The method has been demonstrated to be precise, accurate, and sufficiently robust for analysis of clinical samples in human plasma.

Written By:

_____ _____

[redacted] Date

[redacted]

Bioanalytical Mass Spectrometry

IX.	Cross-Validation: The HPLC/MS/MS method for the determination of Fluoxetine and Norfluoxetine in human plasma was cross-validated on a PE Sciex API-III+ for the concentration range of 1.00 to 500.00 ng/ml in human plasma in accordance with Eli Lilly and Company SOP DD906-004-03 and the [redacted] IPP (assigned [redacted] Job Number: 132019-004). Calibration standards and quality control samples were prepared by spiking control human plasma with known amounts of drug. Quality control samples were prepared prior to the cross-validation. The following assay cross-validation parameters were determined:

1.	Specificity: No significant interfering peaks due to endogenous compounds or reagents were observed at the retention times of Fluoxetine, Norfluoxetine or internal standards [d_5-Fluoxetine and d_4-Norfluoxetine] in the mass chromatograms of the control human plasma (Figures 1 and 2).
2.	Intra-Day Precision and Accuracy: On the one day of analysis, five replicates of quality control samples at three concentrations (1.00, 250.00 and 500.00 ng/ml) were analyzed. Intra-day precision ranging from 0.48 to 5.53% and intra-day accuracy between -0.39 and 13.40% were obtained for Fluoxetine quality control samples (Table 1). Intra-day precision ranging from 1.10 to 3.16% and intra-day accuracy between -1.55 and 12.00% were obtained for Norfluoxetine quality control samples (Table 2).
3.	Range: A line was fitted through the calibration standards (range 1.00 to 500.00 ng/ml) by weighted regression of the peak area ratio versus concentration ($1/x^2$). A correlation coefficient of 0.998928 for the Fluoxetine calibration curve and 0.998096 for the Norfluoxetine calibration curve were obtained (Tables 1 and 2 and Figures 5 and 6).

	Original printouts of all chromatograms, MacQuan calibration tables, calibration curves, sample queues, an exact copy of the final report, and notebook numbers 3404, 3532, and 3669 will be archived at [redacted] according to [redacted] Standard Operating Procedures AR-1 and AR-2. An exact copy of the cross-validation run, comprising 100% of the chromatograms, are provided to the sponsor.

X.	**SOP Deviation** The Individual Project Protocol (IPP) was inadvertently signed after the date of analysis. It is the opinion of the [redacted] Study Director that this does not adversely affect the results obtained for this cross-validation.

_____ _____

[redacted] Date

[redacted]

Bioanalytical Mass Spectrometry

Instrument (PE Sciex API-III+) Cross-Validation

Table 1: Standard Curve Parameters, Standard Curve Readback Concentrations, and Quality Control (QC) Sample Concentrations Fluoxetine

Standard Curve Parameters

Run Date	Slope (ng/ml)-1	Intercept	Correlation Coefficient
1 9/9/98	0.011481	-0.001535	0.998928

Standard Curve Readback Concentrations

Run Date	Nominal Concentrations (ng/ml) 1.00	2.00	5.00	25.00	100.00	300.00	500.00
1 9/9/98	1.06	1.99	4.91	25.24	96.62	304.17	518.11
	0.97	1.92	4.73	26.78	97.70	292.92	515.63
Mean	1.02	1.96	4.82	26.01	97.16	298.55	516.87
%RE	1.50	-2.25	-3.60	4.04	-2.84	-0.49	3.37
n	2	2	2	2	2	2	2

Quality Control (QC) Sample Concentrations

Run Date	Nominal Concentrations (ng/ml) 1.00	250.00	500.00
1 9/9/98	1.18	248.43	514.99
	1.20	248.61	518.86
	1.15	250.30	508.17
	1.05	247.60	501.42
	1.09	250.23	511.60
Mean	1.13	249.03	511.01
SD	0.06	1.19	6.67
%RSD	5.53	0.48	1.30
%RE	13.40	-0.39	2.20
n	5	5	5

Instrument (PE Sciex API-III+) Cross-Validation

Table 2: Standard Curve Parameters, Standard Curve Readback Concentrations, and Quality Control (QC) Sample Concentrations Norfluoxetine

Standard Curve Parameters

Run Date	Slope (ng/ml)-1	Intercept	Correlation Coefficient
1 9/9/98	0.011321	0.000846	0.998096

Standard Curve Readback Concentrations

Run Date	Nominal Concentrations (ng/ml) 1.00	2.00	5.00	25.00	100.00	300.00	500.00
1 9/9/98	1.10	1.79	4.86	25.26	99.70	307.46	509.57
	0.99	1.88	4.86	26.88	101.31	289.90	511.82
Mean	1.05	1.84	4.86	26.07	100.51	298.68	510.70
%RE	4.50	-8.25	-2.80	4.28	0.51	-0.44	2.14
n	2	2	2	2	2	2	2

Quality Control (QC) Sample Concentrations

Run Date	Nominal Concentrations (ng/ml) 1.00	250.00	500.00
1 9/9/98	1.10	246.57	500.92
	1.12	243.60	518.24
	1.09	243.85	500.64
	1.11	250.30	496.53
	1.18	246.31	491.32
Mean	1.12	246.13	501.53
SD	0.04	2.70	10.12
%RSD	3.16	1.10	2.02
%RE	12.00	-1.55	0.31
n	5	5	5

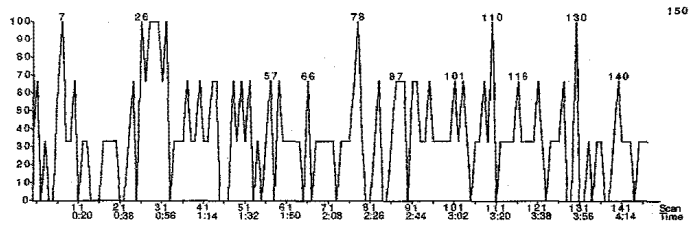
Figure 1: Representative Chromatogram of Fluoxetine and Norfluoxetine in Human Plasma, Human Plasma Blank

MacQuan, version 1.3-FPU Page 2 of 33
Printed: Wed, Sep 30, 1998 16:15
Calibration File: FluoxXVAL1calA Path: Sciex Data Drive:Data 9/98:Lilly:Fluoxetine:Validation:FluoxXVAL1:

1bpb plasma blank
plasma blank

4:29 in 1 period
1: 0:00 MRM, 149 scans
310.1->43.9
Fluoxetine
Internal Standard: D5-Fluoxetine
Use Area
Absolute Retention Time
Noise Threshold 10.0
Quant Threshold 2.0
Min. Width 4.0
Multiplet Width 2.0
Baseline Width 40.0
RT Window (secs) 20.0
Expected RT 1:57
Area 0
Height 0
Start Time 0:00.0
End Time 0:00.0
Integration Width 0:00.0
Retention Time 0:00.0
Signal to Noise 0.00

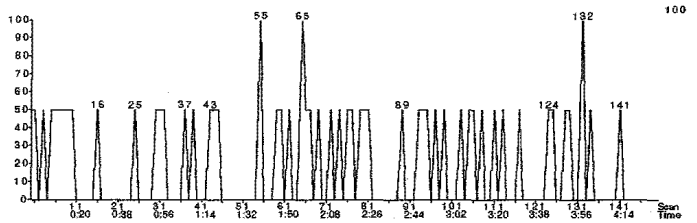
plasma blank Wed, Sep 9, 1998 22:48



1bpb plasma blank
plasma blank

4:29 in 1 period
1: 0:00 MRM, 149 scans
296.1->133.9
Norfluoxetine
Internal Standard: D4-Norfluoxetine
Use Area
Absolute Retention Time
Noise Threshold 10.0
Quant Threshold 2.0
Min. Width 4.0
Multiplet Width 2.0
Baseline Width 40.0
RT Window (secs) 20.0
Expected RT 1:52
Area 0
Height 0
Start Time 0:00.0
End Time 0:00.0
Integration Width 0:00.0
Retention Time 0:00.0
Signal to Noise 0.00

plasma blank Wed, Sep 9, 1998 22:48

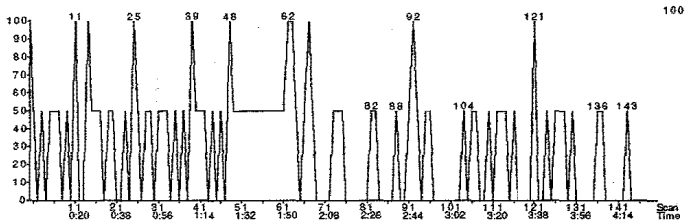


1bpb plasma blank
plasma blank

4:29 in 1 period
1: 0:00 MRM, 149 scans
315.1->43.9
D5-Fluoxetine
use as Internal Standard

Noise Threshold 10.0
Quant Threshold 2.0
Min. Width 4.0
Multiplet Width 2.0
Baseline Width 40.0
RT Window (secs) 20.0
Expected RT 1:57
Area 0
Height 0
Start Time 0:00.0
End Time 0:00.0
Integration Width 0:00.0
Retention Time 0:00.0
Signal to Noise 0.00

plasma blank Wed, Sep 9, 1998 22:48



1bpb plasma blank
plasma blank

4:29 in 1 period
1: 0:00 MRM, 149 scans
300.1->133.9
D4-Norfluoxetine
use as Internal Standard

Noise Threshold 10.0
Quant Threshold 2.0
Min. Width 4.0
Multiplet Width 2.0
Baseline Width 40.0
RT Window (secs) 20.0
Expected RT 1:50
Area 0
Height 0
Start Time 0:00.0
End Time 0:00.0
Integration Width 0:00.0
Retention Time 0:00.0
Signal to Noise 0.00

plasma blank Wed, Sep 9, 1998 22:48

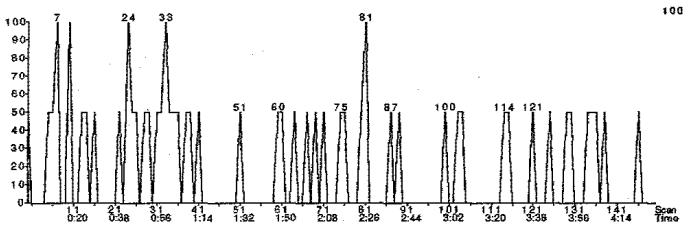


Figure 2: **Representative Chromatogram of d_5-Fluoxetine and d_4-Norfluoxetine in Human Plasma, 0.00 ng/ml Calibration Standard (Internal Standard Only)**

MacQuan, version 1.3-FPU
Printed: Wed, Sep 30, 1998 16:15
Calibration File: FluoxXVAL1calA Path: Sciex Data Drive:Data 9/98:Lilly:Fluoxetine:Validation:FluoxXVAL1:

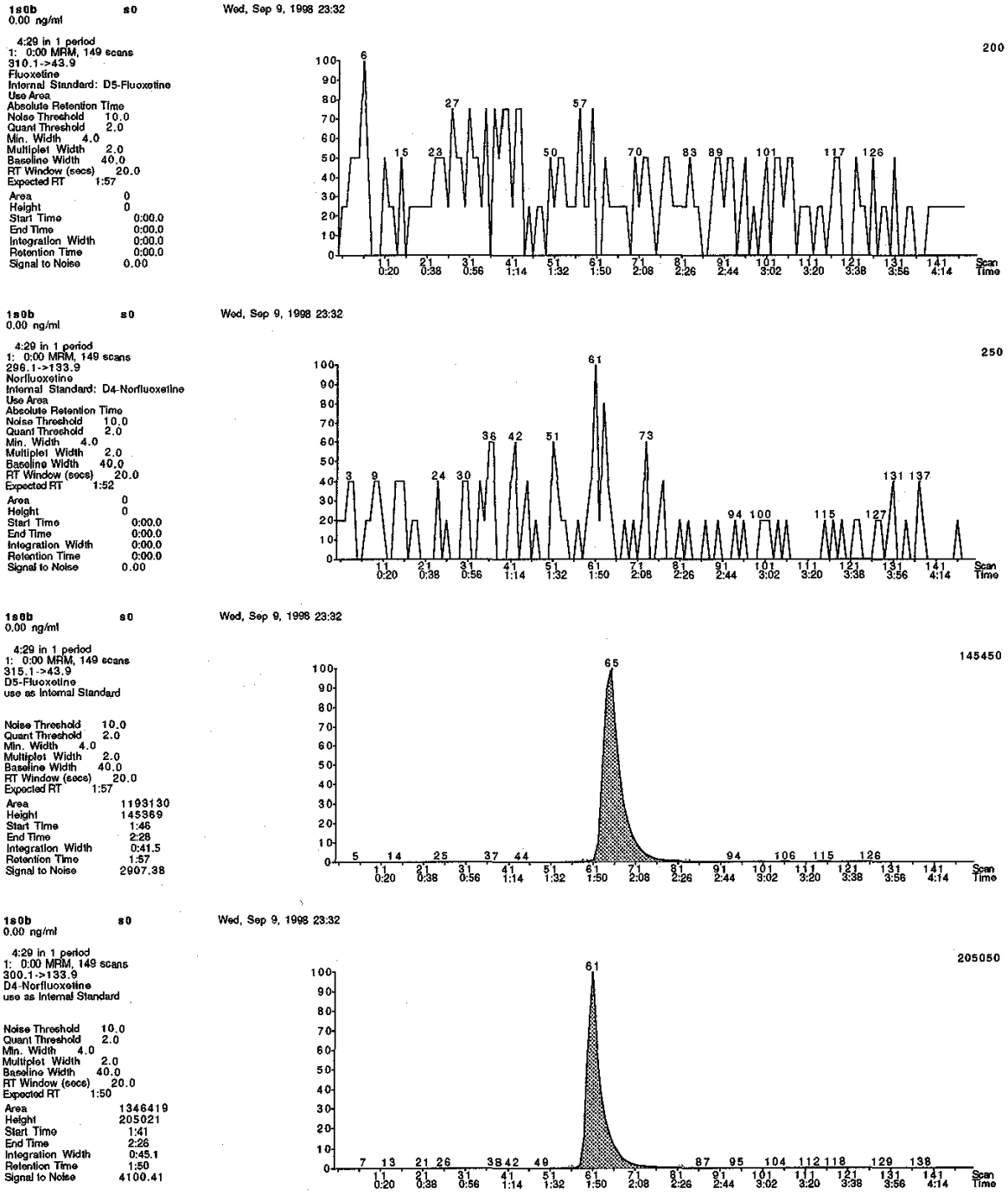


Figure 3: **Representative Chromatogram of Fluoxetine and Norfluoxetine in Human Plasma, 1.00 ng/ml Plasma Calibration Standard**

MacQuan, version 1.3-FPU

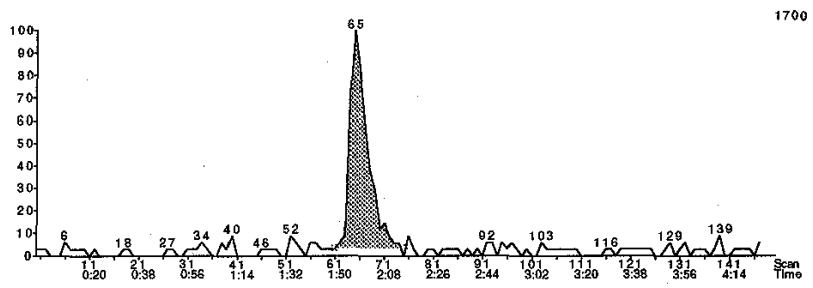
Printed: Wed, Sep 30, 1998 16:15

Calibration File: FluoxXVAL1calA Path: Sciex Data Drive:Data 9/98:Lilly:Fluoxetine:Validation:FluoxXVAL1:

1s1a s1 Wed, Sep 9, 1998 22:53
1.00 ng/ml

4:29 in 1 period
1: 0:00 MRM, 149 scans
310.1->43.9
Fluoxetine
Internal Standard: D5-Fluoxetine
Use Area
Absolute Retention Time
Noise Threshold 10.0
Quant Threshold 2.0
Min. Width 4.0
Multiplet Width 2.0
Baseline Width 40.0
RT Window (secs) 20.0
Expected RT 1:57

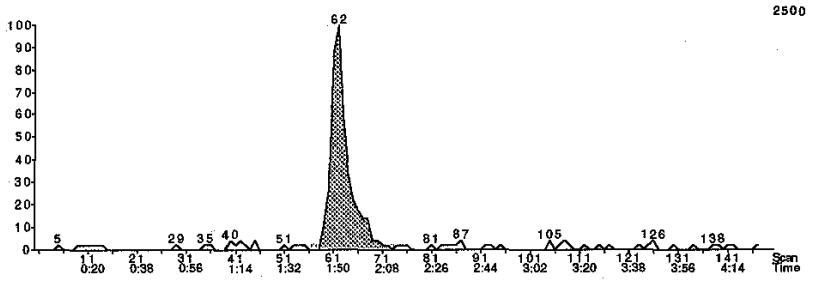
Area	12022
Height	1638
Start Time	1:50
End Time	2:13
Integration Width	0:23.4
Retention Time	1:57
Signal to Noise	32.77



1s1a s1 Wed, Sep 9, 1998 22:53
1.00 ng/ml

4:29 in 1 period
1: 0:00 MRM, 149 scans
296.1->133.9
Norfluoxetine
Internal Standard: D4-Norfluoxetine
Use Area
Absolute Retention Time
Noise Threshold 10.0
Quant Threshold 2.0
Min. Width 4.0
Multiplet Width 2.0
Baseline Width 40.0
RT Window (secs) 20.0
Expected RT 1:52

Area	17055
Height	2477
Start Time	1:43
End Time	2:10
Integration Width	0:27.1
Retention Time	1:52
Signal to Noise	49.55

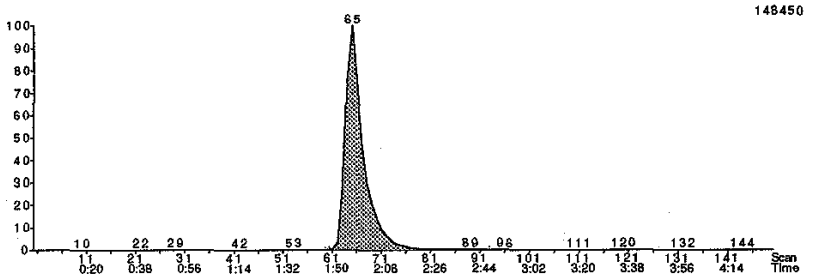


1s1a s1 Wed, Sep 9, 1998 22:53
1.00 ng/ml

4:29 in 1 period
1: 0:00 MRM, 149 scans
315.1->43.9
D5-Fluoxetine
use as Internal Standard

Noise Threshold 10.0
Quant Threshold 2.0
Min. Width 4.0
Multiplet Width 2.0
Baseline Width 40.0
RT Window (secs) 20.0
Expected RT 1:57

Area	1124636
Height	148350
Start Time	1:48
End Time	2:46
Integration Width	0:57.7
Retention Time	1:57
Signal to Noise	2967.00



1s1a s1 Wed, Sep 9, 1998 22:53
1.00 ng/ml

4:29 in 1 period
1: 0:00 MRM, 149 scans
300.1->133.9
D4-Norfluoxetine
use as Internal Standard

Noise Threshold 10.0
Quant Threshold 2.0
Min. Width 4.0
Multiplet Width 2.0
Baseline Width 40.0
RT Window (secs) 20.0
Expected RT 1:50

Area	1279553
Height	187558
Start Time	1:41
End Time	2:35
Integration Width	0:54.1
Retention Time	1:50
Signal to Noise	3686.49

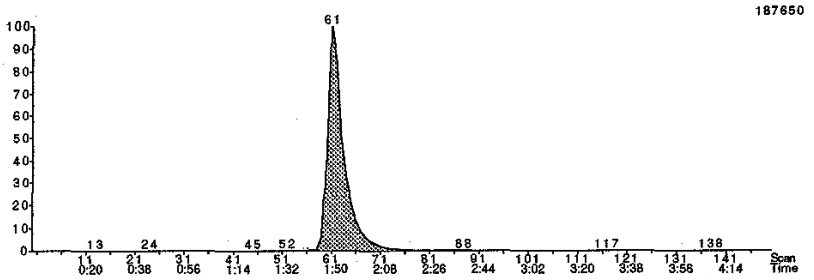


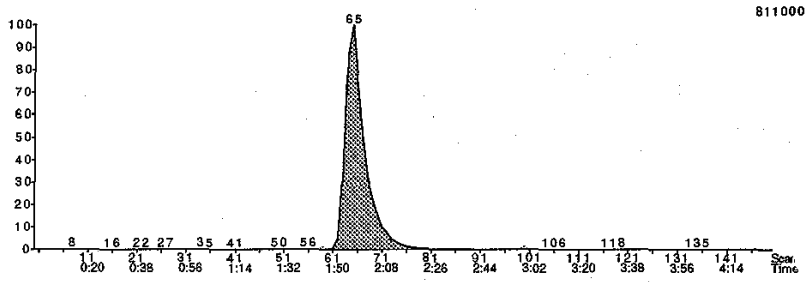
Figure 4: **Representative Chromatogram of Fluoxetine and Norfluoxetine in Human Plasma, 500.00 ng/ml Plasma Calibration Standard**

MacQuan, version 1.3-FPU
Printed: Wed, Sep 30, 1998 16:16
Calibration File: FluoxXVAL1calA Path: Sciex Data Drive:Data 9/98:Lilly:Fluoxetine:Validation:FluoxXVAL1:

1s7a s7 Thu, Sep 10, 1998 00:41
500 ng/ml

4:28 in 1 period
1: 0:00 MRM, 149 scans
310.1->43.9
Fluoxetine
Internal Standard: D5-Fluoxetine
Use Area
Absolute Retention Time
Noise Threshold 10.0
Quant Threshold 2.0
Min. Width 4.0
Multiplet Width 2.0
Baseline Width 40.0
RT Window (secs) 20.0
Expected RT 1:57

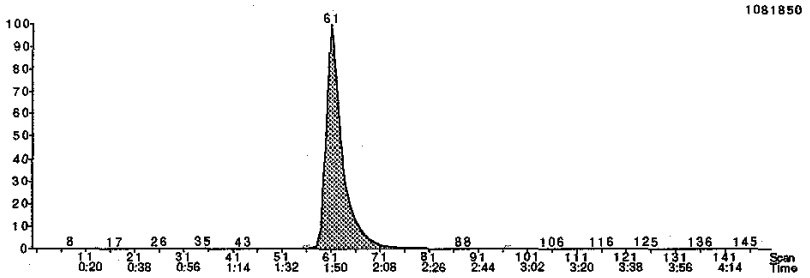
Area	6632871
Height	810734
Start Time	1:46
End Time	2:59
Integration Width	1:12
Retention Time	1:57
Signal to Noise	14452.21



1s7a s7 Thu, Sep 10, 1998 00:41
500 ng/ml

4:28 in 1 period
1: 0:00 MRM, 149 scans
296.1->133.9
Norfluoxetine
Internal Standard: D4-Norfluoxetine
Use Area
Absolute Retention Time
Noise Threshold 10.0
Quant Threshold 2.0
Min. Width 4.0
Multiplet Width 2.0
Baseline Width 40.0
RT Window (secs) 20.0
Expected RT 1:52

Area	7309471
Height	1081701
Start Time	1:41
End Time	2:53
Integration Width	1:12
Retention Time	1:50
Signal to Noise	20552.31

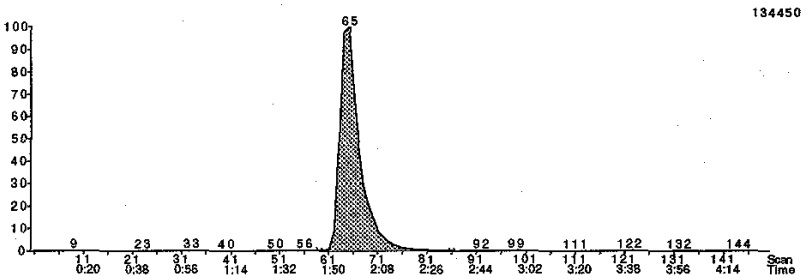


1s7a s7 Thu, Sep 10, 1998 00:41
500 ng/ml

4:28 in 1 period
1: 0:00 MRM, 149 scans
315.1->43.9
D5-Fluoxetine
use as Internal Standard

Noise Threshold 10.0
Quant Threshold 2.0
Min. Width 4.0
Multiplet Width 2.0
Baseline Width 40.0
RT Window (secs) 20.0
Expected RT 1:57

Area	1115388
Height	134341
Start Time	1:46
End Time	2:33
Integration Width	0:46.9
Retention Time	1:57
Signal to Noise	2639.69



1s7a s7 Thu, Sep 10, 1998 00:41
500 ng/ml

4:28 in 1 period
1: 0:00 MRM, 149 scans
300.1->133.9
D4-Norfluoxetine
use as Internal Standard

Noise Threshold 10.0
Quant Threshold 2.0
Min. Width 4.0
Multiplet Width 2.0
Baseline Width 40.0
RT Window (secs) 20.0
Expected RT 1:50

Area	1266856
Height	201350
Start Time	1:41
End Time	2:26
Integration Width	0:45.1
Retention Time	1:50
Signal to Noise	4027.00

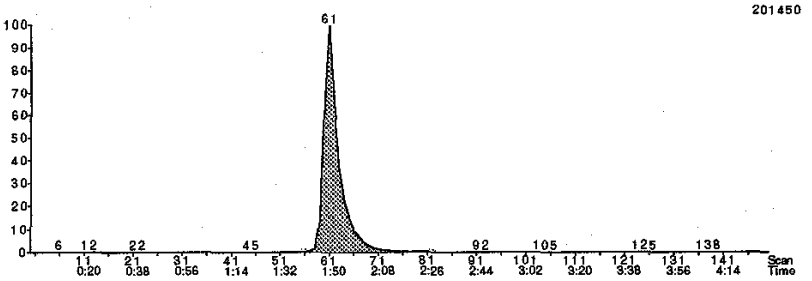


Figure 5: **Standard Curve of Fluoxetine in Human Plasma, Run 1**

MacQuan, version 1.3-FPU
Printed: Wed, Sep 30, 1998 16:14
Calibration File: FluoxXVAL1calA Path: Sciex Data Drive:Data 9/98:Lilly:Fluoxetine:Validation:FluoxXVAL1:

Fluoxetine 310.1->43.9 Internal Standard: D5-Fluoxetine
Weighted (1/x*x)
Intercept = -0.001535
Slope = 0.011481
Correlation Coeff. = 0.998928

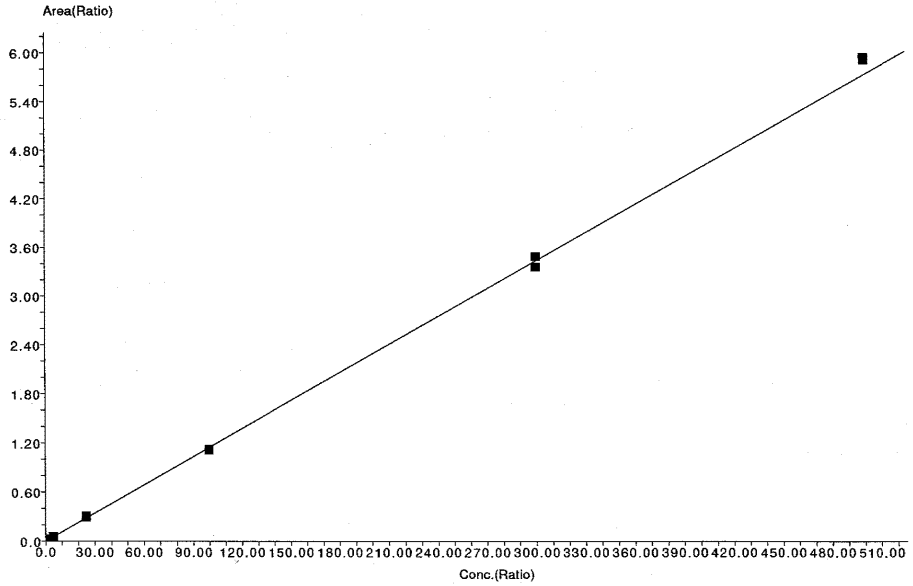
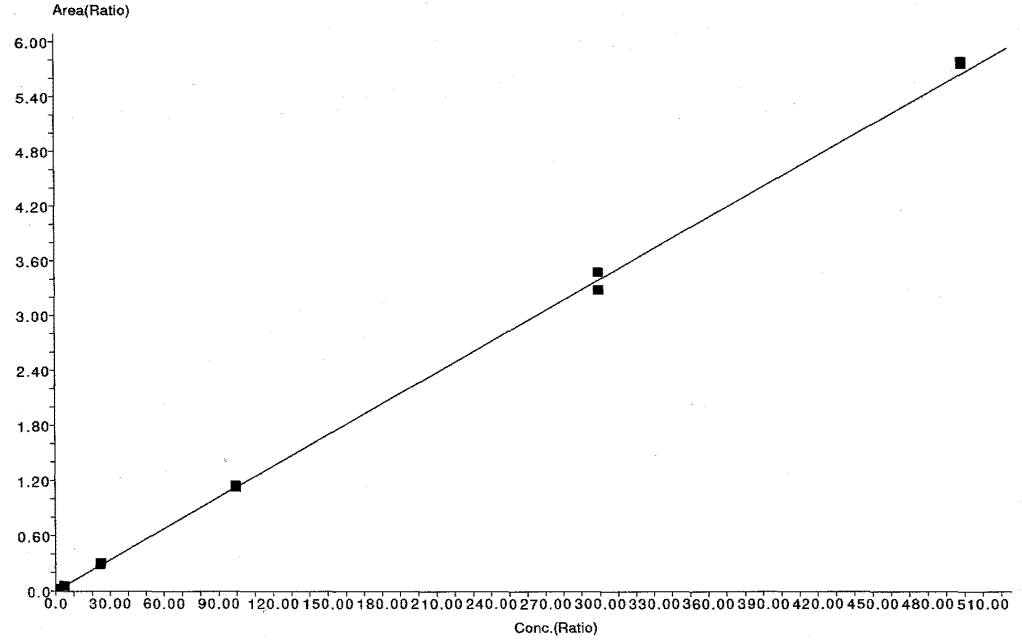


Figure 6: Standard Curve of Norfluoxetine in Human Plasma, Run 1

MacQuan, version 1.3-FPU
Printed: Wed, Sep 30, 1998 16:15
Calibration File: FluoxXVAL1calA Path: Sciex Data Drive:Data 9/98:Lilly:Fluoxetine:Validation:FluoxXVAL1:

Page 1 of 1

Norfluoxetine 296.1->133.9 Internal Standard: D4-Norfluoxetine
Weighted (1/x*x)
Intercept = 0.000846
Slope = 0.011321
Correlation Coeff. = 0.998096



XIII. Appendix A

XIV. Amendments

No amendments have been issued for this report as of the report date.

Instrument (PE Sciex API-III+) Cross Validation
Table 3: Filename System

_____ _____

1 2

1)	Run #	
	1	Cross-Validation Run 1 (9/9/98)
2)	Sample	
	Blanks:	
	bpa, bpb	Plasma Blank
	Calibration Standards:	
	s0a, s0b	Zero Point
	s1a, s1b	1.00 ng/ml
	s2a, s2b	2.00 ng/ml
	s3a, s3b	5.00 ng/ml
	s4a, s4b	25.00 ng/ml
	s5a, s5b	100.00 ng/ml
	s6a, s6b	300.00 ng/ml
	s7a, s7b	500.00 ng/ml
	Quality Control Samples:	
	q1a-q1e	1.00 ng/ml
	q2a-q2e	250.00 ng/ml
	q3a-q3e	500.00 ng/ml

Instrument (PE Sciex API-III+) Cross-Validation

Table 1: Standard Curve Parameters, Standard Curve Readback Concentrations, and Quality Control (QC) Sample Concentrations Fluoxetine

Standard Curve Parameters

Run Date	Slope $(ng/ml)^{-1}$	Intercept	Correlation Coefficient
1 9/9/1998	0.011481	-0.001535	0.998928

Standard Curve Readback Concentrations

Run Date	Nominal Concentrations (ng/ml) 1.00	2.00	5.00	25.00	100.00	300.00	500.00
1	1.06	1.99	4.91	25.24	96.62	304.17	518.11
######	0.97	1.92	4.73	26.78	97.70	292.92	515.63
Mean	1.02	1.96	4.82	26.01	97.16	298.55	516.87
%RE	1.50	-2.25	-3.60	4.04	-2.84	-0.49	3.37
n	2	2	2	2	2	2	2

Quality Control (QC) Sample Concentrations

Run Date	Nominal Concentrations (ng/ml) 1.00	250.00	500.00
1 9/9/1998	1.18	248.43	514.99
	1.20	248.61	518.86
	1.15	250.30	508.17
	1.05	247.60	501.42
	1.09	250.23	511.60
Mean	1.13	249.03	511.01
SD	0.06	1.19	6.67
%RSD	5.53	0.48	1.30
%RE	13.40	-0.39	2.20
n	5	5	5

Instrument (PE Sciex API-III+) Cross-Validation

Table 2: Standard Curve Parameters, Standard Curve Readback Concentrations, and Quality Control (QC) Sample Concentrations Norfluoxetine

Standard Curve Parameters

Run Date	Slope $(ng/ml)^{-1}$	Intercept	Correlation Coefficient
1 9/9/1998	0.011321	0.000846	0.998096

Standard Curve Readback Concentrations

Run Date	Nominal Concentrations (ng/ml) 1.00	2.00	5.00	25.00	100.00	300.00	500.00
1	1.10	1.79	4.86	25.26	99.70	307.46	509.57
######	0.99	1.88	4.86	26.88	101.31	289.90	511.82
Mean	1.05	1.84	4.86	26.07	100.51	298.68	510.70
%RE	4.50	-8.25	-2.80	4.28	0.51	-0.44	2.14
n	2	2	2	2	2	2	2

Quality Control (QC) Sample Concentrations

Run Date	Nominal Concentrations (ng/ml) 1.00	250.00	500.00
1	1.10	246.57	500.92
9/9/1998	1.12	243.60	518.24
	1.09	243.85	500.64
	1.11	250.30	496.53
	1.18	246.31	491.32
Mean	1.12	246.13	501.53
SD	0.04	2.70	10.12
%RSD	3.16	1.10	2.02
%RE	12.00	-1.55	0.31
n	5	5	5

Addendum VI to Validation Report

HPLC/MS/MS Method Validation for the Determination of Fluoxetine and Norfluoxetine in Human Plasma

Frozen Stability Assessment at -20°C and -70°C

[redacted] Job Number 132019 (Lot 007)

Report Written by:
[redacted]
Bioanalytical Group

[redacted]

February 2000

Quality Assurance Review Statement

Title: HPLC/MS/MS Method Validation for the Determination of Fluoxetine and Norfluoxetine in Human Plasma; Frozen Stability Assesment at -20°C and -70°C

Report #: [redacted] Job Number 132019 (Lot 007)

Quality Assurance Inspections:

Date of Inspection	Date Reported to Management	Phase of Study Inspected
1/12/00, 1/13/00	1/24/00	Report (Draft)
2/28/00	2/28/00	Report (Draft)

The Quality Assurance Unit has reviewed the final study report and has determined that the report accurately reflects the raw data generated during the conduct of this study.

_____ _____

[redacted] (Date)

Signatures

Sponsor: Eli Lilly and Company

[redacted] Job Number: 132019 (Lot 007)

Analysts: [redacted]

To the best of our knowledge this report has been reviewed for completeness, accuracy, and compliance with the protocol and SOPs

_____ _____

[redacted] (Date)

Bioanalytical Group

Addendum VI to Validation Report

HPLC/MS/MS Method Validation for the Determination of Fluoxetine and Norfluoxetine in Human Plasma; Frozen Stability Assessment at -20°C and -70°C

Analysis Description

Addendum to Validation of an HPLC/MS/MS Method for the Quantitation of Fluoxetine and Norfluoxetine in Human Plasma using Atmospheric Pressure Chemical Ionization, Performed at [redacted]

Origin and Purpose

An HPLC/MS/MS method for the analysis of Fluoxetine and Norfluoxetine in human plasma was validated in the Bioanalytical Mass Spectrometry Department of [redacted] [Method M2.FluoxLCMS.1, Revision 1] and cross-validated for a PE Sciex API-III+ [Method M2.FluoxLCMS.3, Revision New]. Frozen stability assessment at -20°C and -70°C was performed in accordance with Eli Lilly and Company SOP DD906-004-03 using method M2.FluoxLCMS.3, Revision New and M2.FluoxLCMS.1, Revision 1.

Summary of HPLC/MS/MS Method

Method Summary

2.0 mL of 0.1 M potassium phosphate buffer (pH 6.0) and 50 µL of a 2.00 µg/mL internal standard solution are added to 1.0 mL of human plasma. The samples are then loaded onto Isolute Columns and the analytes eluted with 2% ammonium hydroxide in methylene chloride/methanol (80/20). The eluant is evaporated and then reconstituted in 100 µL of 80/20 methanol/0.05% TFA. A 40 µL aliquot is analyzed by HPLC/MS/MS.

Analytical Reference Standards

Fluoxetine HCl, salt correction factor = 0.89456, lot no. 001PD5, potency 99.80%, expiry: 10/28/2000, Norfluoxetine HCl, lot no. U096FK20, potency 87.60% as a freebase, expiry: 10/28/2001, R-isomer, Fluoxetine internal standard - SN141999-[$^{2}H_{5}$] (also referenced as d_5-Fluoxetine), used at 100% purity, lot no. 067, expiry: None as per client's request; and Norfluoxetine internal standard - 215229-[$^{2}H_{4}$] HCl (also referenced

as d_4-Norfluoxetine) used at 100% purity, lot no. 253A, expiry: None as per client's request. All analytical reference standards were supplied by the sponsor.

Frozen Stability Assessment

Quality control (QC) samples at concentrations of 2.50, 250.00, and 400.00 ng/mL were prepared in human plasma in replicates of five and an initial analysis was performed on 2/25/98. The samples were stored at -20°C and -70°C. Subsequent analyses were performed at time periods of approximately 1 month (3/26/98), 3 months (5/19/98), 6 months (9/1/98), 12 months (2/26/99), 15 months (5/20/99), and 18 months (8/25/99). Standard curve parameters, standard curve readback concentrations, and run acceptance quality control sample results for these runs are provided in Tables 1a, 1b, 2a, 2b, 3a, and 3b. In Run 49 (3/26/98), run acceptance quality control samples were not analyzed.

For samples stored at -20°C, the accuracy, as measured by %RE for the initial QC samples, ranged from -2.84% to 3.36% for Fluoxetine and from -4.64% to 0.34% for Norfluoxetine. The accuracy for the QC samples stored for approximately 1 month ranged from 5.60% to 8.85% for Fluoxetine and from 0.40% to 7.01% for Norfluoxetine. The accuracy for the QC samples stored for approximately 3 months ranged from -2.24% to 0.27% for Fluoxetine and from -2.64% to 2.74% for Norfluoxetine. The accuracy for the QC samples stored for approximately 6 months ranged from 0.23% to 5.92% for Fluoxetine and from -0.06% to 5.12% for Norfluoxetine. The accuracy for the QC samples stored for approximately 12 months ranged from -4.86% to 9.76% for Fluoxetine and from -10.02% to 3.76% for Norfluoxetine. The accuracy for the QC samples stored for approximately 15 months ranged from -6.00% to -2.04% for Fluoxetine and from -11.97% to -4.00% for Norfluoxetine. The accuracy for the QC samples stored for approximately 18 months ranged from -4.88% to -0.93% for Fluoxetine and from -5.52% to -1.34% for Norfluoxetine (Tables 4a and 4b).

For samples stored at -70°C, the accuracy, as measured by %RE for the initial QC samples, ranged from -2.84% to 3.36% for Fluoxetine and from -4.64% to 0.34% for Norfluoxetine. The accuracy for the QC samples stored for approximately 1 month ranged from 7.14% to 11.44% for Fluoxetine and from -3.12% to 4.73% for Norfluoxetine. The accuracy for the QC samples stored at approximately 3 months ranged from -2.06% to 2.32% for Fluoxetine and from -3.99% to -2.26% for Norfluoxetine. The accuracy for the QC samples stored for approximately 6 months ranged from -1.15% to 7.44% for Fluoxetine and from -1.95% to 3.36% for Norfluoxetine. The accuracy for the QC samples stored for approximately 12 months ranged from -1.67% to 9.36% for Fluoxetine and from -5.95% to 2.72% for Norfluoxetine. The accuracy for the QC samples stored for approximately 15 months ranged from -3.63% to 0.16% for Fluoxetine and from -7.84% to 0.80% for Norfluoxetine. The accuracy for the QC samples stored for approximately 18 months ranged from -0.24% to 0.51% for Fluoxetine and from -0.56% to 2.26% for Norfluoxetine (Tables 5a and 5b).

Raw Data

Original printouts of chromatograms, MacQuan calibration tables, calibration curves, sample queues, an exact copy of the final report, and notebook numbers 3404, 3532, 3668, 3669, 3745, 3827, 3835, and 3856 will be archived at [redacted] according to [redacted] Standard Operating Procedures AR-1 and AR-2. Included in this report are exact copies of 100% of the chromatograms that were generated.

Deviations

Method Deviations

In Run 64 (2/26/99), 15 µL injections were made on the HPLC/MS/MS system instead of 40 µL injections.

In Run 66 (5/20/99), 10 µL injections were made on the HPLC/MS/MS system instead of 40 µL injections.

IPP Deviations

The validation IPP states that two concentrations (1.00 and 500.00 ng/mL) would be assessed at 1, 3, 6, 9, and 12 months. Instead, three concentrations (2.50, 250.00, and 400.00 ng/mL) were assessed at 1, 3, 6, 12, 15, and 18 months.

It is the opinion of the [redacted] Study Director that the above deviations do not impact the integrity of the data.

_____ _____

[redacted] (Date)

Conclusion

The HPLC/MS/MS method for Fluoxetine and Norfluoxetine in human plasma has demonstrated frozen stability for up to approximately 18 months when samples are stored at -20°C or -70°C.

Table 1a: Frozen Stability Assessment at -20°C and -70°C, Standard Curve Parameters, Fluoxetine

Run	Date	Slope $(ng/mL)^{-1}$	Intercept	Correlation Coefficient
44	2/25/98	0.012603993	-0.000936081	0.997719
49	3/26/98	0.011044719	-0.002396814	0.996017
53	5/19/98	0.010710325	-0.001468767	0.995285
61	9/1/98	0.007282171	-0.001008668	0.995303
64	2/26/99	0.013047	-0.001554	0.999369
66	5/20/99	0.013636	-0.000032	0.996717
1	8/25/99	0.012095389	0.001635192	0.998997
	Mean	0.011489	-0.000823	0.997058
	SD	0.00213	-	0.00168
	% RSD	18.5	-	0.169
	n	7	7	7

Table 1b: Frozen Stability Assessment at -20°C and -70°C, Standard Curve Parameters, Norfluoxetine

Run	Date	Slope $(ng/mL)^{-1}$	Intercept	Correlation Coefficient
44	2/25/98	0.012045874	0.001395238	0.998005
49	3/26/98	0.012823081	-0.001835035	0.991135
53	5/19/98	0.011433072	-0.000656898	0.994425
61	9/1/98	0.013259484	-0.000769667	0.996350
64	2/26/99	0.012131	0.000658	0.998842
66	5/20/99	0.012800	0.000694	0.998093
1	8/25/99	0.011436353	0.001231790	0.998764
	Mean	0.012276	0.000102	0.996516
	SD	0.000711	-	0.00284
	% RSD	5.79	-	0.285
	n	7	7	7

Table 2a: Frozen Stability Assessment at -20°C and -70°C, Standard Curve Readback Concentrations, Fluoxetine

			Acceptance Criteria				
-30%	0.70	1.40	3.50	17.50	70.00	210.00	350.00
+30%	1.30	2.60	6.50	32.50	130.00	390.00	650.00
			Nominal Concentrations (ng/mL)				
Run	1.00	2.00	5.00	25.00	100.00	300.00	500.00
44	1.07	2.17	5.08	25.70	105.77	313.16	479.67
	0.94	1.83	4.80	24.99	97.60	313.04	456.19
49	1.03	1.78	4.38	24.75	107.87	324.15	519.88
	1.10	1.90	4.52	25.23	101.15	326.08	481.64
53	1.18	1.83	4.95	23.29	100.21	307.47	551.69
	0.86	2.04	4.82	25.83	93.36	317.71	489.48
61	1.07	1.85	4.64	26.23	98.93	301.37	587.27
	1.07	1.72	4.57	26.40	94.44	303.90	504.19
64	0.97	2.02	4.94	25.42	100.10	303.35	502.67
	1.05	1.99	4.59	25.55	101.68	295.71	506.32
66	0.96	2.02	4.25	23.95	101.30	303.15	524.53
	1.11	1.76	5.27	25.68	101.03	307.95	518.06
1	1.00	2.20	4.71	25.64	97.16	298.23	504.29
	0.96	2.01	4.91	26.08	97.74	298.72	497.25
Mean	1.03	1.94	4.75	25.34	99.88	308.14	508.80
SD	0.08	0.15	0.28	0.86	3.89	9.50	32.10
%RSD	8.11	7.72	5.84	3.41	3.90	3.08	6.31
%RE	2.64	-3.14	-5.10	1.35	-0.12	2.71	1.76
n	14	14	14	14	14	14	14

Table 2b: Frozen Stability Assessment at -20°C and -70°C, Standard Curve Readback Concentrations, Norfluoxetine

			Acceptance Criteria				
-30%	0.70	1.40	3.50	17.50	70.00	210.00	350.00
+30%	1.30	2.60	6.50	32.50	130.00	390.00	650.00
			Nominal Concentrations (ng/mL)				
Run	1.00	2.00	5.00	25.00	100.00	300.00	500.00
44	1.02	1.84	4.82	26.93	105.98	298.81	506.04
	1.07	1.85	4.79	24.89	100.16	316.96	473.11
49	1.09	1.74	3.97	24.46	99.57	321.44	575.05
	1.11	1.75	4.25	24.69	104.30	324.96	552.13
53	1.12	2.03	4.73	21.91	100.62	309.01	577.48
	0.90	2.07	4.27	24.57	93.79	318.61	539.49
61	0.99	1.89	4.82	25.09	97.73	318.97	555.65
	1.13	1.76	4.49	25.36	96.48	303.05	527.41

(continued)

Table 2b: (continued) Frozen Stability Assessment at -20°C and -70°C, Standard Curve Readback Concentrations, Norfluoxetine

			Acceptance Criteria				
-30%	0.70	1.40	3.50	17.50	70.00	210.00	350.00
+30%	1.30	2.60	6.50	32.50	130.00	390.00	650.00
			Nominal Concentrations (ng/mL)				
Run	1.00	2.00	5.00	25.00	100.00	300.00	500.00
64	0.96	2.14	5.02	26.05	103.20	287.46	468.42
	1.00	2.02	4.86	25.83	104.51	289.23	484.70
66	0.96	2.13	4.80	24.46	102.92	303.45	513.74
	1.08	1.75	5.17	25.90	96.65	297.33	497.65
1	0.97	2.10	4.67	25.18	95.48	301.61	534.39
	1.04	1.94	4.88	24.57	95.84	310.68	523.73
Mean	1.03	1.93	4.68	24.99	99.80	307.26	523.50
SD	0.07	0.15	0.33	1.15	3.91	11.90	35.04
%RSD	6.86	7.83	6.98	4.59	3.92	3.87	6.69
%RE	3.14	-3.54	-6.37	-0.03	-0.20	2.42	4.70
n	14	14	14	14	14	14	14

Table 3a: Frozen Stability Assessment at -20°C and -70°C, Quality Control (QC) Sample Concentrations, Fluoxetine

		Acceptance Criteria		
-20%	2.00	200.00	320.00	
+20%	3.00	300.00	480.00	
		Nominal Concentrations (ng/mL)		Acceptance
Run	2.50	250.00	400.00	Ratio[a]
44	2.45	231.66	381.52	6/6
	2.50	226.95	384.09	
53	2.41	257.95	410.89	6/6
	2.58	260.75	401.35	
61	2.64	266.75	416.17	6/6
	2.48	251.56	393.04	
64	2.70	284.48	442.60	6/6
	2.76	264.96	436.34	
66	2.73	274.71	450.20	6/6
	2.30	273.10	460.71	
1	2.52	281.96	463.52	6/6
	2.57	272.06	464.91	
Mean	2.55	262.24	425.45	
SD	0.14	18.08	31.40	
%RSD	5.39	6.89	7.38	
%RE	2.13	4.90	6.36	
n	12	12	12	

(continued)

Table 3a: (continued) Frozen Stability Assessment at -20°C and -70°C, Quality Control (QC) Sample Concentrations, Fluoxetine

		Acceptance Criteria		
-20%	2.00	200.00	320.00	
+20%	3.00	300.00	480.00	
		Nominal Concentrations (ng/mL)		Acceptance
Run	2.50	250.00	400.00	Ratio[a]

[a]Acceptance Ratio = Number of QC samples quantitating within the QC acceptance range/number of QC samples analyzed.

Table 3b: Frozen Stability Assessment at -20°C and -70°C, Quality Control (QC) Sample Concentrations, Norfluoxetine

		Acceptance Criteria		
-20%	2.00	200.00	320.00	
+20%	3.00	300.00	480.00	
		Nominal Concentrations (ng/mL)		Acceptance
Run	2.50	250.00	400.00	Ratio[a]
44	2.36	233.41	384.80	6/6
	2.35	237.21	368.23	
53	2.26	265.70	411.71	6/6
	2.51	250.75	404.33	
61	2.84	259.56	400.81	6/6
	2.43	253.63	395.69	
64	2.69	276.05	409.55	6/6
	2.74	254.39	403.95	
66	2.61	260.40	435.93	6/6
	2.67	258.04	430.66	
1	2.53	274.78	459.49	6/6
	2.67	270.52	470.01	
Mean	2.56	257.87	414.60	
SD	0.18	13.32	29.60	
%RSD	6.97	5.17	7.14	
%RE	2.20	3.15	3.65	
n	12	12	12	

[a]Acceptance Ratio = Number of QC samples quantitating within the QC acceptance range/the number of QC samples analyzed.

Table 4a: Frozen Stability Assessment at -20°C and -70°C, Frozen (-20°C) Stability QC Sample Concentrations, Fluoxetine

	-20%	2.00	200.00	320.00
	+20%	3.00	300.00	480.00
			Nominal Concentrations (ng/mL)	
Run	Timepoint	2.50	250.00	400.00
44	initial	2.59	244.09	394.53
		2.67	252.02	389.49
		2.55	248.50	387.17
		2.63	248.81	383.75
		2.48	249.96	388.28
	Mean	2.58	248.68	388.64
	SD	0.07	2.91	3.92
	%RSD	2.84	1.17	1.01
	%RE	3.36	-0.53	-2.84
	n	5	5	5
49	~1 month	2.61	272.72	429.59
		2.88	276.21	426.03
		2.64	275.07	412.27
		2.61	271.37	418.00
		2.57	265.20	426.15
	Mean	2.66	272.11	422.41
	SD	0.12	4.31	7.09
	%RSD	4.67	1.58	1.68
	%RE	6.48	8.85	5.60
	n	5	5	5
53	~3 month	2.42	250.56	405.42
		2.58	231.89	394.50
		2.55	243.03	409.48
		2.53	246.43	405.05
		2.39	250.15	390.88
	Mean	2.49	244.41	401.07
	SD	0.08	7.64	7.94
	%RSD	3.36	3.13	1.98
	%RE	-0.24	-2.24	0.27
	n	5	5	5

(continued)

Table 4a: (continued) Frozen Stability Assessment at -20°C and -70°C, Frozen (-20°C) Stability QC Sample Concentrations, Fluoxetine

	-20%	2.00	200.00	320.00
	+20%	3.00	300.00	480.00
			Nominal Concentrations (ng/mL)	
Run	Timepoint	2.50	250.00	400.00
61	~6 month	2.91	271.83	388.46
		2.65	257.76	416.39
		2.59	251.16	391.81
		2.52	249.91	395.44
		2.57	256.59	412.44
	Mean	2.65	257.45	400.91
	SD	0.15	8.72	12.65
	%RSD	5.80	3.39	3.16
	%RE	5.92	2.98	0.23
	n	5	5	5
64	~12 month	2.67	250.26	381.84
		2.82	250.34	370.07
		2.68	246.93	398.71
		2.84	243.54	374.05
		2.71	251.64	378.12
	Mean	2.74	248.54	380.56
	SD	0.08	3.29	11.06
	%RSD	2.92	1.33	2.91
	%RE	9.76	-0.58	-4.86
	n	5	5	5
66	~15 month	2.35	252.41	378.09
		2.13	238.39	388.71
		2.48	241.19	376.18
		2.55	245.80	376.33
		2.24	246.74	400.41
	Mean	2.35	244.91	383.94
	SD	0.17	5.40	10.56
	%RSD	7.29	2.21	2.75
	%RE	-6.00	-2.04	-4.01
	n	5	5	5

(continued)

Table 4a: (continued) Frozen Stability Assessment at -20°C and -70°C, Frozen (-20°C) Stability QC Sample Concentrations, Fluoxetine

	-20%	2.00	200.00	320.00
	+20%	3.00	300.00	480.00
		Nominal Concentrations (ng/mL)		
Run	Timepoint	2.50	250.00	400.00
1	~18 month	2.45	249.05	383.91
		2.43	243.58	388.63
		2.42	249.24	387.49
		2.33	247.42	391.04
		2.26	249.03	406.24
	Mean	2.38	247.66	391.46
	SD	0.08	2.40	8.65
	%RSD	3.38	0.97	2.21
	%RE	-4.88	-0.93	-2.13
	n	5	5	5

Table 4b: Frozen Stability Assessment at -20°C and -70°C, Frozen (-20°C) Stability QC Sample Concentrations, Norfluoxetine

	-20%	2.00	200.00	320.00
	+20%	3.00	300.00	480.00
		Nominal Concentrations (ng/mL)		
Run	Timepoint	2.50	250.00	400.00
44	initial	2.23	248.05	405.82
		2.33	253.92	397.36
		2.39	255.80	397.58
		2.58	249.98	393.58
		2.39	246.56	393.69
	Mean	2.38	250.86	397.61
	SD	0.13	3.90	4.98
	%RSD	5.35	1.56	1.25
	%RE	-4.64	0.34	-0.60
	n	5	5	5
49	~1 month	2.62	264.84	427.55
		2.51	254.19	434.69
		2.41	248.97	436.06
		2.63	253.86	420.23
		2.38	260.70	421.71

(continued)

Table 4b: (continued) Frozen Stability Assessment at -20°C and -70°C, Frozen (-20°C) Stability QC Sample Concentrations, Norfluoxetine

	-20%	2.00	200.00	320.00
	+20%	3.00	300.00	480.00
		Nominal Concentrations (ng/mL)		
Run	Timepoint	2.50	250.00	400.00
	Mean	2.51	256.51	428.05
	SD	0.12	6.25	7.24
	%RSD	4.60	2.44	1.69
	%RE	0.40	2.60	7.01
	n	5	5	5
53	~3 month	2.36	250.02	409.69
		2.40	247.27	413.38
		2.50	235.77	432.18
		2.50	239.14	408.58
		2.41	252.38	390.99
	Mean	2.43	244.92	410.96
	SD	0.06	7.15	14.68
	%RSD	2.59	2.92	3.57
	%RE	-2.64	-2.03	2.74
	n	5	5	5
61	~6 month	2.75	255.96	376.72
		2.52	256.97	402.90
		2.51	247.54	394.09
		2.64	252.75	396.85
		2.72	248.75	428.17
	Mean	2.63	252.39	399.75
	SD	0.11	4.20	18.63
	%RSD	4.21	1.66	4.66
	%RE	5.12	0.96	-0.06
	n	5	5	5
64	~12 month	2.60	241.23	359.15
		2.63	236.71	352.35
		2.50	239.14	373.60
		2.60	231.36	351.98
		2.64	247.02	362.61

(continued)

Table 4b: (continued) Frozen Stability Assessment at -20°C and -70°C, Frozen (-20°C) Stability QC Sample Concentrations, Norfluoxetine

	-20%	2.00	200.00	320.00
	+20%	3.00	300.00	480.00
		Nominal Concentrations (ng/mL)		
Run	Timepoint	2.50	250.00	400.00
	Mean	2.59	239.09	359.94
	SD	0.06	5.76	8.88
	%RSD	2.14	2.41	2.47
	%RE	3.76	-4.36	-10.02
	n	5	5	5
66	~15 month	2.29	228.74	360.14
		2.79	225.95	360.69
		2.38	231.99	343.50
		2.30	229.85	360.83
		2.24	224.56	335.42
	Mean	2.40	228.22	352.12
	SD	0.22	2.99	11.90
	%RSD	9.32	1.31	3.38
	%RE	-4.00	-8.71	-11.97
	n	5	5	5
1	~18 month	2.38	247.55	381.66
		2.59	239.71	391.90
		2.30	248.12	392.17
		2.29	243.61	397.92
		2.25	242.83	409.52
	Mean	2.36	244.36	394.63
	SD	0.14	3.49	10.18
	%RSD	5.75	1.43	2.58
	%RE	-5.52	-2.25	-1.34
	n	5	5	5

Table 5a: Frozen Stability Assessment at -20°C and -70°C, Frozen (-70°C) Stability QC Sample Concentrations, Fluoxetine

	-20%	2.00	200.00	320.00
	+20%	3.00	300.00	480.00
		Nominal Concentrations (ng/mL)		
Run	Timepoint	2.50	250.00	400.00
44	initial	2.59	244.09	394.53
		2.67	252.02	389.49
		2.55	248.50	387.17
		2.63	248.81	383.75
		2.48	249.96	388.28
	Mean	2.58	248.68	388.64
	SD	0.07	2.91	3.92
	%RSD	2.84	1.17	1.01
	%RE	3.36	-0.53	-2.84
	n	5	5	5
49	~1 month	2.49	274.83	416.99
		2.96	270.80	445.36
		2.93	280.77	435.57
		2.81	265.56	417.40
		2.74	271.44	427.57
	Mean	2.79	272.68	428.58
	SD	0.19	5.61	12.15
	%RSD	6.75	2.06	2.84
	%RE	11.44	9.07	7.14
	n	5	5	5
53	~3 month	2.55	248.01	387.94
		2.61	245.94	395.73
		2.43	246.96	393.74
		2.66	254.18	388.07
		2.54	247.74	393.35
	Mean	2.56	248.57	391.77
	SD	0.09	3.24	3.55
	%RSD	3.38	1.30	0.91
	%RE	2.32	-0.57	-2.06
	n	5	5	5

(continued)

Table 5a: (continued) Frozen Stability Assessment at -20°C and -70°C, Frozen (-70°C) Stability QC Sample Concentrations, Fluoxetine

	-20%	2.00	200.00	320.00
	+20%	3.00	300.00	480.00
		Nominal Concentrations (ng/mL)		
Run	Timepoint	2.50	250.00	400.00
61	~6 month	2.89	234.04	404.51
		2.60	251.42	403.45
		2.53	252.26	386.39
		2.77	249.00	388.22
		2.64	248.96	402.12
	Mean	2.69	247.14	396.94
	SD	0.14	7.47	8.86
	%RSD	5.35	3.02	2.23
	%RE	7.44	-1.15	-0.77
	n	5	5	5
64	~12 month	2.78	243.50	401.79
		2.73	245.67	381.87
		2.68	243.94	397.54
		2.71	247.23	403.15
		2.77	248.80	405.70
	Mean	2.73	245.83	398.01
	SD	0.04	2.23	9.49
	%RSD	1.52	0.91	2.39
	%RE	9.36	-1.67	-0.50
	n	5	5	5
66	~15 month	2.40	248.09	395.97
		2.65	241.95	374.74
		2.50	241.43	390.72
		2.04	240.58	383.52
		2.93	239.25	382.45
	Mean	2.50	242.26	385.48
	SD	0.33	3.42	8.15
	%RSD	13.08	1.41	2.11
	%RE	0.16	-3.10	-3.63
	n	5	5	5

(continued)

Table 5a: (continued) Frozen Stability Assessment at -20°C and -70°C, Frozen (-70°C) Stability QC Sample Concentrations, Fluoxetine

	-20%	2.00	200.00	320.00
	+20%	3.00	300.00	480.00
		Nominal Concentrations (ng/mL)		
Run	Timepoint	2.50	250.00	400.00
1	~18 month	2.57	243.98	403.23
		2.36	256.32	406.72
		2.66	249.58	403.40
		2.49	245.27	402.05
		2.39	254.17	394.73
	Mean	2.49	249.86	402.03
	SD	0.12	5.39	4.43
	%RSD	5.00	2.16	1.10
	%RE	-0.24	-0.05	0.51
	n	5	5	5

Table 5b: Frozen Stability Assessment at -20°C and -70°C, Frozen (-70°C) Stability QC Sample Concentrations, Norfluoxetine

	-20%	2.00	200.00	320.00
	+20%	3.00	300.00	480.00
		Nominal Concentrations (ng/mL)		
Run	Timepoint	2.50	250.00	400.00
44	initial	2.23	248.05	405.82
		2.33	253.92	397.36
		2.39	255.80	397.58
		2.58	249.98	393.58
		2.39	246.56	393.69
	Mean	2.38	250.86	397.61
	SD	0.13	3.90	4.98
	%RSD	5.35	1.56	1.25
	%RE	-4.64	0.34	-0.60
	n	5	5	5
49	~1 month	2.31	253.53	424.73
		2.27	249.21	417.06
		2.73	249.84	434.39
		2.33	252.49	400.69
		2.47	242.23	417.68

(continued)

Table 5b: (continued) Frozen Stability Assessment at -20°C and -70°C, Frozen (-70°C) Stability QC Sample Concentrations, Norfluoxetine

	-20%	2.00	200.00	320.00
	+20%	3.00	300.00	480.00
		Nominal Concentrations (ng/mL)		
Run	Timepoint	2.50	250.00	400.00
	Mean	2.42	249.46	418.91
	SD	0.19	4.42	12.35
	%RSD	7.76	1.77	2.95
	%RE	-3.12	-0.22	4.73
	n	5	5	5
53	~3 month	2.46	249.81	378.21
		2.51	239.95	385.70
		2.37	237.13	384.15
		2.57	249.85	372.69
		2.21	244.96	399.44
	Mean	2.42	244.34	384.04
	SD	0.14	5.74	10.03
	%RSD	5.79	2.35	2.61
	%RE	-3.04	-2.26	-3.99
	n	5	5	5
61	~6 month	2.72	239.77	390.57
		2.52	249.08	398.48
		2.39	241.88	387.52
		2.69	244.09	399.10
		2.60	255.47	385.31
	Mean	2.58	246.06	392.20
	SD	0.13	6.30	6.31
	%RSD	5.18	2.56	1.61
	%RE	3.36	-1.58	-1.95
	n	5	5	5
64	~12 month	2.51	236.81	380.44
		2.59	237.52	364.31
		2.63	232.20	371.74
		2.53	240.10	376.64
		2.58	242.67	387.85

(continued)

Table 5b: (continued) Frozen Stability Assessment at -20°C and -70°C, Frozen (-70°C) Stability QC Sample Concentrations, Norfluoxetine

	-20%	2.00	200.00	320.00
	+20%	3.00	300.00	480.00
		Nominal Concentrations (ng/mL)		
Run	Timepoint	2.50	250.00	400.00
	Mean	2.57	237.86	376.20
	SD	0.05	3.92	8.88
	%RSD	1.88	1.65	2.36
	%RE	2.72	-4.86	-5.95
	n	5	5	5
66	~15 month	2.40	237.37	387.27
		2.64	227.48	363.35
		2.60	230.03	378.69
		2.12	224.99	383.40
		2.84	232.11	360.56
	Mean	2.52	230.40	374.65
	SD	0.27	4.73	12.02
	%RSD	10.82	2.05	3.21
	%RE	0.80	-7.84	-6.34
	n	5	5	5
1	~18 month	2.56	247.73	407.24
		2.32	256.08	412.90
		2.58	249.87	407.51
		2.45	247.68	416.40
		2.52	256.44	401.06
	Mean	2.49	251.56	409.02
	SD	0.11	4.38	5.88
	%RSD	4.23	1.74	1.44
	%RE	-0.56	0.62	2.26
	n	5	5	5

BIOANALYTICAL LAB NOTES

Filename System

Filename System

1	2

1) Run #

44	2/25/98
49	3/26/98
53	5/19/98
61	9/1/98
64	2/26/99
66	5/20/99
1	8/25/99

2) Sample

Blanks:

b1a, b1b	Plasma Blank
pba, pbb	Plasma Blank

Calibration Standards:

s0a, s0b	Zero Point
s1a, s1b	1.00 ng/mL
s2a, s2b	2.00 ng/mL
s3a, s3b	5.00 ng/mL
s4a, s4b	25.00 ng/mL
s5a, s5b	100.00 ng/mL
s6a, s6b	300.00 ng/mL
s7a, s7b	500.00 ng/mL

Filename System (continued)

Quality Control Samples for Run Acceptance:

q1a, q1b	2.50 ng/mL
q2a, q2b	250.00 ng/mL
q3a, q3b	400.00 ng/mL

Quality Control Samples for Frozen Stability Assessment

q1c-q1g	2.50 ng/mL initial assessment, Run 44
q2c-q2g	250.00 ng/mL initial assessment, Run 44
q3c-q3g	400.00 ng/mL initial assessment, Run 44
q1a-q1e	2.50 ng/mL stored at -20°C, Run 49
q2a-q2e	250.00 ng/mL stored at -20°C, Run 49
q3a-q3e	400.00 ng/mL stored at -20°C, Run 49
q1f-q1j	2.50 ng/mL stored at -70°C, Run 49
q2f-q2j	250.00 ng/mL stored at -70°C, Run 49
q3f-q3j	400.00 ng/mL stored at -70°C, Run 49
q4a-q4e	2.50 ng/mL stored at -20°C, Runs 53, 61, 66, and 1
q5a-q5e	250.00 ng/mL stored at -20°C, Runs 53, 61, 66, and 1
q6a-q6e	400.00 ng/mL stored at -20°C, Runs 53, 61, 66, and 1
q7a-q7e	2.50 ng/mL stored at -70°C, Runs 53, 61, 66, and 1
q8a-q8e	250.00 ng/mL stored at -70°C, Runs 53, 61, 66, and 1
q9a-q9e	400.00 ng/mL stored at -70°C, Runs 53, 61, 66, and 1
q12a-q12e	2.50 ng/mL stored at -20°C, Run 64
q13a-q13e	250.00 ng/mL stored at -20°C, Run 64
q14a-q14e	400.00 ng/mL stored at -20°C, Run 64
q15a-q15e	2.50 ng/mL stored at -70°C, Run 64
q16a-q16e	250.00 ng/mL stored at -70°C, Run 64
q17a-q17e	400.00 ng/mL stored at -70°C, Run 64

Bioanalytical Clinical Report

Fluoxetine Versus Placebo in Childhood/Adolescent Depression

The Determination of Fluoxetine and Norfluoxetine in Human Plasma Using LC/MS/MS with Atmospheric Pressure Chemical Ionization

Eli Lilly and Company
B1Y-MC-HCJE
[redacted] Job Number 139576

Report Written by:

[redacted]
Bioanalytical Group

[redacted]

January 2000

Quality Assurance Review Statement

Eli Lilly and Company Protocol #:	B1Y-MC-HCJE
Title:	Fluoxetine Versus Placebo in Childhood/Adolescent Depression
Contract Lab Project #:	139576
Contract Lab Report Title:	The Determination of Fluoxetine and Norfluoxetine in Human Plasma Using LC/MS/MS with Atmospheric Pressure Chemical Ionization

Quality Assurance Inspections:

Date of Inspection	Date Reported to Management	Phase of Study Inspected
12, 17, 18, 19-NOV-99	8-DEC-99	In-process
18-JAN-00	14-FEB-00	Draft 1
15-FEB-00	15-FEB-00	Draft 2
27-MAR-00	27-MAR-00	Final

The Quality Assurance Unit has reviewed the final study report and has determined that the report accurately reflects the raw data generated during the conduct of this study.

[redacted] Date

Signatures

Eli Lilly and Company Protocol #:	B1J-MC-HCJE
Title:	Fluoxetine Versus Placebo in Childhood/Adolescent Depression
Contract Lab Project #:	139576
Contract Lab Report Title:	The Determination of Fluoxetine and Norfluoxetine in Human Plasma Using LC/MS/MS with Atmospheric Pressure Chemical Ionization

To the best of our knowledge this report has been reviewed for completeness, accuracy, and compliance with the protocol and SOPs.

_____ _____

[redacted] Date

Bioanalytical Group

Eli Lilly and Company Protocol #:	B1J-MC-HCJE
Title:	Fluoxetine Versus Placebo in Childhood/Adolescent Depression
Contract Lab Project #:	139576
Contract Lab Report Title:	The Determination of Fluoxetine and Norfluoxetine in Human Plasma Using LC/MS/MS with Atmospheric Pressure Chemical Ionization

Heparinized human plasma samples were analyzed for Fluoxetine and Norfluoxetine using a validated LC/MS/MS method over the concentration range 1.00 ng/mL to 500.00 ng/mL. The samples were analyzed at [redacted] Details of the method and validation are provided in the attachments of this report.

Heparinized human plasma obtained during Study B1Y-MC-HCJE was analyzed for Fluoxetine and Norfluoxetine. A summary of the bioanalytical evaluation, including the method used, the precision and accuracy of the method, as well as the data for the standard curves and quality control samples analyzed with the study samples can be found in bioanalytical data summary section of this report. The concentrations of samples from each subject are also listed in the bioanalytical data summary section of this report.

Methods

Sample Collection and Storage

Sample matrix:	Heparinized human plasma
Samples received from:	[redacted]
Shipment condition:	Received frozen on dry ice
Storage temperature:	Approximately -20°C.
Date of sample receipt:	02 NOV 1999 to 25 JAN 2000
Total samples analyzed:	543
Date of first sample analysis:	11 NOV 1999
Date of last sample analysis:	04 FEB 2000

Sample Data Information

Study analysts:	[redacted]
Data reference:	Paper data are located in notebook(s) [redacted]

[redacted] Data and this report are archived at [redacted] or appropriately cross referenced to other locations.

Abstract of Analytical Method (see method attached)

Lab method #:	M2.FluoxLCMS.1, Rev.1 and M2.FluoxLCMS.3, Rev. 1
Method type:	LC/MS/MS
Matrix:	Heparinized human plasma
Internal standard:	d_5-Fluoxetine and d_4-Norfluoxetine
MS type/conditions:	Sciex API-300 and Sciex API-III$^+$ using APCI (heated nebulizer)
Mobile Phase:	80:20 methanol:0.05% trifluoroacetic acid
Column:	Waters Nova-Pak CN HP, 3.9 x 75 mm (ambient)
Flow rate:	1.00 mL/min
Sample preparation:	The analytes were extracted from heparinized human plasma by solid phase extraction with an Isolute HCX 130 mg, 3 mL SPE column.
Validation range:	Lower limit of quantitation = 1.00 ng/mL Upper limit of quantitation = 500.00 ng/mL Samples above the limit of quantitation were diluted and reanalyzed to yield results within the calibrated range.
Validation accuracy:	≤ 6.64% (absolute) for Fluoxetine, ≤ 3.17% (absolute) for Norfluoxetine
Validation precision:	≤ 5.75% for Fluoxetine, ≤ 7.68% for Norfluoxetine
Cross-Validation accuracy:	≤ 13.40% for Fluoxetine, ≤ 12.00% for Norfluoxetine
Cross-Validation precision:	≤ 5.53% for Fluoxetine, ≤ 3.16% for Norfluoxetine
Stability:	Approximately 18 months frozen stability at approximately -20°C and -70°C
Reference Standards:	Fluoxetine HCl, Lot 001PD5, purity 99.80% salt correction factor=0.89456, expiry 10/28/00; Norfluoxetine HCl, Lot U096FK20, defined potency 87.60%, expiry 10/28/01; SN141999-[$^2H_5$] (d_5-Fluoxetine), Lot 067, purity used at 100%, expiry N/A; 215229-[$^2H_4$]•HCl (d_4-Norfluoxetine•HCl), Lot 253A, purity used at 100%, expiry N/A

Results and Discussion

Additional Validation Data

Since it was necessary to dilute some of the study samples, appropriate dilutions of QCs were assayed simultaneously. These results are listed in Tables 3.2 and 3.3. When samples were diluted the BQL level was adjusted appropriately.

Comments

The 0.1 M phosphate buffer used in the extraction procedure in Runs 3-5 was prepared in a different manner than what is presented in the analytical method. The pH of a previously prepared 0.1 M potassium phosphate solution was adjusted to 6.0 and used instead of preparing a fresh solution.

It is the opinion of the [redacted] Study Director that the above item does not impact the integrity of the results.

Standard Curve Data

The data for the standard curve parameters are given in Tables 1 and 1.1. The back calculated calibration standard concentrations are given in Tables 2 and 2.1.

Table 1 Standard Curve Data for the LC/MS/MS Assay for Fluoxetine and Norfluoxetine in Human Plasma for Fluoxetine

Range: 1.00 to 500.00 ng/mL
Databook: 4172
Linear Fit
Weighted ($1/x^2$)

Run	Date	Slope $(ng/mL)^{-1}$	Intercept	Correlation Coefficient
1	11/12/99	0.011405475	0.000065700	0.998486698
2	11/12/99	0.012603951	-0.000584059	0.998764038
3	11/16/99	0.012537008	-0.000323755	0.998934150
4	11/18/99	0.012725106	-0.000147241	0.998248398
5	11/19/99	0.012957098	0.000343573	0.999140739
6	12/16/99	0.013236878	-0.001165265	0.998741269
7	12/22/99	0.012652540	-0.000103441	0.998678029
8	2/4/00	0.014328326	-0.001210377	0.999335229
	Mean	0.012805798	-0.000390608	0.998791069
	SD	0.00	-	0.00
	%RSD	6.35	-	0.03
	n	8	8	8

Table 1.1 **Standard Curve Data for the LC/MS/MS Assay for Fluoxetine and Norfluoxetine in Human Plasma for Norfluoxetine**

Range: 1.00 to 500.00 ng/mL
Databook: 4172
Linear Fit
Weighted ($1/x^2$)

Run	Date	Slope $(ng/mL)^{-1}$	Intercept	Correlation Coefficient
1	11/12/99	0.011923226	-0.000121484	0.998266935
2	11/12/99	0.014139269	0.000313644	0.998863935
3	11/16/99	0.013573135	0.000837981	0.998361707
4	11/18/99	0.013982555	0.000896566	0.998339534
5	11/19/99	0.014323348	0.001356091	0.999370337
6	12/16/99	0.012212590	-0.000041317	0.998789072
7	12/22/99	0.012279290	0.000248575	0.997839570
8	2/4/00	0.012448898	-0.000640605	0.999083042
	Mean	0.013110289	0.000356181	0.998614267
	SD	0.00	-	0.00
	%RSD	7.54	-	0.05
	n	8	8	8

Table 2 **Back Calculated Calibration Standard Concentration Data for LC/MS/MS Assay for Fluoxetine and Norfluoxetine in Human Plasma for Fluoxetine**

Databook: 4172

		Acceptance Criteria						
	-30%	0.70	1.40	3.50	17.50	70.00	210.00	350.00
	+30%	1.30	2.60	6.50	32.50	130.00	390.00	650.00
		Nominal Concentrations (ng/mL)						
Run		1.00	2.00	5.00	25.00	100.00	300.00	500.00
1		a	2.01	4.58	27.03	99.54	312.25	505.06
		1.02	a	4.63	26.02	95.53	291.44	516.56
2		1.02	2.10	4.66	25.43	99.43	313.97	520.90
		0.97	2.02	4.76	25.84	93.53	288.86	515.67
3		0.98	2.07	4.77	26.30	95.74	287.62	512.20
		0.99	2.13	4.69	25.53	100.94	298.12	511.40
4		1.07	1.99	4.62	26.69	102.14	289.79	524.35
		0.93	2.08	4.89	25.06	97.68	283.00	518.04
5		1.00	2.12	4.74	26.36	101.58	296.48	495.85
		0.97	2.05	4.92	25.40	b	285.72	497.24
6		0.98	1.90	4.61	26.91	100.57	308.41	508.02
		1.07	1.93	4.91	25.19	97.51	300.34	505.86

(continued)

Table 2 **(continued) Back Calculated Calibration Standard Concentration Data for LC/MS/MS Assay for Fluoxetine and Norfluoxetine in Human Plasma for Fluoxetine**

Databook: 4172

		Acceptance Criteria						
	-30%	0.70	1.40	3.50	17.50	70.00	210.00	350.00
	+30%	1.30	2.60	6.50	32.50	130.00	390.00	650.00
		Nominal Concentrations (ng/mL)						
Run		1.00	2.00	5.00	25.00	100.00	300.00	500.00
7		1.01	2.15	4.82	26.40	98.39	298.75	492.28
		0.98	1.97	4.65	25.75	95.56	293.79	536.86
8		1.03	1.94	5.11	26.14	96.49	297.46	492.38
		0.96	2.10	4.91	25.40	102.99	290.89	493.44
	Mean	1.00	2.04	4.77	25.97	98.51	296.06	509.13
	SD	0.04	0.08	0.15	0.61	2.81	9.17	12.88
	%RSD	3.89	3.86	3.12	2.36	2.85	3.10	2.53
	%RE	-0.13	1.87	-4.66	3.86	-1.49	-1.31	1.83
	n	15	15	16	16	15	16	16

[a]File not used due to insufficient response.
[b]Sample lost in wet lab.

Table 2.1 **Back Calculated Calibration Standard Concentration Data for LC/MS/MS Assay for Fluoxetine and Norfluoxetine in Human Plasma for Norfluoxetine**

Databook: 4172

		Acceptance Criteria						
	-30%	0.70	1.40	3.50	17.50	70.00	210.00	350.00
	+30%	1.30	2.60	6.50	32.50	130.00	390.00	650.00
		Nominal Concentrations (ng/mL)						
Run		1.00	2.00	5.00	25.00	100.00	300.00	500.00
1		a	2.18	4.70	26.42	98.21	310.01	506.96
		0.98	a	4.62	26.09	94.11	288.14	517.35
2		0.99	2.09	4.67	25.39	98.61	314.12	530.47
		1.01	2.02	4.73	25.24	95.02	289.47	517.43
3		1.02	2.06	4.65	26.06	95.89	283.18	524.53
		0.99	2.03	4.53	25.76	99.52	309.03	531.69
4		1.07	1.94	4.72	26.90	97.93	303.11	528.20
		0.95	2.03	4.79	24.80	96.85	283.22	530.29
5		0.98	2.12	4.76	25.81	100.70	298.87	506.63
		1.00	1.99	4.90	25.59	b	287.33	499.56
6		0.99	2.01	4.62	26.98	99.79	309.11	495.53
		1.02	2.07	4.65	26.05	97.69	298.16	495.07

(continued)

Table 2.1 (continued) Back Calculated Calibration Standard Concentration Data for LC/MS/MS Assay for Fluoxetine and Norfluoxetine in Human Plasma for Norfluoxetine

Databook: 4172

		Acceptance Criteria						
	-30%	0.70	1.40	3.50	17.50	70.00	210.00	350.00
	+30%	1.30	2.60	6.50	32.50	130.00	390.00	650.00
		Nominal Concentrations (ng/mL)						
Run		1.00	2.00	5.00	25.00	100.00	300.00	500.00
7		1.06	2.11	4.50	26.45	100.60	316.45	498.39
		0.93	2.06	4.65	25.42	95.72	289.06	520.94
8		1.02	1.88	5.01	26.40	97.54	301.97	495.69
		1.00	2.08	4.65	25.51	104.19	297.53	490.84
	Mean	1.00	2.04	4.70	25.93	98.16	298.67	511.85
	SD	0.04	0.07	0.13	0.60	2.58	11.04	14.80
	%RSD	3.61	3.60	2.70	2.33	2.63	3.70	2.89
	%RE	0.07	2.23	-6.06	3.72	-1.84	-0.44	2.37
	n	15	15	16	16	15	16	16

[a]File not used due to insufficient response.
[b]Sample lost in wet lab.

Quality Control Data

Results from the quality control samples are found in Tables 3 and 3.1. The overall Relative Standard Deviation (RSD) which is an expression of the precision was ≤ 5.59% at all concentrations for Fluoxetine. The overall RSD was ≤ 5.12% at all concentrations for Norfluoxetine. The overall Relative Error (RE) which is an expression of the accuracy was ≤ 9.78% for all concentrations for Fluoxetine. The overall RE was ≤ 9.18% at all concentrations for Norfluoxetine. Results from the dilution integrity quality control samples can be found in Tables 3.2 and 3.3. The overall RSD was ≤ 2.87% for Fluoxetine. The overall RSD was ≤ 2.83% for Norfluoxetine. The overall RE was ≤ 11.41% for Fluoxetine. The overall RE was ≤ 8.89% for Norfluoxetine.

Table 3 Control Results from the LC/MS/MS Assay for Fluoxetine and Norfluoxetine in Human Plasma for Fluoxetine

Databook: 4172

		Acceptance Criteria			
	-20%	2.00	200.00	320.00	
	+20%	3.00	300.00	480.00	
		Nominal Concentrations (ng/mL)			Acceptance
Run		2.50	250.00	400.00	Ratio[a]
1		2.90	290.24	437.04	6/6
		2.69	270.58	433.86	

(continued)

Principal or Coordinating Investigator(s) Signature(s) or Sponsor's Responsible Medical Officer

Study Title: Fluoxetine versus Placebo in Childhood/Adolescent Depression

Study Author(s): [redacted]

I have read this report and confirm that to the best of my knowledge it accurately describes the conduct and results of the study.

[redacted] 2 August 02

Investigator [redacted] Date
or Sponsor's Responsible Medical Officer

Affiliation: Eli Lilly and Company

Table 3.1 (continued) Control Results from the LC/MS/MS Assay for Fluoxetine and Norfluoxetine in Human Plasma for Norfluoxetine

Databook: 4172

		Acceptance Criteria			
	-20%	2.00	200.00	320.00	
	+20%	3.00	300.00	480.00	
		Nominal Concentrations (ng/mL)			Acceptance
Run		2.50	250.00	400.00	Ratio[a]
2		2.74	269.17	423.95	6/6
		2.73	260.89	431.72	
3		2.75	270.01	424.18	6/6
		2.82	270.05	439.78	
4		2.76	259.54	420.99	6/6
		2.81	268.16	437.59	
5		2.81	258.13	401.53	6/6
		2.64	253.13	394.64	
6		2.75	261.79	404.13	6/6
		2.55	253.25	406.20	
7		2.81	265.81	423.02	6/6
		2.73	245.85	429.44	
8		2.68	237.68	383.48	6/6
		2.48	246.50	368.47	
	Mean	2.73	260.32	416.54	
	SD	0.10	10.60	21.33	
	%RSD	3.63	4.07	5.12	
	%RE	9.18	4.13	4.14	
	n	16	16	16	

[a]Acceptance Ratio = Number of QC samples quantitating within the QC acceptance range / number of QC samples analyzed.

Table 3.2 Dilution Integrity Quality Control (QC) Sample Results from the LC/MS/MS Assay for Fluoxetine and Norfluoxetine in Human Plasma for Fluoxetine

		Acceptance Criteria			
-20%	320.00	320.00	320.00	320.00	
+20%	480.00	480.00	480.00	480.00	
	Nominal Concentrations (ng/mL)				Acceptance
Run	400.00[b]	400.00[c]	400.00[d]	400.00[e]	Ratio[a]
1		460.26			3/3
		436.53			
		440.12			

(continued)

Table 3.2 (continued) Dilution Integrity Quality Control (QC) Sample Results from the LC/MS/MS Assay for Fluoxetine and Norfluoxetine in Human Plasma for Fluoxetine

	Acceptance Criteria				
-20%	320.00	320.00	320.00	320.00	
+20%	480.00	480.00	480.00	480.00	
	Nominal Concentrations (ng/mL)				Acceptance
Run	400.00[b]	400.00[c]	400.00[d]	400.00[e]	Ratio[a]
3	433.15				3/3
	425.74				
	419.88				
5			426.56		3/3
			430.85		
			441.46		
6				430.57	3/3
				429.92	
				418.77	
Mean	426.26	445.64	432.96	426.42	
SD	6.65	12.79	7.67	6.63	
%RSD	1.56	2.87	1.77	1.56	
%RE	6.56	11.41	8.24	6.61	
n	3	3	3	3	

[a]Acceptance Ratio = Number of diluted QC samples quantitating within the QC acceptance range / number of diluted QC samples analyzed.
[b]QCs corrected for a 2.00-fold dilution.
[c]QCs corrected for a 2.50-fold dilution.
[d]QCs corrected for a 4.00-fold dilution.
[e]QCs corrected for a 3.33-fold dilution.

Table 3.3 Dilution Integrity Quality Control (QC) Sample Results from the LC/MS/MS Assay for Fluoxetine and Norfluoxetine in Human Plasma for Norfluoxetine

	Acceptance Criteria				
-20%	320.00	320.00	320.00	320.00	
+20%	480.00	480.00	480.00	480.00	
	Nominal Concentrations (ng/mL)				Acceptance
Run	400.00[b]	400.00[c]	400.00[d]	400.00[e]	Ratio[a]
1		439.89			3/3
		427.40			
		439.38			
3	423.64				3/3
	426.74				
	424.97				

(continued)

Table 3.3 (continued) Dilution Integrity Quality Control (QC) Sample Results from the LC/MS/MS Assay for Fluoxetine and Norfluoxetine in Human Plasma for Norfluoxetine

			Acceptance Criteria		
-20%	320.00	320.00	320.00	320.00	
+20%	480.00	480.00	480.00	480.00	
	Nominal Concentrations (ng/mL)				Acceptance
Run	400.00[b]	400.00[c]	400.00[d]	400.00[e]	Ratio[a]
5			410.78 423.54 434.73		3/3
6				411.78 405.32 420.55	3/3
Mean	425.12	435.56	423.02	412.55	
SD	1.56	7.07	11.98	7.64	
%RSD	0.37	1.62	2.83	1.85	
%RE	6.28	8.89	5.75	3.14	
n	3	3	3	3	

[a]Acceptance Ratio = Number of diluted QC samples quantitating within the QC acceptance range / number of diluted QC samples analyzed.
[b]QCs corrected for a 2.00-fold dilution.
[c]QCs corrected for a 2.50-fold dilution.
[d]QCs corrected for a 4.00-fold dilution.
[e]QCs corrected for a 3.33-fold dilution.

Drug Concentration Data

The concentrations of Fluoxetine and Norfluoxetine in human plasma obtained during Study B1Y-MC-HCJE are provided in Table 4.

Table 4 Sample Results from the LC/MS/MS Assay for Fluoxetine and Norfluoxetine in Human Plasma, Study B1Y-MC-HCJE

Databook: 4172

						Fluoxetine			Norfluoxetine		
Accession #[a]	Patient #	Draw Date	Draw Time	Visit	Country Code	Filename[b]	Test Code	Conc. (ng/mL)	Filename[b]	Test Code	Conc. (ng/mL)
P138361-8	101	27-APR-1998	12:30	001	US	1c1	SRT1322	<1.00	1c1	SRT1323	<1.00
P138371-8	108	27-JUL-1998	10:00	001	US	1c2	SRT1322	<1.00	1c2	SRT1323	<1.00
P138381-8	102	04-MAY-1998	11:30	001	US	1c3	SRT1322	<1.00	1c3	SRT1323	<1.00
Q391632-8	107	10-JUL-1998	10:00	001	US	1c4	SRT1322	<1.00	1c4	SRT1323	<1.00
Q391641-8	104	11-MAY-1998	11:00	001	US	1c5	SRT1322	<1.00	1c5	SRT1323	<1.00
Q391651-8	105	22-JUN-1998	10:30	001	US	1c6	SRT1322	<1.00	1c6	SRT1323	<1.00
Q391661-8	103	06-MAY-1998	10:30	001	US	1c7	SRT1322	<1.00	1c7	SRT1323	<1.00
Q391671-8	112	01-OCT-1998	10:30	001	US	1c8	SRT1322	<1.00	1c8	SRT1323	<1.00
S799801-8	114	05-OCT-1998	10:45	001	US	1c9	SRT1322	<1.00	1c9	SRT1323	<1.00
S799811-8	113	05-OCT-1998	11:00	001	US	1c10	SRT1322	<1.00	1c10	SRT1323	<1.00
S799821-8	110	28-SEP-1998	10:15	001	US	1c11	SRT1322	<1.00	1c11	SRT1323	<1.00
S799831-8	111	30-SEP-1998	10:15	001	US	1c12	SRT1322	<1.00	1c12	SRT1323	<1.00
S799841-8	109	24-AUG-1998	10:30	001	US	1c13	SRT1322	<1.00	1c13	SRT1323	<1.00
V873911-8	118	26-OCT-1998	11:00	001	US	1c14	SRT1322	<2.50	1c14	SRT1323	<2.50
V873921-8	124	24-NOV-1998	10:35	001	US	1c15	SRT1322	<1.00	1c15	SRT1323	<1.00
V873932-8	115	07-OCT-1998	11:30	001	US	1c16	SRT1322	<1.00	1c16	SRT1323	<1.00
V873941-8	116	21-OCT-1998	11:00	001	US	1c17	SRT1322	<1.00	1c17	SRT1323	<1.00
W086321-8	121	10-NOV-1998	10:15	001	US	1c18	SRT1322	<1.00	1c18	SRT1323	16.80
W086331-8	119	30-OCT-1998	10:05	001	US	1c19	SRT1322	<1.00	1c19	SRT1323	<1.00
W086351-8	120	03-NOV-1998	10:35	001	US	1c20	SRT1322	<1.00	1c20	SRT1323	<1.00
X311092-8	127	08-DEC-1998	10:55	001	US	1c21	SRT1322	<1.00	1c21	SRT1323	<1.00
X311101-8	122	13-NOV-1998	11:45	001	US	1c22	SRT1322	<1.00	1c22	SRT1323	<1.00
X311121-8	123	17-NOV-1998	10:45	001	US	1c23	SRT1322	<1.00	1c23	SRT1323	<1.00

(continued)

Table 4 (continued) Sample Results from the LC/MS/MS Assay for Fluoxetine and Norfluoxetine in Human Plasma, Study B1Y-MC-HCJE

Databook: 4172

						Fluoxetine			Norfluoxetine		
Accession #[a]	Pati[redacted] #	Draw Date	Draw Time	Visit	Country Code	[redacted] Filename[b]	Test Code	Conc. (ng/mL)	[redacted] Filename[b]	Test Code	Conc. (ng/mL)
Y252221-8	125	01-DEC-1998	10:35	001	US	1c24	SRT1322	<1.00	1c24	SRT1323	<1.00
Y252241-8	126	07-DEC-1998	10:45	001	US	1c25	SRT1322	<1.00	1c25	SRT1323	<1.00
B561052-8	134	22-FEB-1999	10:30	001	US	1c26	SRT1322	<1.00	1c26	SRT1323	<1.00
B561072-8	135	26-FEB-1999	10:00	001	US	1c27	SRT1322	<1.00	1c27	SRT1323	<1.00
B561082-8	136	23-MAR-1999	11:00	001	US	1c28	SRT1322	<1.00	1c28	SRT1323	<1.00
D047112-8	150	26-APR-1999	11:30	001	US	1c29	SRT1322	<1.00	1c29	SRT1323	<1.00
D047122-8	149	28-APR-1999	11:30	001	US	1c30	SRT1322	<1.00	1c30	SRT1323	<1.00
D047132-8	147	20-APR-1999	0:00	001	US	1c31	SRT1322	<1.00	1c31	SRT1323	<1.00
D047142-8	140	08-APR-1999	11:00	001	US	1c32	SRT1322	<1.00	1c32	SRT1323	<1.00
D410942-8	142	12-APR-1999	10:30	001	US	1c33	SRT1322	<1.00	1c33	SRT1323	<1.00
D410953-8	143	13-APR-1999	13:30	001	US	1c34	SRT1322	<1.00	1c34	SRT1323	<1.00
D410973-8	141	09-APR-1999	11:15	001	US	1c35	SRT1322	<1.00	1c35	SRT1323	<1.00
D466633-8	145	15-APR-1999	11:45	001	US	1c36	SRT1322	<1.00	1c36	SRT1323	<1.00
D466653-8	146	16-APR-1999	10:45	001	US	1c37	SRT1322	<1.00	1c37	SRT1323	<1.00
D466662-8	153	11-MAY-1999	10:45	001	US	1c38	SRT1322	<1.00	1c38	SRT1323	<1.00
D466672-8	148	22-APR-1999	10:45	001	US	1c39	SRT1322	<1.00	1c39	SRT1323	<1.00
D466682-8	144	15-APR-1999	11:15	001	US	1c40	SRT1322	<1.00	1c40	SRT1323	<1.00
D866312-8	154	14-MAY-1999	11:00	001	US	1c41	SRT1322	<1.00	1c41	SRT1323	<1.00
D866343-8	151	03-MAY-1999	11:00	001	US	1c42	SRT1322	<1.00	1c42	SRT1323	<1.00
E627823-8	155	21-MAY-1999	10:00	001	US	1c43	SRT1322	<1.00	1c43	SRT1323	<1.00
X311111-8	128	15-DEC-1998	10:15	001	US	1c44	SRT1322	<1.00	1c44	SRT1323	<1.00
Y252232-8	138	29-MAR-1999	10:50	001	US	1c45	SRT1322	<1.00	1c45	SRT1323	<1.00
Y252251-8	131	04-FEB-1999	11:00	001	US	1c46	SRT1322	<1.00	1c46	SRT1323	<1.00
Z055761-8	129	07-JAN-1999	11:30	001	US	1c47	SRT1322	<1.00	1c47	SRT1323	<1.00

(continued)

Table 4 (continued) Sample Results from the LC/MS/MS Assay for Fluoxetine and Norfluoxetine in Human Plasma, Study B1Y-MC-HCJE

Databook: 4172

						Fluoxetine			Norfluoxetine		
Accession #[a]	Pati[redacted] #	Draw Date	Draw Time	Visit	Country Code	[redacted] Filename[b]	Test Code	Conc. (ng/mL)	[redacted] Filename[b]	Test Code	Conc. (ng/mL)
Z055771-8	133	18-FEB-1999	11:00	001	US	1c48	SRT1322	<1.00	1c48	SRT1323	<1.00
Z055782-8	132	11-FEB-1999	14:05	001	US	1c49	SRT1322	<1.00	1c49	SRT1323	<1.00
Z055791-8	130	01-FEB-1999	10:30	001	US	1c50	SRT1322	<1.00	1c50	SRT1323	<1.00
E627783-8	156	04-JUN-1999	11:55	001	US	1c51	SRT1322	<1.00	1c51	SRT1323	<1.00
E627803-8	157	15-JUL-1999	15:00	001	US	1c52	SRT1322	<1.00	1c52	SRT1323	<1.00
E937423-8	214	28-JUN-1999	12:45	001	US	1c53	SRT1322	<1.00	1c53	SRT1323	<1.00
E937442-8	213	02-JUN-1999	13:50	001	US	6c54a	SRT1322	<1.00	6c54a	SRT1323	<1.00
E937452-8	212	28-MAY-1999	13:20	001	US	1c55	SRT1322	<1.00	1c55	SRT1323	<1.00
P138411-8	203	06-OCT-1998	15:45	001	US	1c56	SRT1322	<1.00	1c56	SRT1323	<1.00
P138422-8	201	21-SEP-1998	17:40	001	US	1c57	SRT1322	<1.00	1c57	SRT1323	<1.00
P138431-8	202	02-OCT-1998	18:00	001	US	6c58a	SRT1322	<1.00	6c58a	SRT1323	<1.00
P775251-8	303	17-JUL-1998	16:20	001	US	1c59	SRT1322	<1.00	1c59	SRT1323	<1.00
P775261-8	302	15-JUL-1998	17:30	001	US	6c60a	SRT1322	<3.33	6c60a	SRT1323	<3.33
P775272-8	301	28-MAY-1998	18:30	001	US	1c61	SRT1322	<1.00	1c61	SRT1323	<1.00
R451482-8	307	23-JUL-1998	18:30	001	US	1c62	SRT1322	<1.00	1c62	SRT1323	<1.00
R451491-8	309	31-JUL-1998	13:30	001	US	1c63	SRT1322	<1.00	1c63	SRT1323	<1.00
R451501-8	308	24-JUL-1998	18:40	001	US	1c64	SRT1322	<1.00	1c64	SRT1323	<1.00
R451511-8	305	22-JUL-1998	14:20	001	US	1c65	SRT1322	<1.00	1c65	SRT1323	<1.00
R451521-8	306	22-JUL-1998	19:55	001	US	1c66	SRT1322	<1.00	1c66	SRT1323	<1.00
T362221-8	312	04-AUG-1998	21:30	001	US	1c67	SRT1322	<1.00	1c67	SRT1323	<1.00
T362251-8	311	04-AUG-1998	15:30	001	US	1c68	SRT1322	<1.00	1c68	SRT1323	<1.00
V501732-8	205	05-NOV-1998	11:10	001	US	1c69	SRT1322	<1.00	1c69	SRT1323	<1.00
V501741-8	204	01-NOV-1998	13:03	001	US	1c70	SRT1322	<1.00	1c70	SRT1323	<1.00
V501761-8	208	03-MAY-1999	14:25	001	US	1c71	SRT1322	<1.00	1c71	SRT1323	<1.00

(continued)

Table 4 (continued) Sample Results from the LC/MS/MS Assay for Fluoxetine and Norfluoxetine in Human Plasma, Study B1Y-MC-HCJE

Databook: 4172

						Fluoxetine			Norfluoxetine		
Accession #[a]	Pati[redacted] #	Draw Date	Draw Time	Visit	Country Code	[redacted] Filename[b]	Test Code	Conc. (ng/mL)	[redacted] Filename[b]	Test Code	Conc. (ng/mL)
V501772-8	204	14-NOV-1998	10:45	001	US	1c72	SRT1322	<1.00	1c72	SRT1323	<1.00
X455171-8	206	04-FEB-1999	15:30	001	US	1c73	SRT1322	<1.00	1c73	SRT1323	<1.00
X455181-8	209	20-MAY-1999	13:00	001	US	1c74	SRT1322	<1.00	1c74	SRT1323	<1.00
X455201-8	210	21-MAY-1999	14:50	001	US	1c75	SRT1322	<1.00	1c75	SRT1323	<1.00
B315772-8	340	18-FEB-1999	19:00	001	US	1c76	SRT1322	<1.00	1c76	SRT1323	<1.00
B315792-8	343	11-FEB-1999	17:20	001	US	1c77	SRT1322	<1.00	1c77	SRT1323	<1.00
B315802-8	347	27-JAN-1999	17:00	001	US	1c78	SRT1322	<1.00	1c78	SRT1323	<1.00
B315822-8	346	13-FEB-1999	13:30	001	US	1c79	SRT1322	<1.00	1c79	SRT1323	<1.00
T362161-8	316	18-AUG-1998	19:27	001	US	1c80	SRT1322	<1.00	1c80	SRT1323	<1.00
T362171-8	315	17-AUG-1998	20:00	001	US	1c81	SRT1322	<1.00	1c81	SRT1323	<1.00
T362191-8	317	27-AUG-1998	18:10	001	US	1c82	SRT1322	<1.00	1c82	SRT1323	<1.00
T362201-8	314	11-AUG-1998	18:00	001	US	6c83a	SRT1322	<1.00	6c83a	SRT1323	<1.00
T362212-8	313	11-AUG-1998	13:10	001	US	1c84	SRT1322	<1.00	1c84	SRT1323	<1.00
T362232-8	318	02-SEP-1998	21:30	001	US	1c85	SRT1322	<1.00	1c85	SRT1323	<1.00
T362241-8	334	21-DEC-1998	17:00	001	US	6c86a	SRT1322	<2.00	6c86a	SRT1323	<2.00
U505012-8	322	10-SEP-1998	20:15	001	US	1c87	SRT1322	<1.00	1c87	SRT1323	<1.00
U505021-8	323	15-SEP-1998	18:50	001	US	1c88	SRT1322	<1.00	1c88	SRT1323	<1.00
U505032-8	321	09-SEP-1998	17:25	001	US	1c89	SRT1322	<1.00	1c89	SRT1323	<1.00
U505041-8	320	09-SEP-1998	17:17	001	US	1c90	SRT1322	<1.00	1c90	SRT1323	<1.00
U505051-8	319	08-SEP-1998	18:50	001	US	1c91	SRT1322	<1.00	1c91	SRT1323	<1.00
V184762-8	327	20-OCT-1998	11:30	001	US	1c92	SRT1322	<1.00	1c92	SRT1323	<1.00
V184781-8	326	14-OCT-1998	18:40	001	US	1c93	SRT1322	<1.00	1c93	SRT1323	<1.00
V184801-8	328	27-OCT-1998	18:00	001	US	1c94	SRT1322	<1.00	1c94	SRT1323	<1.00
V184811-8	330	09-DEC-1998	19:00	001	US	1c95	SRT1322	<1.00	1c95	SRT1323	<1.00

(continued)

Table 4 (continued) Sample Results from the LC/MS/MS Assay for Fluoxetine and Norfluoxetine in Human Plasma, Study B1Y-MC-HCJE

Databook: 4172

						Fluoxetine			Norfluoxetine		
Accession #[a]	Pati[redacted] #	Draw Date	Draw Time	Visit	Country Code	[redacted] Filename[b]	Test Code	Conc. (ng/mL)	[redacted] Filename[b]	Test Code	Conc. (ng/mL)
V184821-8	335	28-DEC-1998	20:00	001	US	1c96	SRT1322	<1.00	1c96	SRT1323	<1.00
V184831-8	332	19-DEC-1998	9:30	001	US	2c97	SRT1322	<1.00	2c97	SRT1323	<1.00
V184852-8	337	13-JAN-1999	19:45	001	US	2c98	SRT1322	<1.00	2c98	SRT1323	<1.00
V184861-8	339	30-JAN-1999	11:40	001	US	2c99	SRT1322	<1.00	2c99	SRT1323	<1.00
V184872-8	336	09-JAN-1999	10:00	001	US	2c100	SRT1322	<1.00	2c100	SRT1323	<1.00
B315763-8	350	01-MAR-1999	17:00	001	US	2c101	SRT1322	<1.00	2c101	SRT1323	<1.00
B315812-8	348	05-MAR-1999	15:00	001	US	2c102	SRT1322	<1.00	2c102	SRT1323	<1.00
C216312-8	353	24-MAR-1999	16:00	001	US	2c103	SRT1322	<1.00	2c103	SRT1323	<1.00
C216322-8	355	28-MAY-1999	13:50	001	US	2c104	SRT1322	<1.00	2c104	SRT1323	<1.00
C216342-8	354	25-MAY-1999	19:40	001	US	2c105	SRT1322	<1.00	2c105	SRT1323	<1.00
C216373-8	352	17-MAR-1999	16:30	001	US	2c106	SRT1322	<1.00	2c106	SRT1323	<1.00
C216382-8	351	13-MAR-1999	12:15	001	US	2c107	SRT1322	<1.00	2c107	SRT1323	<1.00
E468312-8	356	18-JUN-1999	19:50	001	US	2c108	SRT1322	<1.00	2c108	SRT1323	<1.00
P138461-8	407	12-JUN-1998	10:45	001	US	2c109	SRT1322	<1.00	2c109	SRT1323	<1.00
P138471-8	401	28-APR-1998	14:55	001	US	2c110	SRT1322	<1.00	2c110	SRT1323	<1.00
Q391722-8	402	12-MAY-1998	14:35	001	US	2c111	SRT1322	<1.00	2c111	SRT1323	<1.00
Q391742-8	405	02-JUN-1998	12:15	001	US	2c112	SRT1322	<1.00	2c112	SRT1323	<1.00
Q391751-8	403	14-MAY-1998	14:50	001	US	2c113	SRT1322	<1.00	2c113	SRT1323	<1.00
Q391761-8	404	20-MAY-1998	13:05	001	US	2c114	SRT1322	<1.00	2c114	SRT1323	<1.00
R565761-8	416	30-NOV-1998	11:55	001	US	2c115	SRT1322	<1.00	2c115	SRT1323	<1.00
R565771-8	419	08-JAN-1999	12:25	001	US	2c116	SRT1322	<1.00	2c116	SRT1323	<1.00
R565781-8	409	15-JUL-1998	13:23	001	US	2c117	SRT1322	<1.00	2c117	SRT1323	<1.00
R565801-8	410	23-JUL-1998	10:54	001	US	2c118	SRT1322	<1.00	2c118	SRT1323	<1.00
R565812-8	417	11-DEC-1998	9:45	001	US	2c119	SRT1322	<1.00	2c119	SRT1323	<1.00

(continued)

Table 4 (continued) Sample Results from the LC/MS/MS Assay for Fluoxetine and Norfluoxetine in Human Plasma, Study B1Y-MC-HCJE

Databook: 4172

						Fluoxetine			Norfluoxetine		
Accession #[a]	Pati[redacted] #	Draw Date	Draw Time	Visit	Country Code	[redacted] Filename[b]	Test Code	Conc. (ng/mL)	[redacted] Filename[b]	Test Code	Conc. (ng/mL)
R565821-8	420	28-JAN-1999	12:10	001	US	2c120	SRT1322	<1.00	2c120	SRT1323	<1.00
R565832-8	408	19-JUN-1998	10:40	001	US	2c121	SRT1322	<1.00	2c121	SRT1323	<1.00
T470622-8	414	15-SEP-1998	11:20	001	US	2c122	SRT1322	<1.00	2c122	SRT1323	<1.00
T470631-8	415	28-OCT-1998	11:45	001	US	2c123	SRT1322	<1.00	2c123	SRT1323	<1.00
T470651-8	412	09-SEP-1998	12:05	001	US	2c124	SRT1322	<1.00	2c124	SRT1323	<1.00
T470671-8	413	10-SEP-1998	10:45	001	US	2c125	SRT1322	<1.00	2c125	SRT1323	<1.00
A064392-8	433	27-APR-1999	11:20	001	US	2c126	SRT1322	<1.00	2c126	SRT1323	<1.00
A064402-8	425	19-MAR-1999	12:25	001	US	2c127	SRT1322	<1.00	2c127	SRT1323	<1.00
A064412-8	432	21-APR-1999	11:45	001	US	2c128	SRT1322	<1.00	2c128	SRT1323	<1.00
A064422-8	422	02-MAR-1999	11:30	001	US	2c129	SRT1322	<1.00	2c129	SRT1323	<1.00
A064432-8	423	15-MAR-1999	11:45	001	US	2c130	SRT1322	<1.00	2c130	SRT1323	<1.00
A064443-8	431	20-APR-1999	11:50	001	US	2c131	SRT1322	<1.00	2c131	SRT1323	<1.00
A064452-8	427	30-MAR-1999	11:55	001	US	2c132	SRT1322	<1.00	2c132	SRT1323	<1.00
E471672-8	441	30-JUN-1999	11:00	001	US	2c133	SRT1322	<1.00	2c133	SRT1323	<1.00
E471692-8	439	23-JUN-1999	15:05	001	US	2c134	SRT1322	<1.00	2c134	SRT1323	<1.00
E471702-8	438	23-JUN-1999	11:25	001	US	2c135	SRT1322	<1.00	2c135	SRT1323	<1.00
E471713-8	437	17-JUN-1999	15:15	001	US	2c136	SRT1322	<1.00	2c136	SRT1323	<1.00
E471722-8	435	21-MAY-1999	11:25	001	US	2c137	SRT1322	<1.00	2c137	SRT1323	<1.00
P138521-8	505	16-OCT-1998	15:00	001	US	2c138	SRT1322	<1.00	2c138	SRT1323	<1.00
P138532-8	503	20-JUL-1998	15:30	001	US	2c139	SRT1322	<1.00	2c139	SRT1323	<1.00
P138561-8	601	05-AUG-1998	13:30	001	US	2c140	SRT1322	<1.00	2c140	SRT1323	<1.00
P138661-8	801	21-JUL-1998	13:00	001	US	2c141	SRT1322	<1.00	2c141	SRT1323	<1.00
P138671-8	807	23-NOV-1998	15:30	001	US	2c142	SRT1322	<1.00	2c142	SRT1323	<1.00
P138681-8	806	17-NOV-1998	10:45	001	US	2c143	SRT1322	<1.00	2c143	SRT1323	<1.00

(continued)

Table 4 (continued) Sample Results from the LC/MS/MS Assay for Fluoxetine and Norfluoxetine in Human Plasma, Study B1Y-MC-HCJE

Databook: 4172

							Fluoxetine			Norfluoxetine	
Accession #[a]	Pati[redacted] #	Draw Date	Draw Time	Visit	Country Code	[redacted] Filename[b]	Test Code	Conc. (ng/mL)	[redacted] Filename[b]	Test Code	Conc. (ng/mL)
T172672-8	507	16-NOV-1998	16:05	001	US	2c144	SRT1322	<1.00	2c144	SRT1323	<1.00
T223531-8	803	17-SEP-1998	18:30	001	US	2c145	SRT1322	<1.00	2c145	SRT1323	<1.00
T223542-8	802	02-SEP-1998	17:50	001	US	2c146	SRT1322	<1.00	2c146	SRT1323	<1.00
T223551-8	804	23-SEP-1998	0:00	001	US	2c147	SRT1322	<1.00	2c147	SRT1323	<1.00
T470641-8	424	17-MAR-1999	11:20	001	US	2c148	SRT1322	<1.00	2c148	SRT1323	<1.00
T470681-8	430	12-APR-1999	12:15	001	US	2c149	SRT1322	<1.00	2c149	SRT1323	<1.00
T470701-8	434	30-APR-1999	12:30	001	US	2c150	SRT1322	<1.00	2c150	SRT1323	<1.00
B559963-8	812	22-FEB-1999	10:38	001	US	2c151	SRT1322	<1.00	2c151	SRT1323	<1.00
B559972-8	815	18-MAY-1999	13:15	001	US	2c152	SRT1322	<1.00	2c152	SRT1323	<1.00
B559992-8	814	01-APR-1999	12:20	001	US	2c153	SRT1322	<1.00	2c153	SRT1323	<1.00
B560002-8	813	01-MAR-1999	15:05	001	US	2c154	SRT1322	<1.00	2c154	SRT1323	<1.00
C594842-8	913	21-APR-1999	0:00	001	US	2c155	SRT1322	<1.00	2c155	SRT1323	<1.00
C594852-8	915	21-MAY-1999	12:23	001	US	2c156	SRT1322	<1.00	2c156	SRT1323	<1.00
C594862-8	912	16-APR-1999	12:45	001	US	2c157	SRT1322	<1.00	2c157	SRT1323	<1.00
C594872-8	910	19-MAR-1999	12:45	001	US	2c158	SRT1322	<1.00	2c158	SRT1323	<1.00
C594883-8	911	14-APR-1999	12:35	001	US	2c159	SRT1322	<1.00	2c159	SRT1323	<1.00
E029062-8	917	09-JUN-1999	12:30	001	US	2c160	SRT1322	<1.00	2c160	SRT1323	<1.00
E029073-8	916	26-MAY-1999	0:00	001	US	2c161	SRT1322	<1.00	2c161	SRT1323	<1.00
E029082-8	919	16-JUN-1999	12:36	001	US	2c162	SRT1322	<1.00	2c162	SRT1323	<1.00
E029093-8	918	11-JUN-1999	13:00	001	US	2c163	SRT1322	<1.00	2c163	SRT1323	<1.00
E029113-8	920	18-JUN-1999	12:05	001	US	2c164	SRT1322	<1.00	2c164	SRT1323	<1.00
P138711-8	902	08-OCT-1998	13:45	001	US	2c165	SRT1322	<1.00	2c165	SRT1323	<1.00
P138721-8	901	01-OCT-1998	13:00	001	US	2c166	SRT1322	<1.00	2c166	SRT1323	<1.00
T223561-8	808	25-NOV-1998	17:00	001	US	2c167	SRT1322	<1.00	2c167	SRT1323	<1.00

(continued)

Table 4 (continued) Sample Results from the LC/MS/MS Assay for Fluoxetine and Norfluoxetine in Human Plasma, Study B1Y-MC-HCJE

Databook: 4172

						Fluoxetine			Norfluoxetine		
Accession #[a]	Pati[redacted] #	Draw Date	Draw Time	Visit	Country Code	[redacted] Filename[b]	Test Code	Conc. (ng/mL)	[redacted] Filename[b]	Test Code	Conc. (ng/mL)
V872231-8	907	10-FEB-1999	13:10	001	US	2c168	SRT1322	<1.00	2c168	SRT1323	<1.00
V872242-8	906	04-FEB-1999	12:40	001	US	2c169	SRT1322	<1.00	2c169	SRT1323	<1.00
V872251-8	908	10-MAR-1999	12:50	001	US	2c170	SRT1322	<1.00	2c170	SRT1323	<1.00
V872262-8	905	13-JAN-1999	10:00	001	US	2c171	SRT1322	<1.00	2c171	SRT1323	<1.00
V872271-8	909	12-MAR-1999	12:55	001	US	2c172	SRT1322	<1.00	2c172	SRT1323	<1.00
X904642-8	809	05-FEB-1999	15:20	001	US	2c173	SRT1322	<1.00	2c173	SRT1323	<1.00
X904651-8	810	11-FEB-1999	11:00	001	US	2c174	SRT1322	<1.00	2c174	SRT1323	<1.00
X904662-8	811	15-FEB-1999	15:45	001	US	2c175	SRT1322	<1.00	2c175	SRT1323	<1.00
P138811-8	1102	15-MAY-1998	13:00	001	US	2c176	SRT1322	<1.00	2c176	SRT1323	<1.00
P138821-8	1104	28-MAY-1998	15:35	001	US	2c177	SRT1322	<1.00	2c177	SRT1323	<1.00
P138831-8	1101	13-MAY-1998	13:40	001	US	2c178	SRT1322	<1.00	2c178	SRT1323	<1.00
Q586971-8	1108	29-JUN-1998	15:45	001	US	2c179	SRT1322	<1.00	2c179	SRT1323	<1.00
Q586982-8	1109	06-JUL-1998	14:10	001	US	2c180	SRT1322	<1.00	2c180	SRT1323	<1.00
Q586991-8	1107	25-JUN-1998	14:58	001	US	2c181	SRT1322	<1.00	2c181	SRT1323	<1.00
Q587002-8	1110	09-JUL-1998	9:55	001	US	2c182	SRT1322	<1.00	2c182	SRT1323	<1.00
Q587011-8	1105	16-JUN-1998	13:58	001	US	2c183	SRT1322	<1.00	2c183	SRT1323	<1.00
Q587022-8	1112	15-JUL-1998	14:57	001	US	2c184	SRT1322	<1.00	2c184	SRT1323	<1.00
Q587031-8	1117	07-AUG-1998	10:00	001	US	2c185	SRT1322	<1.00	2c185	SRT1323	<1.00
S690961-8	1106	17-JUL-1998	9:32	001	US	2c186	SRT1322	<1.00	2c186	SRT1323	<1.00
S690972-8	1113	15-JUL-1998	15:05	001	US	2c187	SRT1322	<1.00	2c187	SRT1323	<1.00
S690981-8	1115	29-JUL-1998	10:23	001	US	2c188	SRT1322	<1.00	2c188	SRT1323	<1.00
S690992-8	1114	28-JUL-1998	10:50	001	US	2c189	SRT1322	<1.00	2c189	SRT1323	<1.00
S691001-8	1116	03-AUG-1998	10:43	001	US	2c190	SRT1322	<1.00	2c190	SRT1323	<1.00
T495511-8	1127	01-DEC-1998	14:10	001	US	2c191	SRT1322	<1.00	2c191	SRT1323	<1.00

(continued)

Table 4 (continued) Sample Results from the LC/MS/MS Assay for Fluoxetine and Norfluoxetine in Human Plasma, Study B1Y-MC-HCJE

Databook: 4172

						Fluoxetine			Norfluoxetine		
Accession #[a]	Pati[redacted] #	Draw Date	Draw Time	Visit	Country Code	[redacted] Filename[b]	Test Code	Conc. (ng/mL)	[redacted] Filename[b]	Test Code	Conc. (ng/mL)
T495522-8	1126	20-NOV-1998	11:50	001	US	2c192	SRT1322	<1.00	2c192	SRT1323	<1.00
T495542-8	1124	18-NOV-1998	11:02	001	US	3c193	SRT1322	<1.00	3c193	SRT1323	<1.00
T495551-8	1123	06-NOV-1998	16:00	001	US	3c194	SRT1322	<1.00	3c194	SRT1323	<1.00
T617701-8	1121	19-AUG-1998	11:25	001	US	3c195	SRT1322	<1.00	3c195	SRT1323	<1.00
T617711-8	1119	12-AUG-1998	15:30	001	US	3c196	SRT1322	<1.00	3c196	SRT1323	<1.00
T617721-8	1118	11-AUG-1998	14:45	001	US	6c197a	SRT1322	<1.00	6c197a	SRT1323	<1.00
T617731-8	1122	22-SEP-1998	14:43	001	US	3c198	SRT1322	<1.00	3c198	SRT1323	<1.00
T617741-8	1120	18-AUG-1998	14:32	001	US	3c199	SRT1322	<1.00	3c199	SRT1323	<1.00
Y213922-8	1128	03-DEC-1998	11:30	001	US	3c200	SRT1322	<1.00	3c200	SRT1323	<1.00
C872562-8	1144	30-MAR-1999	11:20	001	US	3c201	SRT1322	<1.00	3c201	SRT1323	<1.00
C872582-8	1146	14-APR-1999	11:35	001	US	3c202	SRT1322	<1.00	3c202	SRT1323	<1.00
C872592-8	1147	14-APR-1999	14:00	001	US	3c203	SRT1322	<1.00	3c203	SRT1323	<1.00
C872602-8	1149	22-APR-1999	15:12	001	US	3c204	SRT1322	<1.00	3c204	SRT1323	<1.00
D830002-8	1151	03-MAY-1999	15:15	001	US	3c205	SRT1322	<1.00	3c205	SRT1323	<1.00
D830013-8	1152	04-MAY-1999	16:40	001	US	3c206	SRT1322	<2.00	3c206	SRT1323	<2.00
D830022-8	1153	19-MAY-1999	14:45	001	US	3c207	SRT1322	<1.00	3c207	SRT1323	<1.00
D830033-8	1155	07-JUN-1999	15:27	001	US	3c208	SRT1322	<1.00	3c208	SRT1323	<1.00
D830042-8	1156	30-JUN-1999	11:20	001	US	3c209	SRT1322	<1.00	3c209	SRT1323	<1.00
P138921-8	1201	01-MAY-1998	16:15	001	US	3c210	SRT1322	<1.00	3c210	SRT1323	<1.00
Y082132-8	1129	07-DEC-1998	12:07	001	US	3c211	SRT1322	<1.00	3c211	SRT1323	<1.00
Y082141-8	1136	03-FEB-1999	11:55	001	US	3c212	SRT1322	<1.00	3c212	SRT1323	<1.00
Y082151-8	1130	09-DEC-1998	10:09	001	US	3c213	SRT1322	<1.00	3c213	SRT1323	<1.00
Y082161-8	1140	15-MAR-1999	15:00	001	US	3c214	SRT1322	<1.00	3c214	SRT1323	<1.00
Y082171-8	1133	18-DEC-1998	11:00	001	US	3c215	SRT1322	<1.00	3c215	SRT1323	<1.00

(continued)

Table 4 (continued) Sample Results from the LC/MS/MS Assay for Fluoxetine and Norfluoxetine in Human Plasma, Study B1Y-MC-HCJE

Databook: 4172

						Fluoxetine			Norfluoxetine		
Accession #[a]	Pati[redacted] #	Draw Date	Draw Time	Visit	Country Code	[redacted] Filename[b]	Test Code	Conc. (ng/mL)	[redacted] Filename[b]	Test Code	Conc. (ng/mL)
Y082181-8	1134	30-DEC-1998	11:40	001	US	3c216	SRT1322	<1.00	3c216	SRT1323	<1.00
Y213902-8	1132	16-DEC-1998	10:55	001	US	3c217	SRT1322	<1.00	3c217	SRT1323	<1.00
Y213911-8	1131	14-DEC-1998	15:43	001	US	3c218	SRT1322	<1.00	3c218	SRT1323	<1.00
Y213931-8	1135	07-JAN-1999	13:45	001	US	3c219	SRT1322	<1.00	3c219	SRT1323	<1.00
Y214061-8	1143	24-MAR-1999	11:00	001	US	3c220	SRT1322	<1.00	3c220	SRT1323	<1.00
Z837041-8	1142	23-MAR-1999	15:00	001	US	6c221a	SRT1322	<1.00	6c221a	SRT1323	<1.00
Z837051-8	1141	17-MAR-1999	11:45	001	US	3c222	SRT1322	<1.00	3c222	SRT1323	<1.00
Z837061-8	1139	22-MAR-1999	16:00	001	US	3c223	SRT1322	<1.00	3c223	SRT1323	<1.00
Z837071-8	1137	23-FEB-1999	15:30	001	US	3c224	SRT1322	<1.00	3c224	SRT1323	<1.00
Z837081-8	1138	03-MAR-1999	11:45	001	US	3c225	SRT1322	<1.00	3c225	SRT1323	<1.00
C195402-8	1222	15-APR-1999	15:30	001	US	3c226	SRT1322	<1.00	3c226	SRT1323	<1.00
C195412-8	1223	19-APR-1999	14:45	001	US	3c227	SRT1322	<1.00	3c227	SRT1323	<1.00
D911112-8	1225	17-MAY-1999	13:30	001	US	3c228	SRT1322	<1.00	3c228	SRT1323	<1.00
D911123-8	1227	07-JUN-1999	14:20	001	US	6c229a	SRT1322	<1.00	6c229a	SRT1323	<1.00
D911152-8	1224	22-APR-1999	15:05	001	US	3c230	SRT1322	<1.00	3c230	SRT1323	<1.00
P138931-8	1203	28-MAY-1998	11:20	001	US	3c231	SRT1322	<1.00	3c231	SRT1323	<1.00
P138941-8	1202	13-MAY-1998	11:00	001	US	3c232	SRT1322	<1.00	3c232	SRT1323	<1.00
Q499011-8	1211	03-SEP-1998	11:50	001	US	3c233	SRT1322	<1.00	3c233	SRT1323	<1.00
Q499021-8	1206	16-JUL-1998	16:45	001	US	3c234	SRT1322	<1.00	3c234	SRT1323	<1.00
Q499031-8	1205	13-JUL-1998	11:30	001	US	3c235	SRT1322	<1.00	3c235	SRT1323	<1.00
Q499042-8	1204	05-JUN-1998	12:10	001	US	3c236	SRT1322	<1.00	3c236	SRT1323	<1.00
T044541-8	1209	28-AUG-1998	11:20	001	US	3c237	SRT1322	<1.00	3c237	SRT1323	<1.00
T044551-8	1210	28-AUG-1998	15:35	001	US	3c238	SRT1322	<1.00	3c238	SRT1323	<1.00
T044571-8	1208	14-AUG-1998	15:45	001	US	3c239	SRT1322	<1.00	3c239	SRT1323	<1.00

(continued)

Table 4 (continued) Sample Results from the LC/MS/MS Assay for Fluoxetine and Norfluoxetine in Human Plasma, Study B1Y-MC-HCJE

Databook: 4172

						Fluoxetine			Norfluoxetine		
Accession #[a]	Pati[redacted] #	Draw Date	Draw Time	Visit	Country Code	[redacted] Filename[b]	Test Code	Conc. (ng/mL)	[redacted] Filename[b]	Test Code	Conc. (ng/mL)
T044581-8	1207	27-JUL-1998	13:40	001	US	3c240	SRT1322	<1.00	3c240	SRT1323	<1.00
U798641-8	1213	12-OCT-1998	14:45	001	US	3c241	SRT1322	<1.00	3c241	SRT1323	<1.00
U798651-8	1212	09-OCT-1998	16:00	001	US	6c242a	SRT1322	<2.00	6c242a	SRT1323	<2.00
U798661-8	1214	22-OCT-1998	16:40	001	US	3c243	SRT1322	<1.00	3c243	SRT1323	<1.00
U798671-8	1215	11-NOV-1998	15:20	001	US	3c244	SRT1322	<1.00	3c244	SRT1323	<1.00
U798681-8	1216	23-NOV-1998	16:00	001	US	3c245	SRT1322	<1.00	3c245	SRT1323	<1.00
V665912-8	1301	07-DEC-1998	11:45	001	US	3c246	SRT1322	<1.00	3c246	SRT1323	<1.00
Y252102-8	1218	08-FEB-1999	17:00	001	US	3c247	SRT1322	<1.00	3c247	SRT1323	<1.00
Y252122-8	1219	28-JAN-1999	15:20	001	US	3c248	SRT1322	<1.00	3c248	SRT1323	<1.00
Y252141-8	1221	05-MAR-1999	16:30	001	US	3c249	SRT1322	<1.00	3c249	SRT1323	<1.00
Y252151-8	1220	05-FEB-1999	14:15	001	US	6c250a	SRT1322	<1.25	6c250a	SRT1323	<1.25
D400382-8	1310	13-MAY-1999	10:30	001	US	3c251	SRT1322	96.46	3c251	SRT1323	119.30
D400393-8	1307	16-APR-1999	11:00	001	US	3c252	SRT1322	<1.00	3c252	SRT1323	<1.00
D400402-8	1308	06-MAY-1999	11:30	001	US	3c253	SRT1322	<1.00	3c253	SRT1323	<1.00
D400412-8	1309	10-MAY-1999	13:15	001	US	3c254	SRT1322	<1.00	3c254	SRT1323	<1.00
E104272-8	1513	11-MAY-1999	9:15	001	US	3c255	SRT1322	<1.00	3c255	SRT1323	<1.00
E104292-8	1516	27-MAY-1999	9:20	001	US	3c256	SRT1322	<1.00	3c256	SRT1323	<1.00
E104302-8	1515	14-MAY-1999	9:44	001	US	3c257	SRT1322	<1.00	3c257	SRT1323	<1.00
E104312-8	1512	06-MAY-1999	9:50	001	US	3c258	SRT1322	<1.00	3c258	SRT1323	<1.00
E698483-8	1311	14-JUN-1999	14:00	001	US	3c259	SRT1322	<1.00	3c259	SRT1323	<1.00
F188362-8	1517	10-JUN-1999	9:50	001	US	3c260	SRT1322	<1.00	3c260	SRT1323	<1.00
V665932-8	1302	04-JAN-1999	14:20	001	US	3c261	SRT1322	<1.00	3c261	SRT1323	<1.00
V666681-8	1501	20-NOV-1998	12:15	001	US	3c262	SRT1322	<1.00	3c262	SRT1323	<1.00
V666691-8	1514	13-MAY-1999	9:25	001	US	3c263	SRT1322	<1.00	3c263	SRT1323	<1.00

(continued)

Table 4 (continued) Sample Results from the LC/MS/MS Assay for Fluoxetine and Norfluoxetine in Human Plasma, Study B1Y-MC-HCJE

Databook: 4172

						Fluoxetine			Norfluoxetine		
Accession #[a]	Pati[redacted] #	Draw Date	Draw Time	Visit	Country Code	[redacted] Filename[b]	Test Code	Conc. (ng/mL)	[redacted] Filename[b]	Test Code	Conc. (ng/mL)
V666751-8	1601	20-NOV-1998	12:00	001	US	3c264	SRT1322	<1.00	3c264	SRT1323	<1.00
Y019071-8	1602	25-NOV-1998	12:30	001	US	3c265	SRT1322	<1.00	3c265	SRT1323	<1.00
Y019082-8	1603	29-DEC-1998	13:00	001	US	3c266	SRT1322	<1.00	3c266	SRT1323	<1.00
Y089151-8	1510	22-APR-1999	9:45	001	US	3c267	SRT1322	<1.00	3c267	SRT1323	<1.00
Y089161-8	1504	08-JAN-1999	11:55	001	US	3c268	SRT1322	<1.00	3c268	SRT1323	<1.00
Y089171-8	1503	04-DEC-1998	12:25	001	US	3c269	SRT1322	<1.00	3c269	SRT1323	<1.00
Y089181-8	1506	22-JAN-1999	11:50	001	US	3c270	SRT1322	<1.00	3c270	SRT1323	<1.00
Y089192-8	1508	12-FEB-1999	12:25	001	US	3c271	SRT1322	<1.00	3c271	SRT1323	<1.00
Y718631-8	1306	01-APR-1999	13:15	001	US	3c272	SRT1322	<1.00	3c272	SRT1323	<1.00
Y718641-8	1305	12-FEB-1999	11:15	001	US	3c273	SRT1322	<1.00	3c273	SRT1323	<1.00
Y718661-8	1303	29-JAN-1999	11:00	001	US	3c274	SRT1322	<1.00	3c274	SRT1323	<1.00
Y718672-8	1304	08-FEB-1999	10:45	001	US	3c275	SRT1322	<1.00	3c275	SRT1323	<1.00
B382053-8	1607	23-FEB-1999	15:00	001	US	3c276	SRT1322	<1.00	3c276	SRT1323	<1.00
B382092-8	1608	27-MAY-1999	14:10	001	US	3c277	SRT1322	<1.00	3c277	SRT1323	<1.00
C742012-8	1654	22-MAR-1999	15:15	001	US	3c278	SRT1322	<1.00	3c278	SRT1323	<1.00
C742022-8	1656	23-MAR-1999	16:00	001	US	3c279	SRT1322	<1.00	3c279	SRT1323	<1.00
C891832-8	1610	07-JUL-1999	12:30	001	US	3c280	SRT1322	<1.00	3c280	SRT1323	<1.00
C891843-8	1612	13-JUL-1999	15:00	001	US	3c281	SRT1322	<1.00	3c281	SRT1323	<1.00
C891852-8	1609	11-JUN-1999	13:00	001	US	3c282	SRT1322	<1.33	3c282	SRT1323	<1.33
C983993-8	1657	06-APR-1999	1:20	001	US	3c283	SRT1322	<1.00	3c283	SRT1323	<1.00
C984002-8	1655	07-APR-1999	15:00	001	US	3c284	SRT1322	<1.00	3c284	SRT1323	<1.00
C984012-8	1658	12-APR-1999	13:00	001	US	3c285	SRT1322	<1.00	3c285	SRT1323	<1.00
C984022-8	1659	20-APR-1999	13:30	001	US	3c286	SRT1322	<1.00	3c286	SRT1323	<1.00
D169032-8	1702	22-APR-1999	12:15	001	US	3c287	SRT1322	<1.00	3c287	SRT1323	<1.00

(continued)

Table 4 (continued) Sample Results from the LC/MS/MS Assay for Fluoxetine and Norfluoxetine in Human Plasma, Study B1Y-MC-HCJE

Databook: 4172

						Fluoxetine			Norfluoxetine		
Accession #[a]	Pati[redacted] #	Draw Date	Draw Time	Visit	Country Code	[redacted] Filename[b]	Test Code	Conc. (ng/mL)	[redacted] Filename[b]	Test Code	Conc. (ng/mL)
D169042-8	1703	27-APR-1999	12:45	001	US	3c288	SRT1322	<1.00	3c288	SRT1323	<1.00
D169053-8	1704	30-APR-1999	12:30	001	US	4c289	SRT1322	<1.00	4c289	SRT1323	<1.00
D736752-8	1664	24-MAY-1999	14:00	001	US	4c290	SRT1322	<1.00	4c290	SRT1323	<1.00
D736762-8	1669	21-JUN-1999	14:00	001	US	4c291	SRT1322	<1.00	4c291	SRT1323	<1.00
D736772-8	1661	27-APR-1999	17:30	001	US	4c292	SRT1322	<1.00	4c292	SRT1323	<1.00
D736783-8	1668	02-JUN-1999	17:30	001	US	4c293	SRT1322	<1.00	4c293	SRT1323	<1.00
D736792-8	1667	02-JUN-1999	12:00	001	US	4c294	SRT1322	<1.00	4c294	SRT1323	<1.00
V666742-8	1651	15-MAR-1999	15:20	001	US	4c295	SRT1322	7.05	4c295	SRT1323	43.20
V667031-8	1701	25-MAR-1999	12:10	001	US	4c296	SRT1322	<1.00	4c296	SRT1323	<1.00
Y019091-8	1604	19-JAN-1999	14:00	001	US	4c297	SRT1322	<1.00	4c297	SRT1323	<1.00
Y019102-8	1605	22-JAN-1999	14:30	001	US	4c298	SRT1322	<1.00	4c298	SRT1323	<1.00
Y019111-8	1606	08-FEB-1999	12:00	001	US	4c299	SRT1322	<1.00	4c299	SRT1323	<1.00
C954222-8	1924	18-MAY-1999	13:30	001	US	4c300	SRT1322	<1.00	4c300	SRT1323	<1.00
C954233-8	1927	15-JUN-1999	13:20	001	US	4c301	SRT1322	<1.00	4c301	SRT1323	<1.00
C954242-8	1926	14-JUN-1999	15:00	001	US	4c302	SRT1322	<1.00	4c302	SRT1323	4.66
C954253-8	1920	19-APR-1999	13:10	001	US	4c303	SRT1322	<1.00	4c303	SRT1323	<1.00
C954262-8	1925	21-MAY-1999	10:00	001	US	4c304	SRT1322	<1.00	4c304	SRT1323	<1.00
C954282-8	1921	20-APR-1999	13:00	001	US	4c305	SRT1322	<1.00	4c305	SRT1323	<1.00
C954292-8	1919	15-APR-1999	10:40	001	US	4c306	SRT1322	<1.00	4c306	SRT1323	<1.00
C954302-8	1918	31-MAR-1999	8:30	001	US	4c307	SRT1322	<1.00	4c307	SRT1323	<1.00
C954312-8	1922	27-APR-1999	10:30	001	US	4c308	SRT1322	<1.00	4c308	SRT1323	<1.00
D169022-8	1707	29-JUN-1999	12:45	001	US	4c309	SRT1322	<1.00	4c309	SRT1323	<1.00
V666791-8	1906	08-DEC-1998	11:40	001	US	4c310	SRT1322	<1.00	4c310	SRT1323	<1.00
V666801-8	1901	20-NOV-1998	11:30	001	US	4c311	SRT1322	<1.00	4c311	SRT1323	<1.00

(continued)

Table 4 (continued) Sample Results from the LC/MS/MS Assay for Fluoxetine and Norfluoxetine in Human Plasma, Study B1Y-MC-HCJE

Databook: 4172

						Fluoxetine			Norfluoxetine		
Accession #[a]	Pati[redacted] #	Draw Date	Draw Time	Visit	Country Code	[redacted] Filename[b]	Test Code	Conc. (ng/mL)	[redacted] Filename[b]	Test Code	Conc. (ng/mL)
V667021-8	1705	13-MAY-1999	12:15	001	US	4c312	SRT1322	<1.00	4c312	SRT1323	<1.00
Y091621-8	1908	23-DEC-1998	7:25	001	US	4c313	SRT1322	<1.00	4c313	SRT1323	<1.00
Y091631-8	1915	04-MAR-1999	14:00	001	US	4c314	SRT1322	<1.00	4c314	SRT1323	<1.00
Y091641-8	1914	19-MAR-1999	9:00	001	US	4c315	SRT1322	<1.00	4c315	SRT1323	<1.00
Y091651-8	1923	03-MAY-1999	7:30	001	US	4c316	SRT1322	<1.00	4c316	SRT1323	<1.00
Y733952-8	1911	27-JAN-1999	9:50	001	US	4c317	SRT1322	<1.00	4c317	SRT1323	<1.00
Y733961-8	1912	08-FEB-1999	13:50	001	US	4c318	SRT1322	<1.00	4c318	SRT1323	<1.00
Y733971-8	1910	18-JAN-1999	10:10	001	US	4c319	SRT1322	<1.00	4c319	SRT1323	<1.00
Y733981-8	1905	21-DEC-1998	12:00	001	US	4c320	SRT1322	<1.00	4c320	SRT1323	<1.00
Y733991-8	1904	15-DEC-1998	7:30	001	US	4c321	SRT1322	<1.00	4c321	SRT1323	<1.00
Y734001-8	1902	16-DEC-1998	7:45	001	US	4c322	SRT1322	<1.00	4c322	SRT1323	<1.00
Y734011-8	1907	14-DEC-1998	10:50	001	US	4c323	SRT1322	<1.00	4c323	SRT1323	<1.00
Y734021-8	1913	16-FEB-1999	11:50	001	US	4c324	SRT1322	<1.00	4c324	SRT1323	<1.00
A051992-8	2207	14-MAY-1999	11:50	001	US	4c325	SRT1322	<1.00	4c325	SRT1323	<1.00
A052003-8	2204	19-MAR-1999	13:10	001	US	4c326	SRT1322	<1.00	4c326	SRT1323	<1.00
A052012-8	2209	18-FEB-1999	13:05	001	US	4c327	SRT1322	<1.00	4c327	SRT1323	<1.00
B818902-8	2203	18-MAR-1999	13:00	001	US	4c328	SRT1322	<1.00	4c328	SRT1323	<1.00
B818912-8	2205	15-APR-1999	12:05	001	US	4c329	SRT1322	<1.00	4c329	SRT1323	<1.00
B818922-8	2206	06-MAY-1999	11:45	001	US	4c330	SRT1322	<1.00	4c330	SRT1323	<1.00
B818932-8	2201	25-FEB-1999	12:10	001	US	4c331	SRT1322	<1.00	4c331	SRT1323	<1.00
B818942-8	2202	04-MAR-1999	11:45	001	US	4c332	SRT1322	<1.00	4c332	SRT1323	<1.00
C954272-8	1928	22-JUN-1999	8:50	001	US	4c333	SRT1322	<1.00	4c333	SRT1323	<1.00
D027682-8	2210	27-MAY-1999	10:45	001	US	4c334	SRT1322	<1.00	4c334	SRT1323	<1.00
D027692-8	2211	02-JUN-1999	11:05	001	US	4c335	SRT1322	<1.00	4c335	SRT1323	<1.00

(continued)

Table 4 (continued) Sample Results from the LC/MS/MS Assay for Fluoxetine and Norfluoxetine in Human Plasma, Study B1Y-MC-HCJE

Databook: 4172

						Fluoxetine			Norfluoxetine		
Accession #[a]	Pati[redacted] #	Draw Date	Draw Time	Visit	Country Code	[redacted] Filename[b]	Test Code	Conc. (ng/mL)	[redacted] Filename[b]	Test Code	Conc. (ng/mL)
D027702-8	2208	20-MAY-1999	11:50	001	US	4c336	SRT1322	<1.00	4c336	SRT1323	<1.00
D027713-8	2221	01-JUL-1999	10:45	001	US	4c337	SRT1322	<1.00	4c337	SRT1323	<1.00
D027733-8	2220	30-JUN-1999	14:50	001	US	4c338	SRT1322	<1.00	4c338	SRT1323	<1.00
F292082-8	2217	23-JUN-1999	10:30	001	US	4c339	SRT1322	<1.00	4c339	SRT1323	<1.00
F292092-8	2219	24-JUN-1999	10:55	001	US	4c340	SRT1322	<1.00	4c340	SRT1323	<1.00
F292122-8	2216	16-JUN-1999	15:15	001	US	4c341	SRT1322	<1.00	4c341	SRT1323	<1.00
F292133-8	2218	23-JUN-1999	15:05	001	US	4c342	SRT1322	<1.00	4c342	SRT1323	<1.00
F292173-8	2215	16-JUN-1999	11:30	001	US	4c343	SRT1322	<1.00	4c343	SRT1323	<1.00
F292182-8	2214	10-JUN-1999	10:50	001	US	4c344	SRT1322	<1.00	4c344	SRT1323	<1.00
F292202-8	2213	09-JUN-1999	11:10	001	US	4c345	SRT1322	<1.00	4c345	SRT1323	<1.00
F797372-8	1930	12-JUL-1999	14:15	001	US	4c346	SRT1322	<1.00	4c346	SRT1323	<1.00
F797382-8	1929	28-JUN-1999	8:10	001	US	4c347	SRT1322	<1.00	4c347	SRT1323	<1.00
B561092-2	127	02-MAR-1999	14:00	010	US	4c348	SRT1322	123.53	4c348	SRT1323	183.78
B561113-7	124	20-APR-1999	15:00	015	US	4c349	SRT1322	291.16	4c349	SRT1323	343.55
D277342-7	133	25-MAY-1999	15:45	011	US	4c350	SRT1322	138.85	4c350	SRT1323	215.96
E627852-2	150	20-JUL-1999	15:15	010	US	4c351	SRT1322	435.01	4c351	SRT1323	198.02
F120432-7	124	03-AUG-1999	16:30	021	US	4c352	SRT1322	<1.00	4c352	SRT1323	<1.00
F616003-2	142	02-JUL-1999	11:25	010	US	4c353	SRT1322	81.92	4c353	SRT1323	184.35
F616043-2	139	23-JUN-1999	17:00	010	US	4c354	SRT1322	225.95	4c354	SRT1323	151.01
S532161-2	104	31-JUL-1998	13:00	010	US	4c355	SRT1322	51.06	4c355	SRT1323	119.03
S532171-2	114	29-DEC-1998	15:15	010	US	4c356	SRT1322	66.65	4c356	SRT1323	166.03
U031812-7	114	02-FEB-1999	1:15	012	US	4c357	SRT1322	46.97	4c357	SRT1323	177.95
U031821-7	127	19-MAR-1999	11:45	011	US	4c358	SRT1322	82.10	4c358	SRT1323	167.09
U505061-2	307	14-OCT-1998	19:00	010	US	4c359	SRT1322	48.05	4c359	SRT1323	97.49

(continued)

Table 4 (continued) Sample Results from the LC/MS/MS Assay for Fluoxetine and Norfluoxetine in Human Plasma, Study B1Y-MC-HCJE

Databook: 4172

						Fluoxetine			Norfluoxetine		
Accession #[a]	Pati[redacted] #	Draw Date	Draw Time	Visit	Country Code	[redacted] Filename[b]	Test Code	Conc. (ng/mL)	[redacted] Filename[b]	Test Code	Conc. (ng/mL)
V259891-7	104	29-SEP-1998	17:00	013	US	4c360	SRT1322	<1.00	4c360	SRT1323	42.47
V990741-2	305	24-OCT-1998	11:30	010	US	4c361	SRT1322	159.57	4c361	SRT1323	239.95
V990761-7	307	11-NOV-1998	20:00	012	US	4c362	SRT1322	63.47	4c362	SRT1323	139.33
X455222-2	204	01-FEB-1999	19:00	010	US	4c363	SRT1322	57.13	4c363	SRT1323	158.87
X748701-2	319	02-DEC-1998	16:30	010	US	4c364	SRT1322	86.52	4c364	SRT1323	93.44
X748751-7	305	30-JAN-1999	10:53	017	US	4c365	SRT1322	<1.00	4c365	SRT1323	50.96
X748761-7	305	04-JAN-1999	14:20	015	US	4c366	SRT1322	173.85	4c366	SRT1323	352.60
Y252261-2	133	11-MAY-1999	14:00	010	US	4c367	SRT1322	107.14	4c367	SRT1323	192.65
Y252291-7	118	02-FEB-1999	2:00	011	US	4c368	SRT1322	66.49	4c368	SRT1323	237.11
Z055811-2	151	27-JUL-1999	13:00	010	US	4c369	SRT1322	132.33	4c369	SRT1323	212.34
Z055822-2	118	19-JAN-1999	2:30	010	US	4c370	SRT1322	109.58	4c370	SRT1323	220.32
Z726541-7	319	17-MAR-1999	17:00	014	US	4c371	SRT1322	<1.00	4c371	SRT1323	<1.00
A932793-7	413	18-FEB-1999	13:50	015	US	4c372	SRT1322	38.54	4c372	SRT1323	126.29
C216402-2	353	07-JUL-1999	17:35	010	US	4c373	SRT1322	115.85	4c373	SRT1323	115.30
C216422-2	346	24-MAY-1999	12:21	010	US	4c374	SRT1322	104.48	4c374	SRT1323	141.68
C216463-2	354	08-SEP-1999	20:00	010	US	4c375	SRT1322	69.81	4c375	SRT1323	102.56
C216483-2	355	26-AUG-1999	12:08	010	US	4c376	SRT1322	83.70	4c376	SRT1323	188.72
E001172-7	416	04-MAY-1999	15:15	015	US	4c377	SRT1322	21.54	4c377	SRT1323	105.70
E468352-7	334	15-JUN-1999	19:55	015	US	4c378	SRT1322	49.53	4c378	SRT1323	94.13
E468372-7	346	07-AUG-1999	11:03	015	US	4c379	SRT1322	133.02	4c379	SRT1323	160.77
E471863-7	422	19-AUG-1999	16:45	015	US	4c380	SRT1322	208.15	4c380	SRT1323	194.12
E531322-7	416	10-JUN-1999	8:55	018	US	4c381	SRT1322	<1.00	4c381	SRT1323	1.87
H613872-7	422	21-SEP-1999	15:25	018	US	4c382	SRT1322	<1.00	4c382	SRT1323	3.98
Q391781-7	401	14-AUG-1998	15:15	012	US	4c383	SRT1322	114.32	4c383	SRT1323	140.31

(continued)

Table 4 (continued) Sample Results from the LC/MS/MS Assay for Fluoxetine and Norfluoxetine in Human Plasma, Study B1Y-MC-HCJE

Databook: 4172

						Fluoxetine			Norfluoxetine		
Accession #[a]	Pati[redacted] #	Draw Date	Draw Time	Visit	Country Code	[redacted] Filename[b]	Test Code	Conc. (ng/mL)	[redacted] Filename[b]	Test Code	Conc. (ng/mL)
R906811-2	401	23-JUL-1998	13:25	010	US	4c384	SRT1322	125.99	4c384	SRT1323	129.05
T107181-2	404	11-AUG-1998	15:44	010	US	4c385	SRT1322	93.03	4c385	SRT1323	174.66
T107201-2	415	19-JAN-1999	16:05	010	US	4c386	SRT1322	116.73	4c386	SRT1323	79.54
U433481-2	419	09-APR-1999	16:30	010	US	4c387	SRT1322	72.77	4c387	SRT1323	199.60
U433492-2	416	25-FEB-1999	17:00	010	US	4c388	SRT1322	62.52	4c388	SRT1323	131.37
U433501-2	413	08-DEC-1998	16:20	010	US	4c389	SRT1322	38.33	4c389	SRT1323	134.47
U433511-7	415	30-MAR-1999	15:00	015	US	5c390	SRT1322	109.57	5c390	SRT1323	74.02
W131531-7	415	06-MAY-1999	10:15	018	US	5c391	SRT1322	44.05	5c391	SRT1323	51.17
X748691-2	334	29-MAR-1999	19:41	010	US	5c392	SRT1322	46.07	5c392	SRT1323	89.50
X748712-2	326	12-JAN-1999	18:40	010	US	5c393	SRT1322	78.67	5c393	SRT1323	132.96
X748732-7	353	22-SEP-1999	18:51	015	US	5c394	SRT1322	93.26	5c394	SRT1323	103.53
X748741-7	326	23-MAR-1999	18:30	015	US	5c395	SRT1322	45.17	5c395	SRT1323	106.33
Z726532-7	326	06-APR-1999	19:26	016	US	5c396	SRT1322	2.82	5c396	SRT1323	62.82
B444183-2	906	27-APR-1999	15:45	010	US	5c397	SRT1322	46.46	5c397	SRT1323	113.66
B444192-7	906	06-JUL-1999	13:35	015	US	5c398	SRT1322	15.57	5c398	SRT1323	66.43
D820482-2	813	28-MAY-1999	14:30	010	US	5c399	SRT1322	82.00	5c399	SRT1323	94.71
D820493-2	814	25-JUN-1999	9:40	010	US	5c400	SRT1322	59.43	5c400	SRT1323	138.59
D820502-7	810	29-JUL-1999	10:50	015	US	5c401	SRT1322	117.04	5c401	SRT1323	154.59
E471772-2	424	11-JUN-1999	13:30	010	US	5c402	SRT1322	129.64	5c402	SRT1323	152.24
E471852-7	424	25-AUG-1999	14:45	015	US	5c403	SRT1322	75.50	5c403	SRT1323	128.03
F805653-2	915	16-AUG-1999	0:00	010	US	5c404	SRT1322	42.73	5c404	SRT1323	51.50
G164402-2	433	04-AUG-1999	11:00	010	US	5c405	SRT1322	178.35	5c405	SRT1323	226.04
G439493-7	810	09-SEP-1999	16:15	018	US	5c406	SRT1322	<1.00	5c406	SRT1323	5.25
G439502-7	814	09-AUG-1999	9:30	013	US	5c407	SRT1322	11.82	5c407	SRT1323	114.32

(continued)

Table 4 (continued) Sample Results from the LC/MS/MS Assay for Fluoxetine and Norfluoxetine in Human Plasma, Study B1Y-MC-HCJE

Databook: 4172

						Fluoxetine			Norfluoxetine		
Accession #[a]	Pati[redacted] #	Draw Date	Draw Time	Visit	Country Code	[redacted] Filename[b]	Test Code	Conc. (ng/mL)	[redacted] Filename[b]	Test Code	Conc. (ng/mL)
G899792-2	920	17-SEP-1999	0:00	010	US	5c408	SRT1322	74.28	5c408	SRT1323	184.90
I300493-7	433	29-SEP-1999	11:35	013	US	5c409	SRT1322	63.62	5c409	SRT1323	158.58
Q075361-2	1109	29-SEP-1998	16:10	010	US	5c410	SRT1322	111.93	5c410	SRT1323	107.00
T108911-2	1101	06-AUG-1998	13:00	010	US	5c411	SRT1322	178.58	5c411	SRT1323	239.52
T495561-2	1109	13-OCT-1998	15:39	011	US	5c412	SRT1322	104.00	5c412	SRT1323	101.58
U797941-2	815	16-AUG-1999	17:00	010	US	5c413	SRT1322	139.14	5c413	SRT1323	103.25
V025881-2	1129	02-MAR-1999	9:10	010	US	5c414	SRT1322	138.61	5c414	SRT1323	266.11
V025931-7	1101	14-OCT-1998	15:50	015	US	6c415a	SRT1322	540.28	5c415	SRT1323	472.50
V872291-7	901	18-FEB-1999	17:40	014	US	5c416	SRT1322	76.12	5c416	SRT1323	243.76
W500482-2	1118	02-NOV-1998	16:12	010	US	5c417	SRT1322	8.28	5c417	SRT1323	99.12
X549052-2	811	20-MAY-1999	17:45	010	US	5c418	SRT1322	35.12	5c418	SRT1323	132.29
X549081-2	810	14-MAY-1999	15:40	010	US	5c419	SRT1322	119.67	5c419	SRT1323	143.17
Y214011-7	1129	10-MAY-1999	16:40	015	US	5c420	SRT1322	150.52	5c420	SRT1323	231.69
Y673271-2	901	21-DEC-1998	12:45	010	US	5c421	SRT1322	44.20	5c421	SRT1323	147.42
A844452-2	1503	26-FEB-1999	8:45	010	US	5c422	SRT1322	20.64	5c422	SRT1323	41.77
B514272-2	1305	10-MAY-1999	14:50	010	US	5c423	SRT1322	39.05	5c423	SRT1323	68.07
C195433-2	1220	11-MAY-1999	16:20	010	US	5c424	SRT1322	22.26	5c424	SRT1323	93.05
C195453-7	1213	25-MAR-1999	16:50	015	US	5c425	SRT1322	207.77	5c425	SRT1323	255.69
C195473-7	1202	15-JUN-1999	16:30	026	US	5c426	SRT1322	71.23	5c426	SRT1323	109.62
C195612-7	1205	15-SEP-1999	16:30	026	US	5c427	SRT1322	62.08	5c427	SRT1323	144.58
E576953-2	1137	18-MAY-1999	16:00	010	US	5c428	SRT1322	160.35	5c428	SRT1323	235.53
E698433-7	1305	15-JUL-1999	14:45	015	US	5c429	SRT1322	81.23	5c429	SRT1323	82.93
F945443-7	1137	03-AUG-1999	15:15	015	US	5c430	SRT1322	121.90	5c430	SRT1323	231.64
R691131-2	1217	01-MAR-1999	18:30	010	US	5c431	SRT1322	71.69	5c431	SRT1323	133.75

(continued)

Table 4 (continued) Sample Results from the LC/MS/MS Assay for Fluoxetine and Norfluoxetine in Human Plasma, Study B1Y-MC-HCJE

Databook: 4172

						Fluoxetine			Norfluoxetine		
Accession #[a]	Pati[redacted] #	Draw Date	Draw Time	Visit	Country Code	[redacted] Filename[b]	Test Code	Conc. (ng/mL)	[redacted] Filename[b]	Test Code	Conc. (ng/mL)
T044601-2	1204	04-SEP-1998	16:50	010	US	5c432	SRT1322	28.63	5c432	SRT1323	42.79
T044611-2	1202	04-AUG-1998	17:45	010	US	5c433	SRT1322	172.77	5c433	SRT1323	174.66
T170111-2	1208	12-NOV-1998	14:50	010	US	5c434	SRT1322	131.85	5c434	SRT1323	82.69
T495571-2	1141	09-JUN-1999	14:35	010	US	5c435	SRT1322	189.65	5c435	SRT1323	116.97
V025862-2	1156	21-SEP-1999	9:55	010	US	5c436	SRT1322	169.42	5c436	SRT1323	76.62
V025891-2	1131	17-MAR-1999	9:27	010	US	5c437	SRT1322	59.88	5c437	SRT1323	85.84
V025921-2	1153	23-AUG-1999	11:00	010	US	5c438	SRT1322	198.80	5c438	SRT1323	143.84
V547961-7	1208	28-JAN-1999	16:05	015	US	5c439	SRT1322	157.41	5c439	SRT1323	90.66
V547981-7	1202	15-OCT-1998	18:45	015	US	5c440	SRT1322	2.75	5c440	SRT1323	65.71
X252921-2	1211	03-DEC-1998	16:25	010	US	5c441	SRT1322	8.87	5c441	SRT1323	75.23
X252931-2	1209	16-NOV-1998	15:50	010	US	5c442	SRT1322	95.74	5c442	SRT1323	179.52
X252941-7	1209	30-NOV-1998	16:28	011	US	5c443	SRT1322	4.44	5c443	SRT1323	104.37
X252951-7	1205	30-DEC-1998	11:50	015	US	5c444	SRT1322	51.48	5c444	SRT1323	139.33
Y089201-7	1503	12-MAR-1999	9:30	011	US	5c445	SRT1322	13.92	5c445	SRT1323	12.98
Y252161-2	1213	11-JAN-1999	17:40	010	US	5c446	SRT1322	203.00	5c446	SRT1323	260.10
A733822-2	1515	12-AUG-1999	9:35	010	US	5c447	SRT1322	55.71	5c447	SRT1323	124.40
A844432-2	1510	13-JUL-1999	9:10	010	US	5c448	SRT1322	37.01	5c448	SRT1323	31.57
A844443-2	1516	19-AUG-1999	8:15	010	US	5c449	SRT1322	217.09	5c449	SRT1323	209.07
B585112-2	1904	25-MAR-1999	15:20	010	US	5c450	SRT1322	99.25	5c450	SRT1323	145.04
C058612-7	1602	21-APR-1999	10:00	013	US	5c451	SRT1322	13.88	5c451	SRT1323	35.77
D575523-7	1601	28-APR-1999	12:00	015	US	5c452	SRT1322	102.02	5c452	SRT1323	188.00
E363972-2	1606	07-MAY-1999	13:20	010	US	5c453	SRT1322	177.26	5c453	SRT1323	293.45
E363983-7	1604	22-JUN-1999	12:30	015	US	5c454	SRT1322	420.91	5c454	SRT1323	283.07
E363992-7	1605	02-JUL-1999	15:30	015	US	5c455	SRT1322	137.84	5c455	SRT1323	90.67

(continued)

Table 4 (continued) Sample Results from the LC/MS/MS Assay for Fluoxetine and Norfluoxetine in Human Plasma, Study B1Y-MC-HCJE

Databook: 4172

						Fluoxetine			Norfluoxetine		
Accession #[a]	Pati[redacted] #	Draw Date	Draw Time	Visit	Country Code	[redacted] Filename[b]	Test Code	Conc. (ng/mL)	[redacted] Filename[b]	Test Code	Conc. (ng/mL)
E819722-7	1658	19-AUG-1999	15:00	013	US	5c456	SRT1322	88.40	5c456	SRT1323	142.31
E939252-2	1652	10-JUN-1999	11:00	010	US	5c457	SRT1322	221.65	5c457	SRT1323	104.96
E939282-2	1654	14-JUN-1999	17:00	010	US	5c458	SRT1322	94.99	5c458	SRT1323	126.24
F274663-2	1701	16-JUN-1999	15:50	010	US	5c459	SRT1322	48.00	5c459	SRT1323	106.70
F274672-2	1702	15-JUL-1999	14:00	010	US	5c460	SRT1322	246.18	5c460	SRT1323	229.68
F587092-2	1659	14-JUL-1999	11:05	010	US	5c461	SRT1322	38.31	5c461	SRT1323	82.27
F587102-2	1658	08-JUL-1999	14:00	010	US	5c462	SRT1322	47.72	5c462	SRT1323	87.17
G991212-7	1659	21-SEP-1999	15:30	015	US	5c463	SRT1322	52.10	5c463	SRT1323	162.46
G991222-7	1654	07-SEP-1999	16:40	015	US	5c464	SRT1322	72.72	5c464	SRT1323	137.50
H426622-7	1510	28-SEP-1999	9:00	015	US	5c465	SRT1322	111.44	5c465	SRT1323	61.29
H673902-2	1609	07-SEP-1999	14:00	010	US	5c466	SRT1322	153.88	5c466	SRT1323	183.21
V667041-7	1701	27-AUG-1999	11:15	015	US	5c467	SRT1322	29.94	5c467	SRT1323	95.21
Z139232-2	1604	13-APR-1999	13:00	010	US	5c468	SRT1322	124.47	5c468	SRT1323	173.66
Z139252-2	1605	16-APR-1999	16:30	010	US	5c469	SRT1322	149.46	5c469	SRT1323	105.12
Z139261-2	1601	12-FEB-1999	16:00	010	US	5c470	SRT1322	131.60	5c470	SRT1323	208.25
Z139271-2	1602	22-FEB-1999	16:45	010	US	5c471	SRT1322	210.30	5c471	SRT1323	145.98
B585122-2	1906	16-MAR-1999	15:50	010	US	5c472	SRT1322	244.18	5c472	SRT1323	101.72
B585133-2	1905	30-MAR-1999	15:25	010	US	5c473	SRT1322	33.26	5c473	SRT1323	74.69
D027742-2	2204	10-JUN-1999	16:40	010	US	5c474	SRT1322	24.21	5c474	SRT1323	118.57
D027772-2	2205	14-JUL-1999	17:03	010	US	5c475	SRT1322	127.55	5c475	SRT1323	139.25
D027792-2	2202	16-JUN-1999	16:25	010	US	5c476	SRT1322	358.62	5c476	SRT1323	254.29
D059012-2	1915	24-MAY-1999	14:20	010	US	5c477	SRT1322	54.56	5c477	SRT1323	140.65
D204742-7	2208	21-OCT-1999	16:07	015	US	5c478	SRT1322	119.18	5c478	SRT1323	187.50
E495042-7	1905	15-JUN-1999	10:05	015	US	5c479	SRT1322	23.67	5c479	SRT1323	70.54

(continued)

Table 4 (continued) Sample Results from the LC/MS/MS Assay for Fluoxetine and Norfluoxetine in Human Plasma, Study B1Y-MC-HCJE

Databook: 4172

						Fluoxetine			Norfluoxetine		
Accession #[a]	Pati[redacted] #	Draw Date	Draw Time	Visit	Country Code	[redacted] Filename[b]	Test Code	Conc. (ng/mL)	[redacted] Filename[b]	Test Code	Conc. (ng/mL)
E495062-7	1906	04-JUN-1999	9:25	015	US	5c480	SRT1322	118.29	5c480	SRT1323	58.75
F463662-2	2214	09-SEP-1999	15:55	010	US	5c481	SRT1322	62.88	5c481	SRT1323	144.48
F463692-2	2216	16-SEP-1999	15:55	010	US	5c482	SRT1322	158.93	5c482	SRT1323	85.90
F463703-2	2208	13-AUG-1999	9:30	010	US	5c483	SRT1322	97.08	5c483	SRT1323	161.27
F883883-2	1919	08-JUL-1999	14:40	010	US	5c484	SRT1322	136.29	5c484	SRT1323	210.98
F883892-2	1921	20-JUL-1999	14:40	010	US	5c485	SRT1322	128.74	5c485	SRT1323	148.99
G657592-2	1924	17-AUG-1999	14:20	010	US	5c486	SRT1322	70.83	5c486	SRT1323	94.03
G657612-7	1921	30-SEP-1999	15:15	015	US	5c487	SRT1322	457.92	5c487	SRT1323	301.22
G657622-7	1924	25-OCT-1999	12:15	015	US	5c488	SRT1322	49.50	5c488	SRT1323	73.46
H343892-2	2220	24-SEP-1999	15:28	010	US	5c489	SRT1322	174.69	5c489	SRT1323	190.97
H344022-7	2202	08-SEP-1999	16:15	014	US	5c490	SRT1322	161.06	5c490	SRT1323	209.91
H477952-7	1919	27-SEP-1999	12:50	015	US	5c491	SRT1322	138.56	5c491	SRT1323	226.58
C195422-2	1225	17-AUG-1999	17:30	010	US	6c492	SRT1322	71.65	6c492	SRT1323	133.60
C195592-7	1225	28-OCT-1999	15:55	015	US	6c493	SRT1322	69.57	6c493	SRT1323	133.88
D204773-7	2214	29-NOV-1999	8:45	015	US	6c494	SRT1322	335.03	6c494	SRT1323	365.27
E215252-7	354	17-NOV-1999	19:00	015	US	6c495	SRT1322	77.87	6c495	SRT1323	105.23
E468382-7	355	03-NOV-1999	16:00	015	US	6c496	SRT1322	104.23	6c496	SRT1323	201.60
E566142-7	1516	28-OCT-1999	9:15	015	US	6c497	SRT1322	203.73	6c497	SRT1323	208.81
E819693-7	1659	19-OCT-1999	15:15	017	US	6c498	SRT1322	<1.00	6c498	SRT1323	13.60
E819713-7	1654	12-OCT-1999	17:00	018	US	6c499	SRT1322	7.78	6c499	SRT1323	86.28
G282103-7	815	27-OCT-1999	11:30	015	US	6c500	SRT1322	127.66	6c500	SRT1323	99.89
G978032-7	139	14-SEP-1999	12:30	015	US	6c501	SRT1322	138.31	6c501	SRT1323	117.64
H343992-7	2220	19-NOV-1999	12:15	014	US	6c502	SRT1322	186.34	6c502	SRT1323	218.19
H657462-7	150	27-SEP-1999	16:00	015	US	6c503	SRT1322	401.11	6c503	SRT1323	186.56

(continued)

Table 4 (continued) Sample Results from the LC/MS/MS Assay for Fluoxetine and Norfluoxetine in Human Plasma, Study B1Y-MC-HCJE

Databook: 4172

						Fluoxetine			Norfluoxetine		
Accession #[a]	Patie[redacted]#	Draw Date	Draw Time	Visit	Country Code	[redacted] Filename[b]	Test Code	Conc. (ng/mL)	[redacted] Filename[b]	Test Code	Conc. (ng/mL)
H957292-7	815	29-NOV-1999	10:30	017	US	6c504	SRT1322	143.54	6c504	SRT1323	111.68
I075532-7	150	22-NOV-1999	16:30	019	US	6c505	SRT1322	403.84	6c505	SRT1323	181.32
I153412-7	920	22-NOV-1999	17:00	015	US	6c506	SRT1322	79.07	6c506	SRT1323	194.30
I153423-7	915	10-NOV-1999	18:00	015	US	6c507	SRT1322	59.96	6c507	SRT1323	69.33
C058592-7	1601	02-DEC-1999	17:30	025	US	7c508	SRT1322	50.60	7c508	SRT1323	147.08
H673912-7	1609	17-NOV-1999	17:20	015	US	7c509	SRT1322	132.89	7c509	SRT1323	187.22
I372072-2	1612	25-OCT-1999	16:30	010	US	7c510	SRT1322	118.28	7c510	SRT1323	285.00
A955393-7	126	08-FEB-1999	9:50	009	US	8c511	SRT1322	120.14	8c511	SRT1323	138.10
C742003-8	1653	22-MAR-1999	16:45	001A	US	8c512	SRT1322	<1.00	8c512	SRT1323	<1.00
C871903-7	1652	21-JUN-1999	17:00	011	US	8c513	SRT1322	170.23	8c513	SRT1323	89.25
C891862-7	1609	20-DEC-1999	17:15	017	US	8c514	SRT1322	<1.00	8c514	SRT1323	6.55
D394173-7	1514	29-JUN-1999	10:10	007	US	8c515	SRT1322	12.57	8c515	SRT1323	132.35
F022563-7	208	09-JUL-1999	11:40	008	US	8c516	SRT1322	58.55	8c516	SRT1323	80.07
F120402-7	141	15-JUN-1999	17:00	009	US	8c517	SRT1322	141.26	8c517	SRT1323	191.53
F120412-7	151	09-AUG-1999	16:00	011	US	8c518	SRT1322	78.81	8c518	SRT1323	192.87
F120423-7	137	15-JUN-1999	17:00	010	US	8c519	SRT1322	52.60	8c519	SRT1323	90.82
F827703-7	149	28-JUL-1999	17:00	011	US	8c520	SRT1322	<1.00	8c520	SRT1323	<1.00
F945422-7	1156	21-DEC-1999	10:30	015	US	8c521	SRT1322	17.55	8c521	SRT1323	16.45
H363882-7	1153	02-NOV-1999	15:35	015	US	8c522	SRT1322	195.12	8c522	SRT1323	149.84
H363903-7	1156	07-DEC-1999	10:02	015	US	8c523	SRT1322	113.95	8c523	SRT1323	47.13
Q499062-7	1201	16-SEP-1998	12:15	013	US	8c524	SRT1322	<1.00	8c524	SRT1323	<1.00
R244081-7	110	24-NOV-1998	18:00	008	US	8c525	SRT1322	181.72	8c525	SRT1323	125.85
R451541-7	302	05-OCT-1998	11:00	009	US	8c526	SRT1322	67.94	8c526	SRT1323	147.86
T170131-2	1217	03-DEC-1998	17:15	001A	US	8c527	SRT1322	<1.00	8c527	SRT1323	<1.00

(continued)

Table 4 (continued) Sample Results from the LC/MS/MS Assay for Fluoxetine and Norfluoxetine in Human Plasma, Study B1Y-MC-HCJE

Databook: 4172

						Fluoxetine			Norfluoxetine		
Accession #[a]	Patie[redacted]#	Draw Date	Draw Time	Visit	Country Code	[redacted] Filename[b]	Test Code	Conc. (ng/mL)	[redacted] Filename[b]	Test Code	Conc. (ng/mL)
U797951-7	813	15-JUL-1999	18:00	013	US	8c528	SRT1322	48.78	8c528	SRT1323	112.40
U797961-7	812	03-MAY-1999	11:00	009	US	8c529	SRT1322	153.89	8c529	SRT1323	128.90
V259881-7	122	24-NOV-1998	15:30	003	US	8c530	SRT1322	<1.00	8c530	SRT1323	<1.00
V501791-7	202	13-NOV-1998	14:17	007	US	8c531	SRT1322	212.29	8c531	SRT1323	147.35
V872281-7	913	02-AUG-1999	13:45	011	US	8c532	SRT1322[redacted]	34.77	8c532	SRT1323	120.80
V990772-7	306	31-OCT-1998	11:00	011	US	8c533	SRT13[redacted]	<1.00	8c533	SRT1323	<1.00
Y070682-7	1603	22-FEB-1999	14:30	008	US	8c534	SRT13[redacted]	218.09	8c534	SRT1323	67.07
Z726521-7	332	20-FEB-1999	11:00	009	US	8c535	SRT1322	5.97	8c535	SRT1323	100.64
B382072-8	1652	16-MAR-1999	14:00	001	US	8c536	SRT1322	<1.00	8c536	SRT1323	<1.00
D027722-8	2212	03-JUN-1999	15:15	001	US	8c537	SRT1322	<1.00	8c537	SRT1323	<1.00
D169062-7	1701	17-DEC-1999	15:15	022	US	8c538	SRT1322	<1.00	8c538	SRT1323	<1.00
E819702-7	1667	13-SEP-1999	10:30	011	US	8c539	SRT1322	217.02	8c539	SRT1323	198.35
H343942-7	2216	08-DEC-1999	15:45	015	US	8c540	SRT1322	177.40	8c540	SRT1323	105.01
H735343-7	1702	24-SEP-1999	15:15	015	US	8c541	SRT1322	232.51	8c541	SRT1323	215.18
H735372-7	1702	04-NOV-1999	14:00	017	US	8c542	SRT1322	<1.00	8c542	SRT1323	19.53
Y843082-7	1903	06-JAN-1999	15:00	001B	US	8c543	SRT1322	<1.00	8c543	SRT1323	<1.00

<1.00 = Below the Limit of Quantitation (BQL).
<1.25 = Below the Limit of Quantitation (BQL); diluted due to insufficient sample.
<1.33 = Below the Limit of Quantitation (BQL); diluted due to insufficient sample.
<2.00 = Below the Limit of Quantitation (BQL); diluted due to insufficient sample.
<2.50 = Below the Limit of Quantitation (BQL); diluted due to insufficient sample.
<3.33 = Below the Limit of Quantitation (BQL); diluted due to insufficient sample.
[a]The Accession # is the only demographic that is verified by[redacted]
[b]The[redacted]filename is made up of the run number, "c", and the[redacted]sample number, followed by any repea[redacted]esignators.

Repeat Analysis

Repeat analyses were conducted on samples in the following tables (Tables 5 and 5.1):

Table 5 Repeat Analysis from the LC/MS/MS Assay for Fluoxetine and Norfluoxetine in Human Plasma for Fluoxetine

[redacted] Sample Number	Reason for Re-analysis	Initial Result (Run#) Concentration (ng/mL)	Repeat Result (Run#) Concentration (ng/mL)	Reported Result Concentration (ng/mL)
54	a	NR(1)	<1.00 (6)	<1.00
58	a	NR(1)	<1.00 (6)	<1.00
60	a	NR(1)	<3.33 (6)	<3.33
83	a	NR(1)	<1.00 (6)	<1.00
86	a	NR(1)	<2.00 (6)	<2.00
197	a	NR(3)	<1.00 (6)	<1.00
221	a	NR(3)	<1.00 (6)	<1.00
229	a	NR(3)	<1.00 (6)	<1.00
242	a	NR(3)	<2.00 (6)	<2.00
250	a	NR(3)	<1.25 (6)	<1.25
415	b	>500.00 (5)	540.28 (6)	540.28

[a]File not used; insufficient IS response to confirm BLQ.
[b]Above the Limit of Quantitation.
NR = No reportable result.
>500.00 = Above the Limit of Quantitation (AQL).

Table 5.1 Repeat Analysis from the LC/MS/MS Assay for Fluoxetine and Norfluoxetine in Human Plasma for Norfluoxetine

[redacted] Sample Number	Reason for Re-analysis	Initial Result (Run#) Concentration (ng/mL)	Repeat Result (Run#) Concentration (ng/mL)	Reported Result Concentration (ng/mL)
54	a	NR(1)	<1.00 (6)	<1.00
58	a	NR(1)	<1.00 (6)	<1.00
60	a	NR(1)	<3.33 (6)	<3.33
83	a	NR(1)	<1.00 (6)	<1.00
86	a	NR(1)	<2.00 (6)	<2.00
197	a	NR(3)	<1.00 (6)	<1.00
221	a	NR(3)	<1.00 (6)	<1.00
229	a	NR(3)	<1.00 (6)	<1.00
242	a	NR(3)	<2.00 (6)	<2.00
250	a	NR(3)	<1.25 (6)	<1.25

[a]File not used; insufficient IS response to confirm BLQ.
NR = No reportable result.

Table 6 **Dilution Factors from the LC/MS/MS Assay for Fluoxetine and Norfluoxetine in Human Plasma, Study B1Y-MC-HCJE for Fluoxetine**

[redacted]Sample Number	Dilution Factor	Run #
14	2.50	1
60	3.33	6
86	2.00	6
206	2.00	3
242	2.00	6
250	1.25	6
282	1.33	3
409	4.00	5
415	2.00	6
427	1.33	5
492	1.25	6
506	1.33	6

Table 6.1 **Dilution Factors from the LC/MS/MS Assay for Fluoxetine and Norfluoxetine in Human Plasma, Study B1Y-MC-HCJE for Norfluoxetine**

[redacted]Sample Number	Dilution Factor	Run #
14	2.50	1
60	3.33	6
86	2.00	6
206	2.00	3
242	2.00	6
250	1.25	6
282	1.33	3
409	4.00	5
427	1.33	5
492	1.25	6
506	1.33	6

Method M2.FluoxLCMS.1, Rev. 1
Determination of Fluoxetine and Norfluoxetine in Human Plasma by APCI HPLC/MS/MS

and

Method M2.FluoxLCMS.3, Rev. 1
Determination of Fluoxetine and Norfluoxetine in Human Plasma by APCI HPLC/MS/MS (PE Sciex API-III+)

Validation Job Number 132019

HPLC/MS/MS Method Validation for the Determination of Fluoxetine and Norfluoxetine in Human Plasma

and

Addendum III to the Report Entitled, "HPLC/MS/MS Method Validation for the Determination of Fluoxetine and Norfluoxetine in Human Plasma[redacted] Job Number: 132019 (Lot: 001)" Instrument (PE Sciex API-III+) Cross-Validation, [redacted] Job Number: 132019 (Lot: 004)

Stability Job Number 132019

Addendum VI to the Report Entitled, "HPLC/MS/MS Method Validation for the Determination of Fluoxetine and Norfluoxetine in Human Plasma[redacted] Job Number: 132019 (Lot: 001)" Frozen Stability Assessment at -20°C and -70°, [redacted] Job Number: 132019 (Lot: 007)

16.2.
Patient Data Listings

16.2.1. Adverse Event Listings by Patient
16.2.2. Discontinued Patients
16.2.3. Significant Protocol Violations
16.2.4. Patients Excluded from the Efficacy Analysis
16.2.5. Demographic Data
16.2.6. Compliance and/or Drug Concentration Data
16.2.7. Individual Efficacy Response Data
16.2.8. Listing of Individual Laboratory Measurements by Patient

16.2.1.
Adverse Event Listings by Patient

Please see SAS Transport file located in Item 11 of this submission.

16.2.2.
Discontinued Patients

Please see SAS Transport file located in Item 11 of this submission.

16.2.3.
Protocol Violations

Type of Violation	Therapy	Patient Number	Visit Number	Comments
Violation of Inclusion/Exclusion Criteria				
	Placebo	806	1	Patient has history of substance abuse, but did not meet criteria for substance abuse disorder. Patient's toxicology (urine) screen was negative and patient was enrolled in a 12-week drug counseling course. Principal Investigator felt it would be acceptable to enroll patient in the study.
	Flx	810	4	Patient had a greater than 30% decrease in the CDRS-R score from visit 3 to visit 4. An error was made in calculating this change and patient was inadvertently randomized. Patient allowed to continue in study under compassionate use guidelines.
	Placebo	1121	5	Patient had prior history of using THC. Visit 1 drug screen was negative. The investigator continued drug screening throughout study to safeguard patient from using. The visit 5 drug screen showed a semi quantity. All other screens were negative.
	Placebo	1139	1	Patient was on Zoloft and had last dose on 3/10/99, 12 days prior to Visit 1. Visit 1 should have been 14 days after last dose.
	Placebo	1310	1	Patient's urine drug screen was positive for desipramine. Patient and parent stated last dose was 4/99. Retest from Visit 4 on 6/3/99 was negative.
	Placebo	1608	2	Patient had taken Ritalin-SR the prior week prior to Visit 2. Patient agreed to stop the medication and the Lilly Research Physician approved patient to continue in the study.

Type of Violation	Therapy	Patient Number	Visit Number	Comments
				Patient was off Ritalin-SR for 2 weeks prior to randomization.
	NR	1610	1	Patient on Adderall 10mg PO daily. Consent signed 6/23/99 and subject to discontinue adderall. Appointment scheduled for 7/3/99 (2 weeks without medication).
	Placebo	1655	1	Patient discontinued Ritalin on 3/24/99 and the ICD was signed on 3/23/99.
	Placebo	1705	1	Patient took Sertraline from 4/1/99-5/2/99, 11 days prior to Visit 1. Visit 1 should have occurred 14 days from last dose. Patient approved by Lilly Research Physician to proceed with study procedures.
	Placebo	2212	1	Patient's urine drug screen was positive for THC at visit 1 and Lilly Research Physician approved random retest. Retest on 7/13/99 at visit 7 was negative.
Missing ICD Information				
	NR	101	1	Original consent did not have the Lilly approval stamp. Patient withdrew from study before signing stamped copy.
	Flx	118	1	Investigator and patient dated ICD with wrong date as 10/28/98. Actual date consent was obtained was 10/26/98
	Flx	137	9	Investigator did not sign revised ICD within 72 hours.
	NR	311	1	Patient consent correctly dated as 8/4/98. However, on child assent, parent incorrectly dated as 8/8/98 when the actual signature was obtained on 8/4/98.
	NR	314	1	Parent signed consent, but did not sign assent.
	NR	328	1	ICD/Assent not signed by

Type of Violation	Therapy	Patient Number	Visit Number	Comments
				investigator on actual visit date.
	Placebo	335	1	Investigator did not sign assent until 3/16/99, but consent was signed by investigator on 12/28/98.
	NR	345	1	Informed consent not signed by Investigator within 72 hours.
	Flx	354	1	Informed consent not signed by investigator within 72 hours.
	NR	357	1	Patient initialed bottoms of informed consent document instead of mother. A note was placed in Visit 1 comments and a letter was written to the IRB.
	NR	805	1	Informed consent not signed by investigator within 72 hours.
	Flx	901	14	Patient did not sign modified ICD dated 2/9/99 because patient was discontinuing at this visit.
	NR	917	1	Patient did not complete the year when dating Youth Assent form. Patient signed assent on 6/9/99.
	NR	1115	1	Physician did not sign ICD within 72 hours.
	NR	1116	1	Physician did not sign ICD within 72 hours.
	NR	1117	1	Physician did not sign ICD within 72 hours.
	Placebo	1121	1	Physician did not sign ICD within 72 hours.
	Placebo	1144	1	Physician did not sign ICD within 72 hours.
	NR	1151	1	Physician did not sign ICD within 72 hours.
	NR	1154	1	Physician did not sign ICD within 72 hours.
	Placebo	1207	1	ICD dated by IRB on 5/4/99 and 6/15/99 not signed by the Investigator within 72-hours.
	Flx	1208	1	ICD not dated by investigator.
	Flx	1209	1	ICD not dated by investigator.
	NR	1210	1	ICD not dated by investigator.
	Flx	1211	1	ICD not dated by investigator.
	Placebo	1212	1	ICD not dated by investigator.

Type of Violation	Therapy	Patient Number	Visit Number	Comments
	Flx	1213	1	ICD dated by IRB on 5/4/99 and 6/15/99 not signed and dated by the Investigator within 72-hours.
	NR	1214	1	ICD not dated by investigator.
	Placebo	1216	1	Patient's initial ICD did not contain the IRB or Lilly approval stamp. ICD was identical to the approved versions minus the stamp.
	Flx	1217	1	Patient mistakenly put wrong date on the original ICD.
	Flx	1217	1	ICD not dated by investigator.
	NR	1218	1	ICD not dated by investigator.
	NR	1219	1	ICD not dated by the Investigator.
	Placebo	1222	12	ICD signed on 4/15/99 not dated by Investigator. ICD signed on 5/6/99 missing relationship to subject (father) and not signed by Investigator within the 72-hour window.
	Placebo	1223	1	ICD not dated by investigator.
	NR	1224	1	ICD not dated by the Investigator.
	Flx	1225	1	Initial ICD not dated by the Investigator.
	NR	1226	1	ICD not signed by investigator within 72 hours and ICD used did not have the Lilly approval stamp.
	NR	1227	1	Investigator did not sign ICD from 5/4/99 and 6/16/99 within the 72-hour window.
	NR	1502	1	Investigator did not sign ICD until 12/4/98. Consent screening was on 11/20/98.
	Placebo	1506	N/A	Patient did not sign amendment to ICD regarding change of site name.
	Flx	1603	1	Investigator did not sign ICD within 72 hours.
	NR	1666	1	Guardian signed consent, but patient did not sign assent and was terminated from the study.
	NR	1804	1	Site unable to verify if patient

Type of Violation	Therapy	Patient Number	Visit Number	Comments
				received a copy of the ICD.
	NR	1909	1	Patient did not sign the California Bill of Rights.
	NR	1910	1	Pages 8 and 9 were missing from informed consent. Patient was lost to follow.
	NR	1912	1	Pages 8 and 9 were missing out of consent.
	Placebo	1913	1	Pages 8 and 9 were missing out of consent. Copies were added to source and given to the patient.
	Flx	1919	1	Principal Investigator did not sign informed consent within 72 hours of consent.
	NR	1926	1	Parent signed assent form but not the consent form. Forms were stapled together and parent and patient received copies of both.
	Placebo	2201	1	Mother signed informed consent with incorrect date and was not available to correct due to patient's discontinuation from the study.
	Flx	2204	1	Principal Investigator did not sign ICD within 72 hours.
	Flx	2204	9	Patient did not date last page of ICD.
	Flx	2205	1	The last page of the informed consent document was not obtained from patient's stepfather.
	Flx	2208	1	The patient and the patient's mother initialed the ICD on pages 1-6 and then the patient and patient's father initialed pages 7-9. Patient's mother signed the ICD.
	Placebo	2210	1	Principal Investigator did not sign the informed consent document within 72 hours.
	NR	2215	1	Missing parent and patient initials on last page of informed consent document and patient did not initial Pages 1-8 of ICD.
	Flx	2216	1	ICD not signed by the Principal

Type of Violation	Therapy	Patient Number	Visit Number	Comments
				Investigator within 72 hours of the date of visit 1.
	NR	2219	1	Patient put 5/24/99 on Youth Assessment Form instead of 6/24/99.
Excluded Concomitant Medication				
	Placebo	131	5	On 1/26/99 patient took 2-3 days of Midrin PRN for headache. Lilly Research Physician asked if it can be discontinued and use tylenol instead.
	Placebo	135	4	Patient took Entex LA BID for sinus congestion, approved for limited use.
	Flx	141	8	Patient took Tylenol #3 PRN from 5/22/99 to 6/1/99 for a broken collarbone, Lilly Research Physician approved patient's continuation in study.
	Flx	142	15	Patient took a suppository for nausea while at camp. Patient and parent unable to identify type of medication.
	Placebo	905	2	Patient took Triaminic which contains phenylpropanolamine and chlorpheniramine.
	Placebo	912	7	Patient took Benadryl, Nyquil and Theraflu for cold symptoms.
	Placebo	916	2	Patient using Periactin prophylactically for migraines. Patient stopped taking Periactin on 5/31/99. Lilly Research Physician approved patient to continue using Periaction in the study.
	Placebo	916	2	Fiortal- codeine taken PRN for migraine. Lilly Research Physician approved patient's continuation in study.
	Placebo	919	9	Patient had foot surgery on 8/13/99 and was prescribed hydrocodone with APAP and ultram PRN for postoperative pain. Patient used medication minimally (2 days of

Type of Violation	Therapy	Patient Number	Visit Number	Comments
				hydrocodone and ultram)
	Placebo	1126	15	Patient took Entex LA 4/6/99.
	Placebo	1144	1	Patient took Butalbital infrequently for serve headaches. Lilly Research Physician approved patient's continuation in study as long as medication use is infrequent.
	Placebo	1212	12	Patient took single dose of Lorazepam for an acute anxiety attack.
	Flx	1605	7	Patient took Nyquil on 2/28/99 for cough.
	Flx	1606	2	Patient took Seldane from 2/14/99 to 2/16/99.
	Flx	1654	1	Patient had a positive drug screen for hydrocodone due to taking Tussionex prior to study entry. Patient advised not to take Tussionex.
	Flx	1701	7	Patient burned finger on 4/30/99 and took ½ tablet of Vicodin 5mg for pain.
	Placebo	1903	9	Site started patient on open label Prozac prior to summary procedures.
	Flx	1906	10	Patient took Prednisone for poison oak and Lilly Research Physician approved patient's continuation in study.
	Placebo	1907	2	Patient took Zoloft 50 mg 1/2/99-1/6/99. Lilly Research Physician approved patient to continue in the study.
	Placebo	2201	6	Patient was hospitalized on 3/26/99 and prescribed Wellbutrin at hospital. Patient was discontinued from the study at that time.
	Flx	2202	1	Patient took Trigestan (contains phenylpropanolamine and dextromethoraphan). Lilly Research Physician approved short-term use.
	Flx	2202	7	Patient took Benadryl for sinus infection, Lilly Research

Type of Violation	Therapy	Patient Number	Visit Number	Comments
				Physician approved patient's continuation in study.
	Flx	2202	7	Patient took Trigestan (phenylpropanolamine and dextromethoraphan) PRN.
	Placebo	2210	7	Patient took 2 doses of Nyquil between 6/3/99 and 7/11/99.
	Flx	2216	12	Patient took Tylenol Cold which contains chlorpheniramine.
	Flx	2216	9	Patient took Dimetapp 2 times, Lilly Research Physician approved short term use.
Dosing Violation				
	Flx	124	14	Patient's sister (patient 131) is enrolled in study and patient accidentally took sister's medication for 1 day on 4/1/99.
	Placebo	131	9	Patients sister (patient 124) is enrolled in study and patient's sister accidentally took 1 day of medication on 4/1/99.
	Flx	137	8	Patient missed the 5/8/99 and 5/9/99 doses of study medication. Patient took double doses, 6 pills on 5/10/99 and 5/11/99 to make up for missed dose.
	Placebo	804	11	Patient took 9 capsules or 3 days of medication on 12/14/98.
	Placebo	911	6	Patient missed dose on 5/22/99 doubled the dose on 5/23/99 to make up for missed dose.
	Flx	1129	9	Patient took extra dose of medication on 2/12/99
	Flx	1204	4	Patient's father instructed patient to only take row a of medication. Occurred during the placebo wash-out phase and Lilly Research Physician approved patient to continue in the study.
	Flx	1503	9	Patient missed 5 consecutive days of column A study drug. Patient approved to continue in

Type of Violation	Therapy	Patient Number	Visit Number	Comments
				the study.
	Placebo	1608	5	Patient mistakenly continued to take medication dispensed at visit 3 from package 1223 instead of starting new card #2444.
	Placebo	1653	Unscheduled	Patient's mother reported 4/28/99 that patient was complaining of dizziness, nausea, and fatigue, dose was decreased by having patient only take rows A and B.
	Flx	2208	7	Patient went to day camp and was given medication from row B from columns 7, 8 and 9. The maximum dose patient could have taken was 30 mg on 6/27/99.
	Flx	2208	9	Patient took rows A and B but not C on 7/27/99.
	Flx	2214	9	On 8/22/99 patient took the pill from row A, but the pills from B & C went down the sink.
	Placebo	2218	4	Patient took row A on 7/23/99, but missed row B and C. On 7/24/99 patient took row C but missed rows A and B.
Drug Accountability				
	Placebo	131	10	Patient lost 4 pills.
	Placebo	312	5	Patient never returned drug package #2102
	Flx	313	9	Patient lost package #1538
	Placebo	323	10	Drug package #2105 never returned.
	Placebo	330	7	Patient threw away drug package #2110 -both cards
	Placebo	330	8	Patient threw away drug package #2112 –card 1of 2.
	Placebo	330	9	Patient threw away drug package #2119 –card 1of 2.
	Flx	346	13	Package #5202 card 1 was discarded and not returned.
	Flx	353	6	Package #2817 lost and not returned.
	Flx	353	8	Package #2230 card 1 was not

Type of Violation	Therapy	Patient Number	Visit Number	Comments
				returned.
	Placebo	804	10	Patient lost card #1 (package 1835). Drug accountability for Visit 10 was done using Card #2.
	Placebo	1135	15	Patient lost 2 medication cards #7377 and 7423 and will return them if they are found.
	Flx	1202	7,8	Patient threw 1 card from each package #1605 and #1610 away.
	Flx	1203	9, 10	Package #1632 and #5037 not returned.
	Placebo	1206	3,7	Package #1619 and #1030 not returned.
	Placebo	1212	6	Patient did not return package #1650
	Flx	1217	12	Study drug from Visit 10 (package #5345) never returned.
	NR	1218	4	Drug dispensed at Visit 3 (package #1149) not returned.
	Flx	1220	11	Study drug from Visit 10 not returned.
	Placebo	1222	4,7,12	Patient reports popping out pills and not taking. Medication was not returned.
	Placebo	1222	15	Patient off of study medication for 1 week and mother decided patient would not continue in study. Study drug package #5283 not returned.
	Placebo	1223	6	Patient accidentally discarded day 7, 8 and 9 of study drug.
	Placebo	1223	12	Package #5278 not returned.
	Flx	1515	8	Patient missing 2 days of study drug from package #2500. Patient does not remember what happened to them.
	Flx	1601	10	Patient did not return Visit 9 study drug package.
	Flx	1601	12	Patient needs to bring back study drug cards 2548 and 5400.
	Flx	1652	5	Patient forgot to return study drug package.
	Flx	1652	9	Patient forgot to return study drug package.

Type of Violation	Therapy	Patient Number	Visit Number	Comments
	Placebo	1656	4	Patient forgot to return drug package.
	Placebo	1657	5	Patient failed to show for Visit 5 and the study drug package #3216 was not returned.
	Flx	1667	4	Patient forgot to return study drug package.
	Placebo	1669	12	Patient did not return study drug.
	NR	1928	3	Patient was dispensed study drug package #1297 (placebo lead in) in error based on CDRS-R score. The patient was not eligible to continue in the study.
	Placebo	2201	3	Patient did not return Visit 3 study drug package (placebo lead in).
	Placebo	2201	6	Patient did not return study drug package #2962 said it was lost.
	Flx	2205	13	Patient's father states Visit 9 study drug package #3090 is lost.
	Placebo	2207	15	Study drug from 10/15/99 was returned loose from blister pack because of a patient error.
Procedures Not Performed According To Protocol or Missing Study Procedures -				
	Flx	202	7	Leads on EKG were reversed patient unable to return in a timely manner to have EKG repeated.
	Flx	204	1	Visit 1 on 11/1/98 and patient returned on 11/14/98 to complete the MAGIC.
	Placebo	206	2	Psychiatric history and FHRDC not reviewed at visit 2 because they were not completed at visit 1.
	NR	207	1	Visit 1 was split over 2 days and patient was hospitalized and discontinued before completion of visit 1.
	NR	214	1	Patient came in for physician part of screen on 6/13/99. Labs and ECG were scheduled on 6/28/99 due to patient's

Type of Violation	Therapy	Patient Number	Visit Number	Comments
				schedule. Visit 1 split over 2 days.
	Placebo	303	14	Visit 14 split due to patient illness of mononucleosis.
	NR	314	1	EKG not done until Visit 2 because of technical problems with EKG machine at visit 1.
	Placebo	330	1	Visit 1 split over 2 days all scales completed on 12/5/98 and labs, PE, and EKG completed on 12/9/98.
	Flx	334	2	Physical examination and medical history completed at Visit 2 due to staff availability.
	Placebo	343	1	Visit 1 split over 2 days, PE and ratings other than MAGIC completed on 2/20/99.
	Flx	346	1	Visit 1 split between 2/13/99 and 2/23/99.
	Flx	346	3	Physical examination completed at Visit 3.
	NR	348	1	Visit 1 split over 2 days because of patient time constraints.
	Placebo	350	1	Physical examination completed at Visit 2 due to physician schedule.
	Flx	353	1	Visit 1 split due to patient's schedule issues.
	Flx	353	10	Parent/guard not available for completing scales (CDRS, etc.) Dr. Saylor feels patient only is a reliable source.
	Flx	354	1	Visit 1 split over 2 days because of patient time constraints.
	Flx	355	1	Visit 1 split over 2 days and PE was done on 6/5/99 due to time constraints.
	Placebo	356	1	Visit 1 split over 2 days due to time constraints, all ratings on 6/18/99 and PE/medical history on 6/19/99.
	Flx	422	2	Patient's mother not able to attend visit 2 on 3/11/99, patient's mother completed visit 2 interviews on 3/12/99.

Type of Violation	Therapy	Patient Number	Visit Number	Comments
	NR	801	1	Visit 1 took place on 7/20/98 and 7/21/98 due to patient's mother's work schedule.
	NR	803	1	Visit 1 split over 2 days with labs completed on 9/17/98, due to time constraints.
	Placebo	806	3	Patient interviews were completed on 12/11/98, patient's mother completed parent interviews on 12/14/98.
	Flx	906	12	Parent interview portion completed over the phone, because mother unable to accompany patient to the visit.
	Flx	906	13	Parent interview portion completed over the phone, because mother unable to accompany patient to the visit.
	Placebo	1506	2	Patient's mother returned on 1/29/99 to complete visit 2 interviews.
	Placebo	1506	9	Patient's mother unavailable to do CDRSR for visit 9, so CDRSR was completed over the phone with patient's mother.
	Flx	1659	5	Patient transported to visit by neighbor and verbal interview was done with father over phone.
	NR	1902	3	Principal Investigator conducted 2 of the first 3 visits.
	NR	1910	2,3	Principal Investigator conducted visits 2 and 3, 2nd rater unavailable.
	NR	1912	3	Principal Investigator conducted 2 of the first 3 visits while additional rater was being trained.
	Placebo	1913	1	Lab procedures completed on 2/16/99 and all other Visit 1 procedures completed on 2/25/99.
	Placebo	1913	1,2	Principal Investigator conducted visits 1 and 3 visits, 2nd rater unavailable.
	Placebo	1914	3	Principal Investigator conducted

Type of Violation	Therapy	Patient Number	Visit Number	Comments
				2 of the first 3 visits for the MAGIC.
	Flx	1915	1,2	Principal Investigator conducted visits 1 and 2 , 2nd rater unavailable.
	Placebo	2203	1	Family history reviewed twice by same rater.
	Flx	2204	1	Throughout the MAGIC-P, study coordinator used incorrect date, date she used was before the visit.
	Flx	2205	3	Parent DICA reviewed by study coordinator 2 times (4/15/99 and 4/30/99) due to shortage of raters.
	Flx	2205	3	Study coordinator conducted the patient portion of the CDRSR and the investigator completed the parent portion..
	Placebo	2206	2,3	Same rater reviewed family history on Visit 2 and Visit 3.
	Placebo	2206	8	Visit # corrected on all source document pages and Study coordinator used source documents marked “patient” for parent interviews and “parent” for patient interviews.
	Placebo	2207	3	2 instead of 3 staff persons reviewed MAGIC/DICA.
	Flx	2208	1	Family history not obtained because patient is adopted obtained family history of adopted family.
	Flx	2208	3	MAGIC/DICA reviewed by 2 raters instead of 3.
	Placebo	2212	3	Only 2 raters for DICA instead of 3.
	Placebo	2212	7	Patient’s mother was interviewed over phone for CDRS-R because mother had transportation problems.
	Placebo	2212	8	Patient’s mother was interviewed over phone for CDRS-R because mother had transportation problems.
	Placebo	2213	1	Patient is adopted and

Type of Violation	Therapy	Patient Number	Visit Number	Comments
				interviewer unable to obtain background history.
	Placebo	2213	3	Child MAGIC/DICA reviewed by study coordinator 2 times at Visit 2 on 6/17/99 and at Visit 3 on 6/22/99.
	Placebo	2213	4	The CGI score was changed to reflect the information gathered in both the KSADS and the CDRSR.
	Flx	2214	3	DICA-P completed and reviewed by 2 raters instead of 3, site error.
	Flx	2214	3	DICA-P and DICA-C was not reviewed by a child psychiatrist.
	Flx	2216	3	DICA-P completed and reviewed by 2 raters instead of 3, site error.
	Placebo	2217	1	Multiple questions in DICA-P not completed due to site error.
	Placebo	2217	3	DICA reviewed by same person instead of different rater.
	Placebo	2218	3	The CDRSR score was changed to reflect the assessment of the initial interviewer and the interviews completed by the investigator.
	Placebo	2221	3	CDRSR was not done by a different rater. It was the same rater as visit 2.
	Placebo	2221	3	DICA reviewed by same person 2 times.
	Placebo	2221	3	DICA parent was not administered or reviewed by a psychiatrist.

Type of Violation	Therapy	Patient Number	Visit Number	Comments
Non-Compliance (Missed Doses)				
	Flx	104	8	Missed 1 Dose
	Flx	104	12	Missed 4 Doses- Nonconsecutive
	Flx	104	13	Missed 14 Doses- 10 Consecutive. Patient discontinued.
	Placebo	112	5	Missed 3 Doses- 2 Consecutive
	Placebo	112	8	Missed 1 Dose
	Placebo	112	10	Missed 21 Doses- 20 Consecutive. Patient discontinued.
	Placebo	113	5	Missed 2 Doses- Consecutive
	Placebo	113	10	Missed 2 Doses- Nonconsecutive
	Placebo	113	11	Missed 2 Doses- Nonconsecutive
	Placebo	113	12	Missed 2 Doses- Nonconsecutive
	Placebo	113	13	Missed 1 Dose
	Placebo	113	14	Missed 1 Dose
	Placebo	113	15	Missed 2 Doses- Nonconsecutive
	Flx	114	4	Missed 1 Dose
	Flx	114	8	Missed 3 Doses- 2 Consecutive
	Flx	114	9	Missed 1 Dose
	Flx	114	10	Missed 2 Doses- Nonconsecutive
	Flx	114	11	Missed 1 Dose
	Flx	114	12	Missed 10 Doses- 7 Consecutive. Patient discontinued.
	Flx	118	8	Missed 2 Doses- Nonconsecutive
	Flx	118	11	Missed 1 Dose
	Placebo	119	9	Missed 1 Dose
	Placebo	119	10	Missed 1 Dose
	Placebo	119	12	Missed 2 Doses- Nonconsecutive
	Placebo	119	13	Missed 3 Doses- Nonconsecutive
	Placebo	119	15	Missed 1 Dose
	Flx	124	14	Missed 1 Dose
	Flx	127	5	Missed 1 Dose
	Flx	127	6	Missed 1 Dose
	Flx	127	8	Missed 2 Doses- Nonconsecutive
	Flx	127	9	Missed 2 Doses- Nonconsecutive
	Flx	127	10	Missed 2 Doses- Nonconsecutive
	Flx	127	11	Missed 2 Doses- Nonconsecutive
	Placebo	135	5	Missed 1 Dose
	Flx	137	6	Missed 1 Dose
	Flx	137	8	Missed 2 Doses- Consecutive
	Flx	137	10	Missed 6 Doses- Consecutive. Patient discontinued.
	Flx	139	13	Missed 1 Dose
	Flx	139	15	Missed 2 Doses- Consecutive

Type of Violation	Therapy	Patient Number	Visit Number	Comments
	Placebo	140	7	Missed 7 Doses- Consecutive. Patient discontinued.
	Flx	141	6	Missed 1 Dose
	Flx	142	10	Missed 1 Dose
	Placebo	149	5	Missed 1 Dose
	Placebo	149	9	Missed 1 Dose
	Placebo	201	4	Missed 1 Dose
	Flx	204	10	Missed 1 Dose
	Placebo	205	4	Missed 1 Dose
	Placebo	206	8	Missed 2 Doses- Nonconsecutive
	Placebo	206	10	Missed 1 Dose
	Placebo	206	12	Missed 6 Doses- 4 Consecutive. Lilly physician approved patient to continue.
	Placebo	206	13	Missed 2 Doses- Nonconsecutive
	Placebo	206	14	Missed 2 Doses- Nonconsecutive
	Placebo	206	15	Missed 2 Doses- Nonconsecutive
	Flx	208	6	Missed 2 Doses- Consecutive
	Flx	208	7	Missed 1 Dose
	Placebo	209	4	Missed 1 Dose
	Placebo	209	5	Missed 1 Dose
	Placebo	209	6	Missed 1 Dose
	Placebo	209	7	Missed 1 Dose
	Placebo	209	8	Missed 3 Doses- 2 Consecutive
	Placebo	209	9	Missed 1 Dose
	Placebo	209	11	Missed 2 Doses- Nonconsecutive
	Placebo	209	12	Missed 2 Doses- Consecutive
	Placebo	209	14	Missed 1 Dose
	Placebo	209	15	Missed 2 Doses- Consecutive
	Placebo	210	4	Missed 1 Dose
	Placebo	210	5	Missed 1 Dose
	Placebo	210	6	Missed 2 Doses- Nonconsecutive
	Placebo	210	8	Missed 2 Doses- Nonconsecutive
	Placebo	210	9	Missed 2 Doses- Nonconsecutive
	Placebo	210	10	Missed 1 Dose
	Placebo	210	11	Missed 3 Doses- Nonconsecutive
	Placebo	210	12	Missed 3 Doses- Nonconsecutive
	Placebo	210	13	Missed 2 Doses- Nonconsecutive
	Placebo	210	14	Missed 13 Doses- Consecutive. Patient discontinued.
	Placebo	301	4	Missed 1 Dose
	Placebo	301	5	Missed 1 Dose
	Placebo	301	6	Missed 3 Doses- Consecutive
	Placebo	301	8	Missed 24 Doses- 23

Type of Violation	Therapy	Patient Number	Visit Number	Comments
				Consecutive. Patient discontinued.
	Flx	302	9	Missed 2 Doses- Consecutive
	Placebo	303	5	Missed 1 Dose
	Placebo	303	8	Missed 1 Dose
	Placebo	303	10	Missed 1 Dose
	Placebo	303	11	Missed 1 Dose
	Placebo	303	14	Missed 5 Doses- 2 Consecutive. Patient discontinued.
	Flx	305	15	Missed 4 Doses- Consecutive. Lilly physician approved patient to continue.
	Placebo	306	10	Missed 3 Doses- Nonconsecutive
	Placebo	306	11	Missed 18 Doses- Consecutive. Patient discontinued.
	Flx	307	8	Missed 1 Dose
	Flx	307	9	Missed 2 Doses- Nonconsecutive
	Flx	307	10	Missed 2 Doses- Nonconsecutive
	Flx	307	11	Missed 3 Doses- Nonconsecutive
	Flx	307	12	Missed 4 Doses- 2 Consecutive. Patient discontinued.
	Placebo	312	6	Missed 1 Dose
	Flx	313	9	Missed 40 Doses- Consecutive. Patient discontinued.
	Placebo	315	8	Missed 1 Dose
	Placebo	315	15	Missed 3 Doses- 2 Consecutive
	Flx	318	8	Missed 12 Doses- Consecutive. Patient discontinued.
	Flx	319	14	Missed 51 Doses- Consecutive. Patient discontinued.
	Placebo	323	8	Missed 2 Doses- Nonconsecutive
	Placebo	323	9	Missed 2 Doses- Consecutive
	Flx	326	6	Missed 1 Dose
	Flx	326	8	Missed 2 Doses- Nonconsecutive
	Flx	326	10	Missed 1 Dose
	Flx	326	11	Missed 2 Doses- Nonconsecutive
	Flx	326	13	Missed 1 Dose
	Flx	326	14	Missed 4 Doses- 2 Consecutive
	Flx	326	15	Missed 3 Doses- Nonconsecutive
	Placebo	330	11	Missed 55 Doses- Consecutive. Patient discontinued.
	Flx	332	9	Missed 12 Doses- Consecutive. Patient discontinued.
	Flx	334	6	Missed 1 Dose
	Flx	334	10	Missed 1 Dose

Type of Violation	Therapy	Patient Number	Visit Number	Comments
	Flx	334	14	Missed 1 Dose
	Flx	334	15	Missed 1 Dose
	Placebo	335	4	Missed 1 Dose
	Placebo	335	11	Missed 4 Doses- 2 Consecutive
	Placebo	335	14	Missed 1 Dose
	Placebo	336	4	Missed 1 Dose
	Placebo	336	5	Missed 1 Dose
	Placebo	336	9	Missed 1 Dose
	Placebo	339	6	Missed 1 Dose
	Placebo	339	9	Missed 1 Dose
	Placebo	343	4	Missed 2 Doses- Consecutive
	Placebo	343	5	Missed 1 Dose
	Placebo	343	6	Missed 1 Dose
	Placebo	343	7	Missed 2 Doses- Nonconsecutive
	Placebo	343	8	Missed 2 Doses- Consecutive
	Placebo	343	9	Missed 1 Dose
	Placebo	343	11	Missed 1 Dose
	Placebo	343	12	Missed 1 Dose
	Placebo	350	10	Missed 2 Doses- Consecutive
	Placebo	352	6	Missed 1 Dose
	Placebo	352	9	Missed 1 Dose
	Flx	353	4	Missed 1 Dose
	Flx	353	9	Missed 2 Doses- Consecutive
	Flx	353	13	Missed 1 Dose
	Flx	354	7	Missed 1 Dose
	Flx	354	8	Missed 1 Dose
	Flx	354	10	Missed 1 Dose
	Flx	354	11	Missed 1 Dose
	Placebo	356	4	Missed 5 Doses- Nonconsecutive. Placebo Washout Phase.
	Flx	401	10	Missed 1 Dose
	Placebo	403	11	Missed 1 Dose
	Flx	404	4	Missed 1 Dose
	Flx	404	11	Missed 2 Doses- Consecutive
	Placebo	407	12	Missed 2 Doses- Nonconsecutive
	Placebo	407	13	Missed 3 Doses- Consecutive. Patient discontinued.
	Flx	408	7	Missed 2 Doses- Consecutive
	Flx	408	9	Missed 1 Dose
	Flx	413	6	Missed 2 Doses- Consecutive
	Flx	413	9	Missed 1 Dose
	Flx	415	15	Missed 1 Dose
	Placebo	417	4	Missed 1 Dose
	Placebo	417	7	Missed 2 Doses- 2 Consecutive

Type of Violation	Therapy	Patient Number	Visit Number	Comments
	Placebo	417	8	Missed 1 Dose
	Placebo	417	9	Missed 8 Doses- Consecutive. Patient discontinued.
	Flx	419	7	Missed 1 Dose
	Flx	422	4	Missed 3 Doses- 2 Consecutive
	Flx	422	8	Missed 1 Dose
	Flx	422	9	Missed 2 Doses- Nonconsecutive
	Flx	422	10	Missed 2 Doses- Consecutive
	Flx	422	11	Missed 2 Doses- Nonconsecutive
	Flx	422	12	Missed 1 Dose
	Flx	422	15	Missed 1 Dose
	Flx	424	8	Missed 3 Doses- Nonconsecutive
	Flx	424	9	Missed 1 Dose
	Flx	424	10	Missed 1 Dose
	Flx	424	11	Missed 2 Doses- Consecutive
	Flx	424	12	Missed 2 Doses- Nonconsecutive
	Flx	424	14	Missed 4 Doses- Nonconsecutive
	Flx	424	15	Missed 4 Doses- 3 Consecutive. Lilly physician approved patient to continue.
	Placebo	425	12	Missed 1 Dose
	Placebo	425	14	Missed 1 Dose
	Placebo	427	8	Missed 27 Doses- Consecutive. Patient discontinued.
	Flx	433	4	Missed 2 Doses- Nonconsecutive
	Flx	433	5	Missed 1 Dose
	Flx	433	6	Missed 1 Dose
	Flx	433	7	Missed 2 Doses- Nonconsecutive
	Flx	433	8	Missed 2 Doses- Nonconsecutive
	Flx	433	9	Missed 2 Doses- Nonconsecutive
	Flx	433	10	Missed 2 Doses- Consecutive
	Flx	433	12	Missed 1 Dose
	Flx	433	13	Missed 8 Doses- Consecutive. Patient discontinued.
	Flx	441	7	Missed 1 Dose
	Placebo	601	5	Missed 2 Doses- Consecutive
	Placebo	804	7	Missed 1 Dose
	Placebo	804	8	Missed 1 Dose
	Placebo	804	12	Missed 3 Doses- Nonconsecutive
	Placebo	804	13	Missed 1 Dose
	Placebo	804	14	Missed 2 Doses- Consecutive
	Placebo	806	5	Missed 1 Dose
	Placebo	807	4	Missed 1 Dose
	Placebo	808	4	Missed 1 Dose

Type of Violation	Therapy	Patient Number	Visit Number	Comments
	Placebo	808	8	Missed 1 Dose
	Placebo	808	9	Missed 3 Doses- Consecutive
	Placebo	808	10	Missed 1 Dose
	Placebo	808	11	Missed 2 Doses- Consecutive
	Placebo	808	12	Missed 5 Doses- 3 Consecutive. Patient discontinued.
	Placebo	809	4	Missed 1 Dose
	Placebo	809	5	Missed 2 Doses- Nonconsecutive
	Placebo	809	6	Missed 1 Dose
	Placebo	809	8	Missed 5 Doses- 2 Consecutive
	Placebo	809	9	Missed 2 Doses- Nonconsecutive
	Placebo	809	10	Missed 1 Dose
	Placebo	809	11	Missed 2 Doses- Consecutive
	Flx	810	6	Missed 1 Dose
	Flx	810	7	Missed 1 Dose
	Flx	810	8	Missed 2 Doses- Nonconsecutive
	Flx	810	9	Missed 2 Doses- Nonconsecutive
	Flx	810	10	Missed 6 Doses- 2 Consecutive
	Flx	810	11	Missed 3 Doses- 2 Consecutive
	Flx	810	12	Missed 2 Doses- Nonconsecutive
	Flx	810	13	Missed 2 Doses- Nonconsecutive
	Flx	810	14	Missed 1 Dose
	Flx	810	15	Missed 4 Doses- 2 Consecutive
	Flx	811	4	Missed 1 Dose
	Flx	811	7	Missed 1 Dose
	Flx	811	9	Missed 1 Dose
	Flx	811	10	Missed 2 Doses- Consecutive
	Flx	812	7	Missed 1 Dose
	Flx	813	10	Missed 1 Dose
	Flx	813	13	Missed 11 Doses- Consecutive. Patient discontinued.
	Flx	814	9	Missed 1 Dose
	Flx	814	11	Missed 2 Doses- Nonconsecutive
	Flx	814	12	Missed 2 Doses- Consecutive
	Flx	814	13	Missed 7 Doses- Consecutive. Patient discontinued.
	Flx	815	4	Missed 1 Dose
	Flx	815	5	Missed 2 Doses- Consecutive
	Flx	815	7	Missed 1 Dose
	Flx	815	9	Missed 2 Doses- Nonconsecutive
	Flx	815	10	Missed 4 Doses- 2 Consecutive
	Flx	815	11	Missed 2 Doses- Consecutive
	Flx	815	12	Missed 1 Dose
	Flx	815	13	Missed 3 Doses- 2 Consecutive

Type of Violation	Therapy	Patient Number	Visit Number	Comments
	Flx	815	14	Missed 2 Doses- Consecutive
	Flx	815	15	Missed 5 Doses- 2 Consecutive
	Flx	901	7	Missed 1 Dose
	Flx	901	8	Missed 2 Doses- Consecutive
	Flx	901	12	Missed 1 Dose
	Flx	901	14	Missed 8 Doses- Consecutive. Patient discontinued.
	Flx	906	4	Missed 2 Doses- Consecutive
	Flx	906	6	Missed 2 Doses- Consecutive
	Flx	906	11	Missed 1 Dose
	Placebo	911	6	Missed 1 Dose
	Placebo	911	15	Missed 1 Dose
	Placebo	912	4	Missed 1 Dose
	Placebo	912	5	Missed 1 Dose
	Placebo	912	6	Missed 1 Dose
	Placebo	912	7	Missed 1 Dose
	Placebo	912	8	Missed 4 Doses- 3 Consecutive. Lilly physician approved patient to continue.
	Placebo	912	9	Missed 1 Dose
	Placebo	912	10	Missed 1 Dose
	Placebo	912	11	Missed 3 Doses- Nonconsecutive
	Placebo	912	12	Missed 3 Doses- 2 Consecutive
	Placebo	912	14	Missed 3 Doses- Consecutive. Lilly physician approved patient to continue.
	Placebo	912	15	Missed 2 Doses- Nonconsecutive
	Flx	913	5	Missed 1 Dose
	Flx	913	6	Missed 1 Dose
	Flx	913	7	Missed 1 Dose
	Flx	913	8	Missed 3 Doses- 2 Consecutive
	Flx	913	9	Missed 1 Dose
	Flx	913	10	Missed 1 Dose
	Flx	913	11	Missed 2 Doses- Nonconsecutive
	Flx	915	5	Missed 1 Dose
	Flx	915	6	Missed 1 Dose
	Flx	915	7	Missed 1 Dose
	Flx	915	9	Missed 1 Dose
	Flx	915	10	Missed 2 Doses- Nonconsecutive
	Flx	915	11	Missed 2 Doses- Nonconsecutive
	Flx	915	12	Missed 2 Doses- Nonconsecutive
	Flx	915	13	Missed 4 Doses- 2 Consecutive
	Flx	915	14	Missed 2 Doses- Nonconsecutive
	Flx	915	15	Missed 2 Doses- Nonconsecutive

Type of Violation	Therapy	Patient Number	Visit Number	Comments
	Placebo	916	4	Missed 1 Dose
	Placebo	916	5	Missed 1 Dose
	Placebo	919	9	Missed 1 Dose
	Placebo	919	11	Missed 15 Doses- Consecutive. Patient discontinued.
	Flx	920	9	Missed 1 Dose
	Flx	920	11	Missed 1 Dose
	Flx	920	14	Missed 2 Doses- Nonconsecutive
	Flx	920	15	Missed 2 Doses- Consecutive
	Flx	1101	4	Missed 1 Dose
	Placebo	1105	11	Missed 1 Dose
	Flx	1109	6	Missed 1 Dose
	Flx	1109	8	Missed 2 Doses- Nonconsecutive
	Flx	1109	9	Missed 1 Dose
	Flx	1118	6	Missed 1 Dose
	Flx	1118	7	Missed 1 Dose
	Flx	1118	9	Missed 5 Doses- 3 Consecutive
	Flx	1118	10	Missed 4 Doses- Consecutive. Patient discontinued.
	Placebo	1120	4	Missed 1 Dose
	Placebo	1120	9	Missed 3 Doses- 2 Consecutive
	Placebo	1120	13	Missed 1 Dose
	Placebo	1120	14	Missed 3 Doses- 2 Consecutive
	Placebo	1126	11	Missed 1 Dose
	Placebo	1126	13	Missed 1 Dose
	Placebo	1126	15	Missed 3 Doses- Nonconsecutive
	Flx	1129	6	Missed 1 Dose
	Flx	1129	9	Missed 1 Dose
	Flx	1131	8	Missed 1 Dose
	Placebo	1134	7	Missed 1 Dose
	Placebo	1134	9	Missed 8 Doses- 5 Consecutive. Patient discontinued.
	Placebo	1135	8	Missed 1 Dose
	Placebo	1135	9	Missed 1 Dose
	Placebo	1135	10	Missed 1 Dose
	Placebo	1135	13	Missed 1 Dose
	Flx	1137	8	Missed 1 Dose
	Flx	1137	9	Missed 2 Doses- Consecutive
	Placebo	1138	6	Missed 1 Dose
	Placebo	1138	7	Missed 1 Dose
	Placebo	1138	9	Missed 1 Dose
	Placebo	1138	10	Missed 1 Dose
	Placebo	1138	12	Missed 1 Dose
	Placebo	1138	15	Missed 1 Dose

Type of Violation	Therapy	Patient Number	Visit Number	Comments
	Not Randomized	1139	4	Missed 6 Doses- Consecutive. Patient discontinued.
	Placebo	1143	15	Missed 1 Dose
	Placebo	1144	9	Missed 2 Doses- Nonconsecutive
	Placebo	1144	10	Missed 2 Doses- Nonconsecutive
	Placebo	1144	11	Missed 2 Doses- Nonconsecutive
	Placebo	1144	13	Missed 2 Doses- Consecutive
	Placebo	1144	15	Missed 1 Dose
	Flx	1152	4	Missed 1 Dose
	Flx	1152	5	Missed 1 Dose
	Flx	1152	7	Missed 1 Dose
	Flx	1156	7	Missed 1 Dose
	Flx	1156	9	Missed 2 Doses- Nonconsecutive
	Flx	1156	11	Missed 3 Doses- 2 Consecutive
	Flx	1156	14	Missed 2 Doses- Nonconsecutive
	Placebo	1201	4	Missed 1 Dose
	Placebo	1201	7	Missed 2 Doses- Consecutive
	Placebo	1201	9	Missed 3 Doses- 2 Consecutive
	Placebo	1201	13	Missed 4 Doses- 2 Consecutive. Patient discontinued.
	Flx	1202	6	Missed 1 Dose
	Flx	1202	11	Missed 2 Doses- Nonconsecutive
	Flx	1202	12	Missed 1 Dose
	Flx	1203	4	Missed 2 Doses- Consecutive
	Flx	1203	8	Missed 1 Dose
	Flx	1204	4	Missed 6 Doses- Consecutive. Placebo Washout Phase.
	Flx	1204	10	Missed 2 Doses- Nonconsecutive
	Placebo	1206	4	Missed 2 Doses- Consecutive
	Placebo	1206	8	Missed 1 Dose
	Placebo	1206	9	Missed 1 Dose
	Placebo	1207	9	Missed 1 Dose
	Placebo	1207	15	Missed 1 Dose
	Flx	1208	4	Missed 2 Doses- Consecutive
	Flx	1208	8	Missed 3 Doses- 2 Consecutive
	Flx	1208	9	Missed 1 Dose
	Flx	1208	11	Missed 1 Dose
	Flx	1208	12	Missed 1 Dose
	Flx	1209	11	Missed 10 Doses- Consecutive. Patient discontinued.
	Flx	1211	4	Missed 1 Dose
	Flx	1211	5	Missed 2 Doses- Consecutive
	Flx	1211	7	Missed 1 Dose
	Flx	1211	8	Missed 4 Doses- 2 Consecutive

Type of Violation	Therapy	Patient Number	Visit Number	Comments
	Flx	1211	9	Missed 2 Doses- Nonconsecutive
	Flx	1211	10	Missed 4 Doses- 2 Consecutive
	Flx	1211	12	Missed 20 Doses- Consecutive. Patient discontinued.
	Placebo	1212	4	Missed 2 Doses- Consecutive
	Flx	1213	7	Missed 2 Doses- Consecutive
	Flx	1213	10	Missed 1 Dose
	Flx	1213	12	Missed 2 Doses- Nonconsecutive
	Flx	1213	13	Missed 1 Dose
	Flx	1215	7	Missed 32 Doses- Consecutive. Patient discontinued.
	Placebo	1216	4	Missed 2 Doses- Nonconsecutive
	Placebo	1216	5	Missed 1 Dose
	Placebo	1216	8	Missed 2 Doses- Consecutive
	Placebo	1216	10	Missed 2 Doses- Nonconsecutive
	Placebo	1216	12	Missed 3 Doses- 2 Consecutive
	Placebo	1216	14	Missed 1 Dose
	Placebo	1216	15	Missed 2 Doses- Consecutive
	Flx	1217	4	Missed 1 Dose
	Flx	1217	5	Missed 1 Dose
	Flx	1217	8	Missed 2 Doses- Nonconsecutive
	Flx	1217	10	Missed 2 Doses- Nonconsecutive
	Flx	1220	4	Missed 2 Doses- Consecutive
	Flx	1220	10	Missed 4 Doses- 2 Consecutive
	Placebo	1221	5	Missed 1 Dose
	Placebo	1221	8	Missed 1 Dose
	Placebo	1221	11	Missed 1 Dose
	Placebo	1221	13	Missed 2 Doses- Consecutive
	Placebo	1222	4	Missed 2 Doses- Consecutive
	Placebo	1222	7	Missed 2 Doses- Consecutive
	Placebo	1222	8	Missed 6 Doses- Consecutive
	Placebo	1222	12	Missed 2 Doses- Nonconsecutive
	Placebo	1222	14	Missed 1 Dose
	Placebo	1222	15	Missed 7 Doses- Consecutive. Patient discontinued.
	Placebo	1223	6	Missed 2 Doses- Nonconsecutive
	Placebo	1223	10	Missed 2 Doses- Consecutive
	Placebo	1223	11	Missed 1 Dose
	Placebo	1223	12	Missed 10 Doses- Consecutive. Patient discontinued.
	Flx	1225	4	Missed 1 Dose
	Flx	1225	9	Missed 1 Dose
	Flx	1225	10	Missed 1 Dose
	Flx	1225	12	Missed 1 Dose

Type of Violation	Therapy	Patient Number	Visit Number	Comments
	Flx	1225	13	Missed 1 Dose
	Flx	1225	14	Missed 3 Doses- Nonconsecutive
	Placebo	1301	5	Missed 1 Dose
	Placebo	1301	13	Missed 1 Dose
	Placebo	1301	15	Missed 2 Doses- Nonconsecutive
	Placebo	1303	9	Missed 1 Dose
	Placebo	1303	10	Missed 1 Dose
	Placebo	1303	11	Missed 1 Dose
	Placebo	1303	14	Missed 1 Dose
	Placebo	1303	15	Missed 2 Doses- Nonconsecutive
	Flx	1305	10	Missed 2 Doses- Consecutive
	Placebo	1307	10	Missed 2 Doses- Consecutive
	Placebo	1308	13	Missed 12 Doses- Consecutive. Patient discontinued.
	Placebo	1309	5	Missed 1 Dose
	Placebo	1501	7	Missed 1 Dose
	Placebo	1501	8	Missed 1 Dose
	Placebo	1501	11	Missed 1 Dose
	Placebo	1501	12	Missed 1 Dose
	Placebo	1501	14	Missed 1 Dose
	Flx	1503	9	Missed 5 Doses- Consecutive
	Placebo	1504	4	Missed 1 Dose
	Placebo	1504	9	Missed 21 Doses- Consecutive. Patient discontinued.
	Placebo	1506	12	Missed 1 Dose
	Flx	1510	4	Missed 1 Dose
	Flx	1510	7	Missed 1 Dose
	Flx	1510	8	Missed 2 Doses- Nonconsecutive
	Flx	1510	15	Missed 1 Dose
	Placebo	1513	8	Missed 2 Doses- Nonconsecutive
	Placebo	1513	9	Missed 5 Doses- Consecutive. Patient discontinued.
	Flx	1514	7	Missed 7 Doses- Consecutive. Patient discontinued.
	Flx	1515	7	Missed 1 Dose
	Flx	1515	12	Missed 10 Doses- Consecutive. Patient discontinued.
	Flx	1516	7	Missed 1 Dose
	Flx	1516	14	Missed 1 Dose
	Flx	1602	6	Missed 3 Doses- Nonconsecutive
	Flx	1602	8	Missed 1 Dose
	Flx	1602	9	Missed 1 Dose
	Flx	1602	12	Missed 1 Dose
	Flx	1602	13	Missed 2 Doses- Nonconsecutive

Type of Violation	Therapy	Patient Number	Visit Number	Comments
	Flx	1603	8	Missed 1 Dose
	Flx	1604	6	Missed 1 Dose
	Flx	1604	8	Missed 1 Dose
	Flx	1604	11	Missed 1 Dose
	Flx	1604	12	Missed 1 Dose
	Flx	1604	13	Missed 3 Doses- 2 Consecutive
	Flx	1604	14	Missed 1 Dose
	Flx	1604	15	Missed 1 Dose
	Flx	1606	5	Missed 1 Dose
	Placebo	1608	4	Missed 1 Dose
	Flx	1609	7	Missed 1 Dose
	Flx	1609	10	Missed 1 Dose
	Flx	1609	12	Missed 2 Doses- Consecutive
	Flx	1609	14	Missed 3 Doses- 2 Consecutive
	Flx	1609	15	Missed 2 Doses- Nonconsecutive
	Flx	1612	5	Missed 1 Dose
	Flx	1612	6	Missed 2 Doses- Consecutive
	Flx	1612	8	Missed 1 Dose
	Flx	1612	9	Missed 2 Doses- Nonconsecutive
	Flx	1612	10	Missed 1 Dose
	Placebo	1651	4	Missed 1 Dose
	Placebo	1651	5	Missed 1 Dose
	Flx	1652	11	Missed 2 Doses- Nonconsecutive
	Placebo	1653	4	Missed 1 Dose
	Placebo	1653	8	Missed 11 Doses- Consecutive. Patient discontinued.
	Flx	1654	5	Missed 1 Dose
	Flx	1654	10	Missed 1 Dose
	Flx	1654	11	Missed 1 Dose
	Flx	1654	15	Missed 2 Doses- Nonconsecutive
	Placebo	1655	7	Missed 1 Dose
	Placebo	1655	9	Missed 3 Doses- 2 Consecutive
	Placebo	1655	12	Missed 1 Dose
	Placebo	1655	14	Missed 2 Doses- Nonconsecutive
	Placebo	1655	15	Missed 1 Dose
	Placebo	1656	5	Missed 1 Dose
	Placebo	1656	9	Missed 5 Doses- Consecutive. Lilly physician approved patient to continue.
	Flx	1658	11	Missed 2 Doses- Consecutive
	Flx	1658	12	Missed 1 Dose
	Flx	1659	4	Missed 1 Dose
	Flx	1659	7	Missed 1 Dose
	Flx	1667	8	Missed 1 Dose

Type of Violation	Therapy	Patient Number	Visit Number	Comments
	Placebo	1669	5	Missed 1 Dose
	Placebo	1669	11	Missed 2 Doses- Consecutive
	Flx	1701	5	Missed 1 Dose
	Flx	1701	9	Missed 1 Dose
	Flx	1701	10	Missed 4 Doses- 2 Consecutive
	Flx	1701	12	Missed 3 Doses- Nonconsecutive
	Flx	1701	13	Missed 1 Dose
	Flx	1701	14	Missed 2 Doses- Nonconsecutive
	Flx	1701	15	Missed 4 Doses- Nonconsecutive
	Flx	1702	6	Missed 1 Dose
	Flx	1702	11	Missed 3 Doses- Nonconsecutive
	Flx	1702	12	Missed 1 Dose
	Flx	1702	14	Missed 2 Doses- Nonconsecutive
	Placebo	1705	8	Missed 1 Dose
	Placebo	1705	12	Missed 2 Doses- Consecutive
	Placebo	1705	13	Missed 1 Dose
	Placebo	1705	14	Missed 1 Dose
	Placebo	1707	7	Missed 1 Dose
	Placebo	1707	8	Missed 2 Doses- Nonconsecutive
	Placebo	1707	9	Missed 2 Doses- Consecutive
	Placebo	1707	10	Missed 1 Dose
	Placebo	1707	11	Missed 1 Dose
	Placebo	1707	12	Missed 3 Doses- Nonconsecutive
	Placebo	1707	13	Missed 1 Dose
	Placebo	1707	14	Missed 1 Dose
	Placebo	1707	15	Missed 1 Dose
	Placebo	1903	9	Missed 6 Doses- 5 Consecutive. Patient discontinued.
	Flx	1904	7	Missed 1 Dose
	Flx	1905	7	Missed 2 Doses- Consecutive
	Flx	1905	9	Missed 1 Dose
	Flx	1905	11	Missed 1 Dose
	Flx	1906	7	Missed 1 Dose
	Flx	1906	9	Missed 2 Doses- Consecutive
	Flx	1906	12	Missed 1 Dose
	Flx	1906	14	Missed 1 Dose
	Flx	1906	15	Missed 2 Doses- Consecutive
	Placebo	1907	4	Missed 1 Dose
	Placebo	1907	6	Missed 2 Doses- Consecutive
	Placebo	1907	10	Missed 2 Doses- Consecutive
	Placebo	1913	4	Missed 2 Doses- Consecutive
	Placebo	1913	5	Missed 1 Dose
	Placebo	1913	8	Missed 1 Dose
	Placebo	1913	14	Missed 1 Dose

Type of Violation	Therapy	Patient Number	Visit Number	Comments
	Placebo	1914	8	Missed 1 Dose
	Placebo	1914	9	Missed 1 Dose
	Placebo	1914	15	Missed 1 Dose
	Flx	1915	4	Missed 1 Dose
	Flx	1915	6	Missed 1 Dose
	Flx	1915	7	Missed 1 Dose
	Flx	1919	9	Missed 1 Dose
	Flx	1921	5	Missed 1 Dose
	Flx	1921	12	Missed 1 Dose
	NR	1922	4	Missed 2 Doses- Nonconsecutive
	Flx	1924	12	Missed 2 Doses- Consecutive
	Flx	1924	13	Missed 1 Dose
	Flx	1924	14	Missed 1 Dose
	Placebo	1925	12	Missed 1 Dose
	Placebo	1925	14	Missed 1 Dose
	Placebo	1925	15	Missed 2 Doses- Nonconsecutive
	Placebo	1927	5	Missed 1 Dose
	Placebo	1927	9	Missed 1 Dose
	Placebo	1927	12	Missed 1 Dose
	Placebo	1927	13	Missed 1 Dose
	Placebo	1927	14	Missed 2 Doses- Nonconsecutive
	Placebo	2201	6	Missed 4 Doses- 3 Consecutive. Patient discontinued.
	Flx	2202	10	Missed 1 Dose
	Flx	2202	11	Missed 3 Doses- Consecutive. Lilly physician approved patient to continue.
	Flx	2202	12	Missed 2 Doses- Nonconsecutive
	Flx	2202	14	Missed 8 Doses- Consecutive. Patient discontinued.
	Flx	2204	9	Missed 3 Doses- Consecutive. Lilly physician approved patient to continue.
	Placebo	2206	4	Missed 1 Dose
	Placebo	2206	5	Missed 1 Dose
	Placebo	2206	9	Missed 1 Dose
	Placebo	2206	10	Missed 1 Dose
	Placebo	2206	14	Missed 1 Dose
	Placebo	2206	15	Missed 1 Dose
	Placebo	2207	12	Missed 1 Dose
	Placebo	2207	14	Missed 1 Dose
	Placebo	2207	15	Missed 1 Dose
	Flx	2208	7	Missed 1 Dose
	Flx	2208	9	Missed 1 Dose

Type of Violation	Therapy	Patient Number	Visit Number	Comments
	Placebo	2210	4	Missed 1 Dose
	Placebo	2210	5	Missed 1 Dose
	Placebo	2210	8	Missed 23 Doses- Consecutive. Patient discontinued.
	Placebo	2212	4	Missed 1 Dose
	Placebo	2212	6	Missed 2 Doses- Consecutive
	Placebo	2212	7	Missed 1 Dose
	Placebo	2212	8	Missed 2 Doses- Nonconsecutive
	Placebo	2212	9	Missed 2 Doses- Nonconsecutive
	Placebo	2212	10	Missed 3 Doses- 2 Consecutive
	Placebo	2212	11	Missed 1 Dose
	Placebo	2213	4	Missed 1 Dose
	Placebo	2213	5	Missed 1 Dose
	Placebo	2213	6	Missed 1 Dose
	Placebo	2213	7	Missed 2 Doses- Nonconsecutive
	Placebo	2213	8	Missed 2 Doses- Nonconsecutive
	Placebo	2213	9	Missed 3 Doses- 2 Consecutive
	Placebo	2213	10	Missed 10 Doses- 5 Consecutive. Patient discontinued.
	Flx	2214	5	Missed 1 Dose
	Flx	2214	8	Missed 2 Doses- Nonconsecutive
	Flx	2214	9	Missed 2 Doses- Nonconsecutive
	Flx	2214	12	Missed 1 Dose
	Flx	2214	13	Missed 2 Doses- Consecutive
	Flx	2214	14	Missed 4 Doses- Consecutive. Lilly physician approved patient to continue.
	Flx	2214	15	Missed 2 Doses- Nonconsecutive
	Placebo	2217	8	Missed 1 Dose
	Placebo	2217	14	Missed 1 Dose
	Placebo	2218	4	Missed 2 Doses- Consecutive
	Placebo	2218	5	Missed 3 Doses- 2 Consecutive
	Placebo	2218	10	Missed 1 Dose
	Flx	2220	5	Missed 1 Dose
	Flx	2220	6	Missed 1 Dose
	Flx	2220	8	Missed 1 Dose
	Flx	2220	9	Missed 2 Doses- Nonconsecutive
	Flx	2220	10	Missed 1 Dose
	Flx	2220	11	Missed 1 Dose
	Placebo	2221	5	Missed 3 Doses- 2 Consecutive
	Placebo	2221	8	Missed 1 Dose
	Placebo	2221	9	Missed 1 Dose
	Placebo	2221	10	Missed 21Doses- Consecutive. Patient discontinued.

Type of Violation	Therapy	Patient Number	Visit Number	Comments
Visit Interval Deviation				
	NR	102	2	9 days late, evaluation phase no study drug dispensed
	Placebo	103	3	1 day early, evaluation phase no study drug dispensed
	Placebo	103	6	1 day early
	Flx	104	9	1 day early.
	Flx	104	10	4 days early
	Flx	104	11	2 days early
	Flx	104	12	1 day late
	Flx	104	13	16 days late. Patient discontinued at this visit
	Placebo	107	3	1 day early, evaluation phase no study drug dispensed
	Placebo	112	10	12 days late. Patient discontinued at this visit
	Flx	114	9	1 day early.
	Flx	114	12	5 days late. Patient discontinued at this visit
	NR	116	3	6 days late, evaluation phase no study drug dispensed, patient discontinued at this visit
	Placebo	119	3	1 day early, evaluation phase no study drug dispensed
	NR	121	3	1 day early, evaluation phase no study drug dispensed, patient discontinued at this visit
	NR	122	3	1 day early, evaluation phase no study drug dispensed, patient discontinued at this visit
	Flx	124	5	3 days early, Randomization phase.
	Flx	124	6	1 day late
	Flx	124	12	3 days early
	Flx	124	13	1 day early
	Flx	126	9	7 days early. Patient discontinued at this visit
	Flx	127	11	1 day late. Patient discontinued at this visit
	Placebo	131	7	2 days early
	Placebo	131	9	2 days early.
	Placebo	135	3	1 day early, evaluation phase no study drug dispensed

Type of Violation	Therapy	Patient Number	Visit Number	Comments
	Placebo	135	5	1 day late, Randomization phase.
	Placebo	135	6	2 days early
	Flx	137	3	1 day early, evaluation phase no study drug dispensed
	Flx	137	8	1 day late
	Flx	137	9	2 days early.
	Flx	139	12	1 day late
	Flx	139	13	2 days late
	Flx	139	15	5 days late. Patient discontinued at this visit
	Placebo	140	3	1 day early, evaluation phase no study drug dispensed
	Flx	141	3	1 day early, evaluation phase no study drug dispensed
	Flx	142	9	5 days early.
	Flx	142	11	2 days late
	NR	145	2	1 day early, evaluation phase no study drug dispensed
	NR	145	3	1 day late, evaluation phase no study drug dispensed, patient discontinued at this visit
	Placebo	149	2	1 day early, evaluation phase no study drug dispensed
	Placebo	149	5	1 day late, Randomization phase.
	Placebo	149	6	1 day early
	NR	155	3	1 day early, evaluation phase no study drug dispensed, patient discontinued at this visit
	NR	157	3	1 day early, evaluation phase no study drug dispensed, patient discontinued at this visit
	Flx	204	2	6 days late, evaluation phase no study drug dispensed
	Flx	204	14	6 days early. Patient discontinued at this visit
	Placebo	205	3	2 days late, evaluation phase no study drug dispensed
	Placebo	206	3	1 day late, evaluation phase no study drug dispensed
	Flx	208	2	3 days late, evaluation phase no study drug dispensed
	Flx	208	6	3 days late
	Placebo	209	2	3 days late, evaluation phase no study drug dispensed
	Placebo	210	6	3 days late

Type of Violation	Therapy	Patient Number	Visit Number	Comments
	Placebo	210	8	2 days late
	Placebo	210	9	2 days late
	Placebo	210	10	1 day late
	NR	211	2	7 days late, evaluation phase no study drug dispensed, patient discontinued at this visit
	NR	213	2	7 days late, evaluation phase no study drug dispensed
	NR	214	2	14 days late, evaluation phase no study drug dispensed, patient discontinued at this visit
	Placebo	301	8	11 days late. Patient discontinued at this visit
	Flx	302	3	2 days late, evaluation phase no study drug dispensed
	Flx	302	9	4 days late. Patient discontinued at this visit
	Placebo	303	5	2 days late, Randomization phase.
	Placebo	303	6	1 day early
	Placebo	303	9	1 day early.
	Flx	305	3	11 days late, evaluation phase no study drug dispensed
	Flx	305	9	1 day early.
	Flx	305	11	1 day late
	Flx	305	12	2 days early
	Placebo	306	5	1 day early, Randomization phase.
	Placebo	306	11	2 days late. Patient discontinued at this visit
	Flx	307	4	1 day early, Placebo Washout phase. Only placebo study drug dispensed
	NR	308	3	22 days late, evaluation phase no study drug dispensed, patient discontinued at this visit
	Placebo	309	3	6 days late, evaluation phase no study drug dispensed
	Placebo	309	5	1 day early, Randomization phase.
	Placebo	309	12	2 days late
	Placebo	312	2	29 days late, evaluation phase no study drug dispensed. Patient had a heart murmur and was referred to cardiologists before continuing in the study.
	Placebo	312	3	2 days late, evaluation phase no study drug dispensed

Type of Violation	Therapy	Patient Number	Visit Number	Comments
	Placebo	312	6	2 days late
	Flx	313	6	1 day early
	Flx	313	9	31 days late. Patient discontinued at this visit
	Placebo	315	14	3 days late
	Placebo	315	15	1 day late
	Flx	318	8	2 days late. Patient discontinued at this visit
	Flx	319	14	47 days late. Patient discontinued at this visit
	NR	320	4	3 days early, Placebo Washout phase. Only placebo study drug dispensed, patient discontinued at this visit
	Placebo	323	2	6 days late, evaluation phase no study drug dispensed
	Placebo	323	5	1 day early, Randomization phase.
	Placebo	323	9	1 day early.
	Flx	326	2	4 days late, evaluation phase no study drug dispensed
	Flx	326	3	1 day late, evaluation phase no study drug dispensed
	Flx	326	4	1 day late, Placebo Washout phase. Only placebo study drug dispensed
	Placebo	330	2	5 days late, evaluation phase no study drug dispensed
	Placebo	330	6	2 days early
	Placebo	330	11	43 days late. Patient discontinued at this visit
	Flx	332	2	2 days early, evaluation phase no study drug dispensed
	Flx	332	3	1 day early, evaluation phase no study drug dispensed
	Flx	332	6	2 days early
	Flx	332	9	1 day early. Patient discontinued at this visit
	Flx	334	2	6 days late, evaluation phase no study drug dispensed
	Flx	334	4	1 day early, Placebo Washout phase. Only placebo study drug dispensed
	Flx	334	6	1 day early
	Flx	334	9	1 day late
	Flx	334	10	2 days late

Type of Violation	Therapy	Patient Number	Visit Number	Comments
	Flx	334	15	2 days late
	Placebo	335	3	1 day early, evaluation phase no study drug dispensed
	Placebo	336	3	1 day late, evaluation phase no study drug dispensed
	Placebo	336	4	2 days late, Placebo Washout phase. Only placebo study drug dispensed
	Placebo	339	2	2 days late, evaluation phase no study drug dispensed
	Placebo	343	2	6 days late, evaluation phase no study drug dispensed
	Placebo	343	6	1 day late
	Placebo	343	8	6 days early.
	Placebo	343	9	1 day early.
	Placebo	343	11	2 days late
	Flx	346	2	9 days late, evaluation phase no study drug dispensed
	Flx	346	8	2 days late
	Flx	346	9	3 days early.
	Flx	346	12	1 day early
	Flx	346	13	1 day late
	Flx	346	15	1 day late
	NR	348	2	20 days late, evaluation phase no study drug dispensed, patient discontinued at this visit
	Placebo	350	2	1 day early, evaluation phase no study drug dispensed
	Placebo	350	3	3 days late, evaluation phase no study drug dispensed
	Placebo	350	8	1 Day early
	Placebo	350	12	4 days early
	Placebo	350	13	3 days late
	Placebo	352	3	3 days late, evaluation phase no study drug dispensed
	Placebo	352	4	1 day late, Placebo Washout phase. Only placebo study drug dispensed
	Placebo	352	6	2 days late
	Flx	353	2	4 days late, evaluation phase no study drug dispensed
	Flx	353	3	2 days late, evaluation phase no study drug dispensed
	Flx	353	9	4 days late
	Flx	353	13	4 days late

Type of Violation	Therapy	Patient Number	Visit Number	Comments
	Flx	354	2	15 days late, evaluation phase no study drug dispensed. Patient was traveling.
	Flx	354	4	1 day early, Placebo Washout phase. Only placebo study drug dispensed
	Flx	354	15	2 days early
	Flx	355	2	4 days late, evaluation phase no study drug dispensed
	Flx	355	3	4 days early, evaluation phase no study drug dispensed
	Flx	355	13	1 day early
	Placebo	356	2	4 days late, evaluation phase no study drug dispensed
	Placebo	356	3	1 day early, evaluation phase no study drug dispensed
	Placebo	356	4	4 days late, Placebo Washout phase. Only placebo study drug dispensed
	Flx	401	12	5 days early. Patient discontinued at this visit
	Placebo	403	11	3 days late
	Flx	404	9	1 day early.
	Flx	404	11	5 days late.
	NR	405	2	1 day late, evaluation phase no study drug dispensed, patient discontinued at this visit
	Placebo	407	7	1 day early
	Placebo	407	8	4 days early.
	Flx	408	8	6 days early.
	Flx	408	9	3 days late
	NR	411	4	1 day early, Placebo Washout phase. Only placebo study drug dispensed, patient discontinued at this visit
	Placebo	412	10	1 day early
	Placebo	412	12	1 day early
	Flx	413	3	1 day early, evaluation phase no study drug dispensed
	Flx	413	6	3 days late
	Flx	415	5	1 day early, Randomization phase.
	Flx	415	8	1 day early.
	Flx	415	10	1 day early
	Flx	415	15	1 day early
	Flx	416	11	1 day early

Type of Violation	Therapy	Patient Number	Visit Number	Comments
	Placebo	417	3	3 days late, evaluation phase no study drug dispensed
	Placebo	417	6	1 day early
	Placebo	417	9	5 days early. Patient discontinued at this visit
	Flx	419	3	5 days late, evaluation phase no study drug dispensed
	Flx	419	7	1 day late
	Flx	419	9	2 days early.
	Flx	419	11	6 days early. Patient discontinued at this visit
	NR	420	2	2 days late, evaluation phase no study drug dispensed, patient discontinued at this visit
	Flx	422	3	5 days late, evaluation phase no study drug dispensed
	Flx	422	4	3 days late, Placebo Washout phase. Only placebo study drug dispensed
	Flx	422	13	2 days early
	Flx	422	14	1 day late
	NR	423	3	5 days late, evaluation phase no study drug dispensed, patient discontinued at this visit
	Flx	424	2	1 day early, evaluation phase no study drug dispensed
	Flx	424	3	7 days late, evaluation phase no study drug dispensed
	Flx	424	9	6 days early.
	Flx	424	11	2 days late
	Placebo	425	3	1 day late, evaluation phase no study drug dispensed
	Placebo	425	13	2 days early
	Placebo	425	14	1 day late
	Placebo	425	15	3 days late. Patient discontinued at this visit
	Placebo	427	6	1 day early
	Placebo	427	8	12 days late. Patient discontinued at this visit
	NR	431	3	5 days late, evaluation phase no study drug dispensed, patient discontinued at this visit
	Placebo	432	6	1 day early
	Flx	433	3	5 days late, evaluation phase no study drug dispensed

Type of Violation	Therapy	Patient Number	Visit Number	Comments
	Flx	433	7	1 day late
	Flx	433	12	2 days late
	Flx	433	13	6 days late. Patient discontinued at this visit
	NR	437	3	5 days late, evaluation phase no study drug dispensed, patient discontinued at this visit
	NR	440	3	1 day late, evaluation phase no study drug dispensed
	Flx	441	2	5 days late, evaluation phase no study drug dispensed
	Flx	441	8	5 days early. Patient discontinued at this visit
	Placebo	601	3	1 day early, evaluation phase no study drug dispensed
	Placebo	601	5	1 day early, Randomization phase, patient discontinued at this visit.
	Placebo	804	4	1 day early, Placebo Washout phase. Only placebo study drug dispensed
	Placebo	804	8	5 days early.
	Placebo	804	9	7 days early.
	Placebo	804	12	1 day early
	NR	805	2	3 days early, evaluation phase no study drug dispensed, patient discontinued at this visit
	Placebo	806	3	11 days late, evaluation phase no study drug dispensed
	Placebo	808	12	2 days early. Patient discontinued at this visit
	Placebo	809	2	1 day late, evaluation phase no study drug dispensed
	Placebo	809	12	1 day late. Patient discontinued at this visit
	Flx	810	3	2 days late, evaluation phase no study drug dispensed
	Flx	810	12	1 day early
	Flx	810	15	4 days late
	Flx	811	3	1 day late, evaluation phase no study drug dispensed
	Flx	811	10	4 days late
	Flx	813	2	1 day late, evaluation phase no study drug dispensed
	Flx	813	3	1 day early, evaluation phase no study drug dispensed

Type of Violation	Therapy	Patient Number	Visit Number	Comments
	Flx	813	12	5 days early
	Flx	813	13	11 days late. Patient discontinued at this visit
	Flx	814	13	1 day late. Patient discontinued at this visit
	Flx	815	3	3 days late, evaluation phase no study drug dispensed
	Flx	815	5	2 days early, Randomization phase.
	Flx	815	10	1 day late
	Flx	901	8	1 day early.
	Flx	901	11	2 days late
	Flx	901	14	3 days early. Patient discontinued at this visit
	NR	910	2	1 day early, evaluation phase no study drug dispensed, patient discontinued at this visit
	Placebo	911	3	3 days late, evaluation phase no study drug dispensed
	Placebo	911	15	1 day late
	Placebo	912	2	5 days late, evaluation phase no study drug dispensed
	Placebo	912	10	5 days early
	Placebo	912	11	1 day late
	Flx	913	12	4 days early. Patient discontinued at this visit
	Flx	915	8	1 day late
	Flx	915	9	2 days early.
	Flx	915	10	1 day late
	Flx	915	11	2 days late
	Flx	915	12	3 days late
	Flx	915	13	4 days late
	Placebo	916	5	1 day late, Randomization phase.
	Placebo	916	6	2 days early
	Placebo	916	7	1 day late
	Placebo	916	11	1 day late
	Placebo	916	12	3 days late. Patient discontinued at this visit
	NR	917	2	18 days late, evaluation phase no study drug dispensed
	NR	917	3	1 day late, evaluation phase no study drug dispensed, patient discontinued at this visit
	NR	918	3	1 day late, evaluation phase no study drug dispensed

Type of Violation	Therapy	Patient Number	Visit Number	Comments
	NR	918	4	6 days late, Placebo Washout phase. Only placebo study drug dispensed, patient discontinued at this visit
	Placebo	919	2	1 day early, evaluation phase no study drug dispensed
	Placebo	919	7	1 day early
	Flx	920	2	5 days late, evaluation phase no study drug dispensed
	Flx	920	6	1 day early
	Flx	920	9	1 day late
	Flx	920	15	2 days early
	Placebo	1102	9	4 days early. Patient discontinued at this visit
	Placebo	1107	10	1 day early
	Placebo	1107	13	1 day late
	Placebo	1107	14	3 days early. Patient discontinued at this visit
	Flx	1118	5	1 day early, Randomization phase.
	Flx	1118	8	2 days late
	Flx	1118	10	9 days early. Patient discontinued at this visit
	Placebo	1120	8	1 day early.
	Placebo	1121	4	1 day early, Placebo Washout phase. Only placebo study drug dispensed
	Placebo	1121	10	1 day late
	NR	1123	2	1 day late, evaluation phase no study drug dispensed, patient discontinued at this visit
	Placebo	1126	2	2 days early, evaluation phase no study drug dispensed
	Placebo	1126	6	1 day early
	Placebo	1126	11	1 day early
	Placebo	1126	13	4 days early
	NR	1127	2	1 day late, evaluation phase no study drug dispensed, patient discontinued at this visit
	Flx	1131	6	1 day late
	NR	1132	2	1 day early, evaluation phase no study drug dispensed
	NR	1133	2	1 day late, evaluation phase no study drug dispensed, patient discontinued at this visit
	Placebo	1134	2	1 day early, evaluation phase no

Type of Violation	Therapy	Patient Number	Visit Number	Comments
				study drug dispensed
	Placebo	1134	6	1 day late
	Placebo	1135	3	1 day early, evaluation phase no study drug dispensed
	Placebo	1135	12	1 day early
	Flx	1137	15	3 days late. Patient discontinued at this visit
	NR	1140	2	6 days late, evaluation phase no study drug dispensed, patient discontinued at this visit
	Flx	1141	12	3 days late. Patient discontinued at this visit
	Placebo	1143	2	1 day early, evaluation phase no study drug dispensed
	Placebo	1143	13	2 days early
	Placebo	1143	14	2 days late
	Flx	1153	2	4 days late, evaluation phase no study drug dispensed
	Flx	1153	9	2 days late
	Flx	1156	11	5 days late.
	Placebo	1201	5	1 day late, Randomization phase.
	Placebo	1201	7	2 days late
	Placebo	1201	9	1 day late
	Flx	1202	3	1 day late, evaluation phase no study drug dispensed
	Flx	1202	13	1 day late
	Flx	1202	14	1 day early
	Flx	1204	8	2 days late
	Flx	1204	10	1 day late. Patient discontinued at this visit
	Flx	1205	12	2 days late
	Flx	1205	14	4 days late
	Placebo	1206	4	2 days late, Placebo Washout phase. Only placebo study drug dispensed
	Placebo	1207	11	1 day early
	Placebo	1207	15	3 days late
	Flx	1208	2	1 day late, evaluation phase no study drug dispensed
	Flx	1208	4	1 day late, Placebo Washout phase. Only placebo study drug dispensed
	Flx	1208	11	2 days late
	Flx	1208	13	1 day late
	Flx	1209	5	1 day late, Randomization phase.

Type of Violation	Therapy	Patient Number	Visit Number	Comments
	Flx	1209	8	3 days early.
	Flx	1209	9	2 days early
	NR	1210	3	12 days late, evaluation phase no study drug dispensed, patient discontinued at this visit
	Flx	1211	7	1 day early
	Flx	1211	10	5 days late.
	Flx	1211	12	4 days late. Patient discontinued at this visit
	Placebo	1212	2	1 day early, evaluation phase no study drug dispensed
	Placebo	1212	4	2 days late, Placebo Washout phase. Only placebo study drug dispensed
	Placebo	1212	5	1 day late, Randomization phase.
	Placebo	1212	7	17 days late. Patient discontinued at this visit
	Flx	1213	7	2 days late
	Flx	1213	11	1 day late
	Flx	1213	13	2 days early
	Flx	1215	7	23 days late. Patient discontinued at this visit
	Placebo	1216	2	1 day late, evaluation phase no study drug dispensed
	Placebo	1216	12	2 days late
	Placebo	1216	13	1 day late
	Placebo	1216	15	1 day early
	Flx	1217	2	2 days late, evaluation phase no study drug dispensed
	Flx	1217	7	1 day early
	Flx	1217	8	4 days late
	Flx	1217	9	1 day late
	Flx	1217	10	2 days late
	NR	1218	2	5 days late, evaluation phase no study drug dispensed
	NR	1218	3	5 days late, evaluation phase no study drug dispensed
	Flx	1220	2	3 days early, evaluation phase no study drug dispensed
	Flx	1220	3	2 days late, evaluation phase no study drug dispensed
	Flx	1220	6	1 day late
	Flx	1220	9	1 day late
	Flx	1220	10	3 days late
	Placebo	1221	2	1 day early, evaluation phase no

Type of Violation	Therapy	Patient Number	Visit Number	Comments
				study drug dispensed
	Placebo	1221	10	3 days late
	Placebo	1222	2	17 days late, evaluation phase no study drug dispensed.
	Placebo	1222	3	5 days late, evaluation phase no study drug dispensed
	Placebo	1222	6	1 day early
	Placebo	1222	9	1 day early
	Placebo	1222	14	4 days late
	Placebo	1222	15	6 days late. Patient discontinued at this visit
	Placebo	1223	3	8 days late, evaluation phase no study drug dispensed
	Placebo	1223	6	3 days late
	Placebo	1223	10	5 days late.
	Placebo	1223	11	2 days late
	Placebo	1223	12	12 days late. Patient discontinued at this visit
	Flx	1225	2	1 day late, evaluation phase no study drug dispensed
	Flx	1225	3	3 days late, evaluation phase no study drug dispensed
	Flx	1225	10	1 day early
	Flx	1225	12	3 days early
	Flx	1225	13	1 day early
	Flx	1225	14	5 days late.
	Placebo	1301	4	1 day early, Placebo Washout phase. Only placebo study drug dispensed
	Placebo	1301	8	2 days early.
	Placebo	1304	4	1 day late, Placebo Washout phase. Only placebo study drug dispensed
	Placebo	1304	5	2 days early, Randomization phase.
	Flx	1305	10	2 days late
	Flx	1305	11	4 days early
	NR	1306	3	2 days late, evaluation phase no study drug dispensed, patient discontinued at this visit
	Placebo	1311	6	5 days late
	Placebo	1504	9	12 days late. Patient discontinued at this visit
	NR	1508	2	2 days late, evaluation phase no study drug dispensed, patient

Type of Violation	Therapy	Patient Number	Visit Number	Comments
				discontinued at this visit
	Flx	1510	14	1 day late
	Flx	1514	3	1 day early, evaluation phase no study drug dispensed
	Flx	1514	7	4 days late. Patient discontinued at this visit
	Flx	1515	7	1 day late
	Flx	1601	2	1 day early, evaluation phase no study drug dispensed
	Flx	1601	11	1 day late
	Flx	1601	12	2 days late
	Flx	1601	13	2 days early
	Flx	1602	6	3 days late
	Flx	1602	13	3 days early. Patient discontinued at this visit
	Flx	1603	8	1 day early. Patient discontinued at this visit
	Flx	1604	4	1 day early, Placebo Washout phase. Only placebo study drug dispensed
	Flx	1605	11	2 days late
	Flx	1605	14	2 days early
	Flx	1605	15	2 days late. Patient discontinued at this visit
	Flx	1606	3	1 day early, evaluation phase no study drug dispensed
	Flx	1606	6	1 day early
	Flx	1606	10	1 day late
	Flx	1606	11	2 days late
	Placebo	1608	2	3 days late, evaluation phase no study drug dispensed
	Flx	1609	8	1 day late
	Flx	1612	3	5 days late, evaluation phase no study drug dispensed
	Flx	1612	6	2 days late
	Flx	1612	12	2 days late
	Flx	1652	11	2 days early. Patient discontinued at this visit
	Flx	1654	9	1 day late
	Flx	1654	10	2 days early
	Flx	1654	12	2 days early
	Flx	1654	15	2 days late
	Placebo	1655	2	1 day early, evaluation phase no study drug dispensed
	Placebo	1655	10	3 days late

Type of Violation	Therapy	Patient Number	Visit Number	Comments
	Placebo	1655	15	2 days early
	Placebo	1656	9	1 day late
	Placebo	1656	10	2 days early
	Placebo	1656	14	1 day late
	Placebo	1656	15	1 day late
	Placebo	1657	3	4 days late, evaluation phase no study drug dispensed
	Flx	1659	13	1 day early
	NR	1661	4	23 days late, Placebo Washout phase. Only placebo study drug dispensed, patient discontinued at this visit
	Flx	1667	4	1 day late, Placebo Washout phase. Only placebo study drug dispensed
	Flx	1667	5	1 day early, Randomization phase.
	Flx	1667	9	1 day late
	Placebo	1669	2	7 days late, evaluation phase no study drug dispensed
	Placebo	1669	5	2 days late, Randomization phase.
	Placebo	1669	10	1 day late
	Placebo	1669	11	3 days late
	Flx	1701	8	1 day early.
	Flx	1701	12	1 day late
	Flx	1701	13	2 days early
	Flx	1702	6	1 day early
	Flx	1702	9	2 days late
	Flx	1702	10	4 days early
	NR	1703	2	1 day late, evaluation phase no study drug dispensed, patient discontinued at this visit
	NR	1704	3	2 days early, evaluation phase no study drug dispensed, patient discontinued at this visit
	Placebo	1705	2	1 day early, evaluation phase no study drug dispensed
	Placebo	1705	5	1 day early, Randomization phase.
	Placebo	1705	11	1 day early
	Placebo	1705	14	1 day early
	NR	1802	2	6 days late, evaluation phase no study drug dispensed, patient discontinued at this visit
	NR	1804	2	1 day early, evaluation phase no study drug dispensed
	NR	1804	3	4 days early, evaluation phase no

Type of Violation	Therapy	Patient Number	Visit Number	Comments
				study drug dispensed, patient discontinued at this visit
	Placebo	1901	2	3 days late, evaluation phase no study drug dispensed
	Placebo	1901	9	7 days early.
	Placebo	1901	12	1 day early
	NR	1902	2	16 days late, evaluation phase no study drug dispensed
	NR	1902	3	3 days late, evaluation phase no study drug dispensed
	Placebo	1903	2	18 days late, evaluation phase no study drug dispensed
	Placebo	1903	3	1 day late, evaluation phase no study drug dispensed
	Flx	1904	2	14 days late, evaluation phase no study drug dispensed
	Flx	1904	11	12 days late. Patient discontinued at this visit
	Flx	1905	2	4 days late, evaluation phase no study drug dispensed
	Flx	1905	4	1 day early, Placebo Washout phase. Only placebo study drug dispensed
	Flx	1905	11	4 days late
	Flx	1906	3	5 days late, evaluation phase no study drug dispensed
	Flx	1906	4	1 day early, Placebo Washout phase. Only placebo study drug dispensed
	Flx	1906	10	2 days late
	Flx	1906	12	2 days late
	Placebo	1907	2	14 days late, evaluation phase no study drug dispensed
	Placebo	1907	4	2 days late, Placebo Washout phase. Only placebo study drug dispensed
	Placebo	1907	11	2 days late
	Placebo	1907	12	1 day late
	Placebo	1907	13	27 days late. Patient discontinued at this visit
	NR	1908	2	15 days late, evaluation phase no study drug dispensed, patient discontinued at this visit
	NR	1910	2	5 days late, evaluation phase no study drug dispensed

Type of Violation	Therapy	Patient Number	Visit Number	Comments
	NR	1910	3	2 days early, evaluation phase no study drug dispensed
	NR	1910	4	6 days late, Placebo Washout phase. Only placebo study drug dispensed, patient discontinued at this visit
	Placebo	1913	2	7 days late, evaluation phase no study drug dispensed
	Placebo	1913	4	3 days late, Placebo Washout phase. Only placebo study drug dispensed
	Placebo	1913	6	2 days early
	Placebo	1913	7	1 day late
	Placebo	1913	11	1 day late
	Placebo	1913	12	2 days early
	Placebo	1914	2	1 day early, evaluation phase no study drug dispensed
	Placebo	1914	14	2 days late
	Flx	1915	9	1 day early
	Placebo	1918	10	1 day early
	Placebo	1918	11	1 day late
	Placebo	1918	12	2 days late
	Flx	1919	11	2 days late
	Flx	1919	15	2 days late. Patient discontinued at this visit
	Flx	1921	9	2 days late
	NR	1923	3	5 days early, evaluation phase no study drug dispensed, patient discontinued at this visit
	Flx	1924	10	3 days late
	Flx	1924	14	1 day early
	Placebo	1925	2	1 day early, evaluation phase no study drug dispensed
	Placebo	1925	4	1 day early, Placebo Washout phase. Only placebo study drug dispensed
	Placebo	1925	6	1 day late
	Placebo	1925	7	2 days early
	Placebo	1925	10	3 days late
	Placebo	1925	15	3 days late. Patient discontinued at this visit
	Placebo	1927	2	1 day late, evaluation phase no study drug dispensed
	Placebo	1927	3	1 day early, evaluation phase no study drug dispensed

Type of Violation	Therapy	Patient Number	Visit Number	Comments
	Placebo	1927	6	1 day late
	Placebo	1927	12	1 day early
	NR	2101	2	3 days late, evaluation phase no study drug dispensed, patient discontinued at this visit
	Placebo	2201	5	1 day early, Randomization phase.
	Flx	2202	2	5 days late, evaluation phase no study drug dispensed
	Flx	2202	5	1 day late, Randomization phase.
	Flx	2202	9	1 day late
	Flx	2202	10	3 days late
	Flx	2202	11	6 days late.
	Flx	2202	12	3 days late
	Flx	2202	13	1 day late
	Flx	2202	14	10 days late. Patient discontinued at this visit
	Placebo	2203	3	2 days early, evaluation phase no study drug dispensed
	Flx	2204	3	2 days early, evaluation phase no study drug dispensed
	Flx	2205	5	1 day late, Randomization phase.
	Flx	2205	12	2 days late
	Placebo	2206	2	1 day early, evaluation phase no study drug dispensed
	Placebo	2206	3	1 day late, evaluation phase no study drug dispensed
	Placebo	2207	7	1 day late
	Placebo	2207	8	2 days early.
	Flx	2208	5	1 day early, Randomization phase.
	Placebo	2210	3	1 day early, evaluation phase no study drug dispensed
	Placebo	2210	5	1 day late, Randomization phase.
	Placebo	2210	8	18 days late. Patient discontinued at this visit
	Placebo	2212	2	1 day early, evaluation phase no study drug dispensed
	Placebo	2212	12	3 days late
	Placebo	2212	13	2 days late. Patient discontinued at this visit
	Placebo	2213	3	1 day early, evaluation phase no study drug dispensed
	Placebo	2213	8	2 days late
	Flx	2214	3	1 day late, evaluation phase no study drug dispensed
	Flx	2214	4	1 day late, Placebo Washout

Type of Violation	Therapy	Patient Number	Visit Number	Comments
				phase. Only placebo study drug dispensed
	Flx	2214	11	3 days late
	Flx	2214	15	2 days late
	NR	2215	2	4 days late, evaluation phase no study drug dispensed, patient discontinued at this visit
	Flx	2216	6	1 day late
	Flx	2216	12	2 days late
	Flx	2216	13	1 day late
	Flx	2216	14	2 days late
	Placebo	2217	4	1 day early, Placebo Washout phase. Only placebo study drug dispensed
	Placebo	2217	11	1 day late
	Placebo	2217	12	2 days early
	Placebo	2217	14	4 days late
	Placebo	2218	2	10 days late, evaluation phase no study drug dispensed
	Placebo	2218	10	3 days late
	NR	2219	4	19 days late, Placebo Washout phase. Only placebo study drug dispensed, patient discontinued at this visit
	Flx	2220	7	1 day late
	Flx	2220	8	2 days early.
	Flx	2220	13	2 days late
	Flx	2220	14	2 days early. Patient discontinued at this visit
	Placebo	2221	2	5 days late, evaluation phase no study drug dispensed
	Placebo	2221	3	2 days late, evaluation phase no study drug dispensed
	Placebo	2221	4	1 day late, Placebo Washout phase. Only placebo study drug dispensed
	Placebo	2221	5	1 day late, Randomization phase.
	Placebo	2221	10	5 days late. Patient discontinued at this visit
Missing Study Procedures- Vitals- Blood Pressure and Heart Rate				
	Placebo	135	7	Vitals not done.
	NR	136	3	Vitals not done.

Type of Violation	Therapy	Patient Number	Visit Number	Comments
	Placebo	140	7	Vitals not done.
	Placebo	143	6	Vitals not done.
	NR	145	3	Vitals not done.
	Placebo	201	5	Vitals not done.
	Placebo	210	14	Vitals not done.
	NR	213	3	Vitals not done.
	NR	214	2	Vitals not done.
	Flx	313	9	Vitals not done.
	Flx	318	8	Vitals not done.
	Placebo	323	10	Vitals not done.
	NR	402	1	Vitals not done.
	Placebo	403	1	Vitals not done.
	Placebo	407	2	Vitals not done.
	Flx	415	1	Vitals not done.
	Flx	419	11	Vitals not done.
	Flx	424	1	Vitals not done.
	Placebo	427	8	Vitals not done.
	Placebo	432	7	Vitals not done.
	NR	440	1	Vitals not done.
	Flx	441	1	Vitals not done.
	Placebo	806	8	Vitals not done.
	Placebo	808	12	Vitals not done.
	Placebo	905	9	Vitals not done.
	Flx	913	12	Vitals not done.
	Placebo	919	11	Vitals not done.
	Flx	1152	8	Vitals not done.
	Placebo	1206	10	Vitals not done.
	Flx	1211	12	Vitals not done.
	Flx	1215	7	Vitals not done.
	Flx	1217	11	Vitals not done.
	Placebo	1223	12	Vitals not done.
	Placebo	1308	13	Vitals not done.
	Placebo	1309	10	Vitals not done.
	Placebo	1311	6	Vitals not done.
	Placebo	1513	1	Blood pressure not obtained. The patient's arm was too small for adult blood pressure cup. A child cup was ordered and pressure will be taken at next visit.

Type of Violation	Therapy	Patient Number	Visit Number	Comments
	Placebo	1513	9	Vitals not done.
	Flx	1515	12	Vitals not done.
	Flx	1606	12	Vitals not done.
	Flx	1667	6	Vitals not done.
	NR	1908	1	Vitals not done.
	Flx	1915	12	Vitals not done.
	Placebo	2201	6	Vitals not done.
	Placebo	2221	10	Vitals not done.
Procedure Violation or Missing Study Procedures- Vitals- Temperature				
	Flx	104	8	Temperature not done.
	Flx	104	13	Temperature not done.
	Flx	114	3	Temperature not done.
	Flx	114	8	Temperature not done.
	Placebo	119	13	Oral thermometer used because the ear thermometer was not working.
	Flx	133	10	Oral temperature taken because site was out of ear covers.
	Placebo	135	6	Temperature not done.
	Placebo	135	7	Temperature not done.
	NR	136	3	Temperature not done.
	Placebo	140	7	Temperature not done.
	Flx	141	1	Temperature not done.
	Flx	141	4	Temperature not done.
	Flx	141	6	Temperature was taken orally because site was out of ear covers.
	Placebo	143	6	Temperature not done.
	NR	145	3	Temperature not done.
	Flx	150	3	Temperature was taken orally because site was out of ear covers.
	Flx	150	10	Temperature not done.
	Placebo	153	1	Temperature was taken orally because site was out of ear covers.
	Placebo	201	1-4	Oral thermometer used.
	Placebo	201	5	Temperature not done.
	Flx	202	1-6	Oral thermometer used.
	Placebo	203	1-9	Oral thermometer used.
	Flx	204	1-13	Oral thermometer used.

Type of Violation	Therapy	Patient Number	Visit Number	Comments
	Placebo	205	1-8	Oral thermometer used.
	Placebo	206	All	Oral thermometer used.
	Placebo	206	1	Temperature not done.
	Flx	208	1-3	Oral thermometer used.

Type of Violation	Therapy	Patient Number	Visit Number	Comments
	Placebo	210	14	Temperature not done.
	NR	213	3	Temperature not done.
	NR	214	2	Temperature not done.
	Flx	313	9	Temperature not done.
	Flx	318	8	Temperature not done.
	Placebo	323	10	Temperature not done.
	Placebo	339	10	Temperature not done.
	Placebo	403	1	Temperature not done.
	NR	405	1	Temperature not done.
	Flx	415	1	Temperature not done.
	Flx	419	11	Temperature not done.
	Flx	424	1	Temperature not done.
	Placebo	427	8	Temperature not done.
	Placebo	432	7	Temperature not done.
	NR	440	1	Temperature not done.
	Flx	441	1	Temperature not done.
	Placebo	601	2	Temperature not done.
	NR	801	1	Temperature not done.
	NR	801	2	Temperature not done.
	NR	801	3	Temperature not done.
	Placebo	806	8	Temperature not done.
	Placebo	808	12	Temperature not done.
	Flx	810	2	Temperature not done.
	Flx	901	1	Temperature not done.
	NR	902	1	Temperature not done.
	Placebo	905	9	Temperature not done.
	Flx	913	12	Temperature not done.
	Placebo	919	11	Temperature not done.
	Flx	1152	8	Temperature not done.
	Placebo	1206	10	Temperature not done.
	Flx	1211	12	Temperature not done.
	Flx	1215	7	Temperature not done.
	Flx	1217	11	Temperature not done.
	Placebo	1223	12	Temperature not done.
	Placebo	1308	13	Temperature not done.
	Placebo	1309	10	Temperature not done.
	Placebo	1311	6	Temperature not done.
	Placebo	1513	9	Temperature not done.
	Flx	1515	12	Temperature not done.
	Flx	1606	12	Temperature not done.
	Placebo	1608	1	Temperature not done.
	Flx	1612	6	Temperature not done.
	Placebo	1705	7	Temperature not done.
	Placebo	1705	9	Temperature not done.

Type of Violation	Therapy	Patient Number	Visit Number	Comments
	NR	1908	1	Temperature not done.
	Flx	1915	12	Temperature not done.
	Placebo	2201	6	Temperature not done.
	Placebo	2221	10	Temperature not done.
Missing Study Procedures- Weight				
	Placebo	135	7	Weight not done.
	NR	136	3	Weight not done.
	Placebo	140	7	Weight not done.
	Placebo	143	6	Weight not done.
	NR	145	3	Weight not done.
	Placebo	201	5	Weight not done.
	Flx	204	14	Weight not done.
	Placebo	210	14	Weight not done.
	NR	211	2	Weight not done.
	NR	213	3	Weight not done.
	NR	214	2	Weight not done.
	Flx	313	9	Weight not done.
	Flx	318	8	Weight not done.
	Placebo	323	10	Weight not done.
	Flx	401	12	Weight not done.
	Placebo	407	13	Weight not done.
	Flx	419	11	Weight not done.
	Placebo	427	8	Weight not done.
	Placebo	432	7	Weight not done.
	NR	440	4	Weight not done.
	NR	801	4	Weight not done.
	NR	803	4	Weight not done.
	Placebo	806	8	Weight not done.
	Placebo	808	12	Weight not done.
	Flx	814	13	Weight not done.
	Placebo	905	9	Weight not done.
	Placebo	919	11	Weight not done.
	Flx	1152	8	Weight not done.
	Flx	1203	11	Weight not done.
	Flx	1204	10	Weight not done.
	Placebo	1206	10	Weight not done.
	Flx	1217	11	Weight not done.
	Placebo	1223	12	Weight not done.
	Placebo	1308	13	Weight not done.
	Placebo	1309	10	Weight not done.
	Placebo	1311	6	Weight not done.

Type of Violation	Therapy	Patient Number	Visit Number	Comments
	Placebo	1513	9	Weight not done.
	Flx	1515	12	Weight not done.
	Flx	1606	12	Weight not done.
	NR	1902	4	Weight not done.
	NR	1912	4	Weight not done.
	Flx	1915	12	Weight not done.
	NR	1922	4	Weight not done.
	Placebo	2201	6	Weight not done.
	Placebo	2221	10	Weight not done.
Missing Study Procedures- Height				
	Placebo	135	7	Height not done.
	NR	136	3	Height not done.
	Placebo	140	7	Height not done.
	Placebo	143	6	Height not done.
	NR	145	3	Height not done.
	Placebo	201	5	Height not done.
	Flx	204	14	Height not done.
	Placebo	210	14	Height not done.
	NR	211	2	Height not done.
	NR	213	3	Height not done.
	NR	214	2	Height not done.
	Flx	313	9	Height not done.
	Flx	318	8	Height not done.
	Placebo	323	10	Height not done.
	Flx	401	12	Height not done.
	Placebo	407	13	Height not done.
	Flx	419	11	Height not done.
	Placebo	427	8	Height not done.
	Placebo	432	7	Height not done.
	NR	801	4	Height not done.
	NR	803	4	Height not done.
	Placebo	806	8	Height not done.
	Placebo	808	12	Height not done.
	Flx	814	13	Height not done.
	Placebo	905	9	Height not done.
	Placebo	919	11	Height not done.
	Placebo	1102	9	Height not done.
	Flx	1152	8	Height not done.
	Flx	1203	11	Height not done.
	Flx	1204	10	Height not done.
	Placebo	1206	10	Height not done.

Type of Violation	Therapy	Patient Number	Visit Number	Comments
	Flx	1217	11	Height not done.
	Placebo	1223	12	Height not done.
	Placebo	1308	13	Height not done.
	Placebo	1309	10	Height not done.
	Placebo	1311	6	Height not done.
	Placebo	1506	15	Height not done.
	NR	1512	4	Height not done.
	Placebo	1513	9	Height not done.
	Flx	1514	7	Height not done.
	Flx	1515	12	Height not done.
	Flx	1606	12	Height not done.
	Flx	1701	15	Height not done.
	Placebo	1705	15	Height not done.
	NR	1902	4	Height not done.
	NR	1912	4	Height not done.
	Flx	1915	12	Height not done.
	NR	1922	4	Height not done.
	Placebo	2201	6	Height not done.
	Flx	2220	14	Height not done.
	Placebo	2221	10	Height not done.
Procedure Violations or Missing Study Procedures- CDRS-R				
	Placebo	135	7	CDRS-R not done.
	Flx	139	15	CDRS-R not done.
	Placebo	140	7	CDRS-R not done.
	Placebo	143	6	CDRS-R not done.
	Placebo	201	5	CDRS-R not done.
	Flx	204	8	CDRS-R not done.
	Placebo	210	14	CDRS-R not done.
	Placebo	306	11	CDRS-R not done.
	Flx	313	9	CDRS-R not done.
	Flx	318	8	CDRS-R not done.
	Placebo	323	10	CDRS-R not done.
	Placebo	417	9	CDRS-R not done.
	Flx	419	11	CDRS-R not done.
	Placebo	427	8	CDRS-R not done.
	Placebo	432	7	CDRS-R not done.
	Placebo	806	8	CDRS-R not done.
	Placebo	807	5	CDRS-R not done.
	Placebo	808	12	CDRS-R not done.
	Flx	813	13	CDRS-R not done.
	Placebo	905	9	CDRS-R not done.

Type of Violation	Therapy	Patient Number	Visit Number	Comments
	Flx	913	12	CDRS-R not done.
	Placebo	919	11	CDRS-R not done.
	Placebo	1134	7	CDRS-R not done.
	Flx	1152	8	CDRS-R not done.
	Placebo	1206	10	CDRS-R not done.
	Flx	1211	12	CDRS-R not done.
	Flx	1215	7	CDRS-R not done.
	Flx	1217	11	CDRS-R not done.
	Placebo	1223	12	CDRS-R not done.
	Placebo	1308	13	CDRS-R not done.
	Placebo	1309	10	CDRS-R not done.
	Placebo	1311	6	CDRS-R not done.
	Placebo	1513	9	CDRS-R not done.
	Flx	1515	12	CDRS-R not done.
	Flx	1606	12	CDRS-R not done.
	Flx	1654	3	CDRS-R done by same rater at Visits 1 and 2.
	Placebo	1903	9	CDRS-R not done.
	Flx	1915	12	CDRS-R not done.
	Placebo	2201	6	CDRS-R not done.
	Placebo	2203	1	CDRS-R rated by 2 different raters.
	Placebo	2203	2	CDRS-R rated by 2 different raters.
	Placebo	2203	3	CDRS-R rated by 2 different raters.
	Placebo	2203	4	CDRS-R rated by 2 different raters.
	Placebo	2203	5	CDRS-R rated by 2 different raters.
	Placebo	2203	7	CDRS-R rated by 2 different raters.
	Flx	2204	1	CDRS-R rated by 2 different raters.
	Flx	2204	2	CDRS-R rated by 2 different raters.
	Flx	2204	3	CDRS-R rated by 2 different raters.
	Flx	2204	4	CDRS-R rated by 2 different raters.
	Flx	2204	5	CDRS-R rated by 2 different raters.
	Flx	2204	7	CDRS-R rated by 2 different raters.

Type of Violation	Therapy	Patient Number	Visit Number	Comments
	Placebo	2221	10	CDRS-R not done.
Missing Study Procedures- CGI- Improvement				
	Placebo	135	7	CGI-Improvement not done.
	Flx	139	15	CGI-Improvement not done.
	Placebo	140	7	CGI-Improvement not done.
	Placebo	210	14	CGI-Improvement not done.
	Placebo	306	11	CGI-Improvement not done.
	Flx	313	9	CGI-Improvement not done.
	Flx	318	8	CGI-Improvement not done.
	Placebo	323	10	CGI-Improvement not done.
	Placebo	417	9	CGI-Improvement not done.
	Flx	419	11	CGI-Improvement not done.
	Placebo	427	8	CGI-Improvement not done.
	Placebo	432	7	CGI-Improvement not done.
	Placebo	806	8	CGI-Improvement not done.
	Placebo	808	12	CGI-Improvement not done.
	Flx	813	13	CGI-Improvement not done.
	Placebo	905	9	CGI-Improvement not done.
	Flx	913	12	CGI-Improvement not done.
	Placebo	919	11	CGI-Improvement not done.
	Flx	1152	8	CGI-Improvement not done.
	Placebo	1206	10	CGI-Improvement not done.
	Flx	1211	12	CGI-Improvement not done.
	Flx	1215	7	CGI-Improvement not done.
	Flx	1217	11	CGI-Improvement not done.
	Placebo	1223	12	CGI-Improvement not done.
	Placebo	1308	13	CGI-Improvement not done.
	Placebo	1309	10	CGI-Improvement not done.
	Placebo	1311	6	CGI-Improvement not done.
	Placebo	1513	9	CGI-Improvement not done.
	Flx	1515	12	CGI-Improvement not done.
	Flx	1606	12	CGI-Improvement not done.
	Placebo	1903	9	CGI-Improvement not done.
	Flx	1915	12	CGI-Improvement not done.
	Placebo	2201	6	CGI-Improvement not done.
	Placebo	2221	10	CGI-Improvement not done.
Missing Study Procedures- CGI- Severity				
	Placebo	135	7	CGI- Severity not done.
	Flx	139	15	CGI- Severity not done.

Type of Violation	Therapy	Patient Number	Visit Number	Comments
	Placebo	140	7	CGI- Severity not done.
	Placebo	210	14	CGI- Severity not done.
	Placebo	306	11	CGI- Severity not done.
	Flx	313	9	CGI- Severity not done.
	Flx	318	8	CGI- Severity not done.
	Placebo	323	10	CGI- Severity not done.
	Placebo	417	9	CGI- Severity not done.
	Flx	419	11	CGI- Severity not done.
	Placebo	427	8	CGI- Severity not done.
	Placebo	432	7	CGI- Severity not done.
	Placebo	806	8	CGI- Severity not done.
	Placebo	808	12	CGI- Severity not done.
	Flx	813	13	CGI- Severity not done.
	Placebo	905	9	CGI- Severity not done.
	Flx	913	12	CGI- Severity not done.
	Placebo	919	11	CGI- Severity not done.
	Flx	1152	8	CGI- Severity not done.
	Placebo	1206	10	CGI- Severity not done.
	Flx	1211	12	CGI- Severity not done.
	Flx	1215	7	CGI- Severity not done.
	Flx	1217	11	CGI- Severity not done.
	Placebo	1223	12	CGI- Severity not done.
	Placebo	1308	13	CGI- Severity not done.
	Placebo	1309	10	CGI- Severity not done.
	Placebo	1311	6	CGI- Severity not done.
	Placebo	1513	9	CGI- Severity not done.
	Flx	1515	12	CGI- Severity not done.
	Flx	1606	12	CGI- Severity not done.
	Placebo	1903	9	CGI- Severity not done.
	Flx	1915	12	CGI- Severity not done.
	Placebo	2201	6	CGI- Severity not done.
	Placebo	2221	10	CGI- Severity not done.
Procedure Violations or Missing Study Procedures- BDI/CDI				
	Placebo	135	7	BDI/CDI not done.
	NR	136	3	BDI/CDI not done.
	Placebo	140	7	BDI/CDI not done.
	Placebo	143	6	BDI/CDI not done.
	NR	145	3	BDI/CDI not done.
	Placebo	201	5	BDI/CDI not done.
	Flx	204	8	CDI completed instead of BDI.

Type of Violation	Therapy	Patient Number	Visit Number	Comments
	Flx	208	1	BDI done instead of CDI per site error.
	Placebo	210	14	BDI/CDI not done.
	NR	212	2	BDI/CDI not done.
	Flx	302	9	BDI/CDI not done.
	Flx	305	3	BDI/CDI not done.
	Placebo	306	11	BDI/CDI not done.
	Flx	307	12	BDI/CDI not done.
	Placebo	309	15	BDI/CDI not done.
	Flx	313	3	BDI/CDI not done.
	Flx	318	8	BDI/CDI not done.
	Placebo	323	10	BDI/CDI not done.
	Flx	332	9	BDI/CDI not done.
	Placebo	343	12	BDI/CDI not done.
	Flx	401	12	BDI/CDI not done.
	Placebo	407	11	BDI/CDI not done.
	Flx	419	11	BDI/CDI not done.
	Flx	422	10	BDI/CDI not done.
	Placebo	427	8	BDI/CDI not done.
	Placebo	432	7	BDI/CDI not done.
	Placebo	806	8	BDI/CDI not done.
	Placebo	807	3	Patient did not do CDI, rater had patient do BDI in error.
	Placebo	808	8	BDI/CDI not done.
	Placebo	905	9	BDI/CDI not done.
	Flx	913	12	BDI/CDI not done.
	Placebo	919	11	BDI/CDI not done.
	Placebo	1122	1	BDI/CDI not done.
	Flx	1129	10	BDI/CDI not done.
	Flx	1129	11	BDI/CDI not done.
	Flx	1131	8	BDI/CDI not done.
	Placebo	1139	1	BDI/CDI not done.
	NR	1140	1	BDI/CDI not done.
	Flx	1152	2	CDI done instead of BDI.

Type of Violation	Therapy	Patient Number	Visit Number	Comments
	Flx	1152	8	BDI/CDI not done.
	Flx	1156	2	BDI/CDI not done.
	Flx	1203	11	BDI/CDI not done.
	Placebo	1206	10	BDI/CDI not done.
	Flx	1211	12	BDI/CDI not done.
	Flx	1217	11	BDI/CDI not done.
	Placebo	1223	12	BDI/CDI not done.
	Placebo	1308	13	BDI/CDI not done.
	Placebo	1309	10	BDI/CDI not done.
	Placebo	1311	6	BDI/CDI not done.
	Placebo	1513	9	BDI/CDI not done.
	Flx	1514	7	BDI/CDI not done.
	Flx	1515	12	BDI/CDI not done.
	Flx	1606	12	BDI/CDI not done.
	Flx	1658	8	BDI/CDI not done.
	Flx	1702	4	BDI/CDI not done.
	Placebo	1705	1	BDI/CDI not done.
	Placebo	1903	9	BDI/CDI not done.
	Flx	1906	8	BDI/CDI not done.
	NR	1912	3	BDI/CDI not done.
	Placebo	1913	1	BDI/CDI not done.
	Placebo	1913	3	BDI/CDI not done.
	Placebo	1913	8	BDI/CDI not done.
	Flx	1915	3	BDI/CDI not done.
	Placebo	1927	13	BDI/CDI not done.
	NR	2101	1,2	Site unable to locate CDI pages for Visit 1 and Visit 2, therefore the pages were not completed
	Placebo	2201	3	BDI/CDI not done.
	Flx	2202	11	Principal Investigator discarded original pages 1 and 2 of CDI.
	Flx	2204	8	BDI/CDI not done.
	Flx	2205	4	BDI/CDI not done.
	Placebo	2207	13	BDI/CDI not done.
	Flx	2208	2	BDI/CDI not done.
	Flx	2208	3	BDI/CDI not done.
	Flx	2208	4	BDI/CDI not done.
	Flx	2208	8	BDI/CDI not done.
	Flx	2208	10	BDI/CDI not done.
	Flx	2208	2,4,8,10	Patient did not answer Item 6 on CDI because patient believes none of items

Type of Violation	Therapy	Patient Number	Visit Number	Comments
				applied to him.
	Flx	2214	13	BDI/CDI not done.
	Flx	2220	14	BDI/CDI not done.
	Placebo	2221	1	Patient completed CDI instead of the BDI.

Type of Violation	Therapy	Patient Number	Visit Number	Comments
	Placebo	2221	10	BDI/CDI not done.
Missing Study Procedures- HAMA				
	Placebo	135	7	HAMA not done.
	Flx	139	15	HAMA not done.
	Placebo	140	7	HAMA not done.
	Placebo	143	6	HAMA not done.
	Placebo	201	5	HAMA not done.
	Placebo	210	14	HAMA not done.
	Placebo	306	11	HAMA not done.
	Flx	307	12	HAMA not done.
	Placebo	309	2	HAMA not done.
	Flx	313	9	HAMA not done.
	Flx	318	8	HAMA not done.
	Placebo	323	10	HAMA not done.
	Placebo	343	12	HAMA not done.
	Placebo	356	11	HAMA not done.
	Flx	401	12	HAMA not done.
	Flx	419	11	HAMA not done.
	Placebo	427	8	HAMA not done.
	Placebo	432	7	HAMA not done.
	Placebo	806	8	HAMA not done.
	Placebo	808	12	HAMA not done.
	Placebo	905	9	HAMA not done.
	Flx	913	12	HAMA not done.
	Flx	915	4	HAMA not done.
	Placebo	919	11	HAMA not done.
	Placebo	1120	15	HAMA not done.
	Placebo	1121	15	HAMA not done.
	Flx	1152	8	HAMA not done.
	Placebo	1206	10	HAMA not done.
	Flx	1211	12	HAMA not done.
	Flx	1217	11	HAMA not done.
	Placebo	1223	12	HAMA not done.
	Placebo	1308	13	HAMA not done.
	Placebo	1309	10	HAMA not done.
	Placebo	1311	6	HAMA not done.
	Placebo	1513	9	HAMA not done.
	Flx	1515	12	HAMA not done.
	Flx	1606	12	HAMA not done.
	Placebo	1903	9	HAMA not done.
	Flx	1915	12	HAMA not done.
	Placebo	2201	6	HAMA not done.

Type of Violation	Therapy	Patient Number	Visit Number	Comments
	Flx	2204	8	HAMA not done.
	Placebo	2212	13	HAMA not done.
	Placebo	2221	10	HAMA not done.
Missing Study Procedures- GAF				
	Placebo	135	7	GAF not done.
	NR	136	3	GAF not done.
	Flx	139	15	GAF not done.
	Placebo	140	7	GAF not done.
	Placebo	143	6	GAF not done.
	NR	145	3	GAF not done.
	Placebo	210	14	GAF not done.
	NR	214	2	GAF not done.
	Flx	313	9	GAF not done.
	Flx	318	8	GAF not done.
	Placebo	323	10	GAF not done.
	Placebo	343	12	GAF not done.
	Flx	419	11	GAF not done.
	Placebo	427	8	GAF not done.
	Placebo	432	7	GAF not done.
	Placebo	806	8	GAF not done.
	Placebo	808	12	GAF not done.
	Flx	814	13	GAF not done.
	Placebo	905	9	GAF not done.
	Flx	913	12	GAF not done.
	Placebo	919	11	GAF not done.
	Placebo	1120	15	GAF not done.
	Flx	1152	8	GAF not done.
	Placebo	1206	10	GAF not done.
	Flx	1217	11	GAF not done.
	Placebo	1223	12	GAF not done.
	Placebo	1308	13	GAF not done.
	Placebo	1309	10	GAF not done.
	Placebo	1311	6	GAF not done.
	Placebo	1513	9	GAF not done.
	Flx	1514	7	GAF not done.
	Flx	1515	12	GAF not done.
	Flx	1606	12	GAF not done.
	Placebo	1903	9	GAF not done.
	Flx	1915	12	GAF not done.
	Placebo	2201	6	GAF not done.
	Placebo	2221	10	GAF not done.

Type of Violation	Therapy	Patient Number	Visit Number	Comments
Missing Study Procedures- Side Effects Checklist				
	Placebo	103	5	Side Effects Checklist not done.
	Flx	104	4	Side Effects Checklist not done.
	Flx	104	12	Side Effects Checklist not done.
	Placebo	131	11	Side Effects Checklist not done.
	Placebo	143	5	Side Effects Checklist not done.
	Placebo	149	5	Side Effects Checklist not done.
	Placebo	149	6	Side Effects Checklist not done.
	Flx	150	4	Side Effects Checklist not done.
	Flx	302	5	Side Effects Checklist not done.
	Flx	332	6	Side Effects Checklist not done.
	Flx	332	8	Side Effects Checklist not done.
	Placebo	343	4	Side Effects Checklist not done.
	Placebo	350	13	Side Effects Checklist not done.
	Flx	354	7	Side Effects Checklist not done.
	Placebo	425	4	Side Effects Checklist not done.
	Flx	433	4	Side Effects Checklist not done.
	Placebo	912	11	Side Effects Checklist not done.
	Placebo	1120	9	Side Effects Checklist not done.
	Flx	1131	12	Side Effects Checklist not done.
	Flx	1152	6	Side Effects Checklist not done.
	Flx	1156	8	Side Effects Checklist not

Type of Violation	Therapy	Patient Number	Visit Number	Comments
				done.
	Placebo	1653	6	Side Effects Checklist not done.
	Flx	1905	4	Side Effects Checklist not done.
	Placebo	1925	4	Side Effects Checklist not done.
Missing Laboratory Assessments- PK				
	Placebo	103	8	PK not done.
	Placebo	107	9	PK not done.
	Placebo	112	10	PK not done.
	Placebo	119	15	PK not done.
	Placebo	131	12	PK not done.
	Placebo	135	7	PK not done.
	Placebo	140	7	PK not done.
	Flx	142	15	PK not done.
	Placebo	143	6	PK not done.
	Placebo	149	11	PK not done.
	Placebo	153	10	PK not done.
	Placebo	201	5	PK not done.
	Placebo	203	10	PK not done.
	Flx	204	14	PK not done.
	Placebo	205	8	PK not done.
	Placebo	210	14	PK not done.
	Placebo	301	8	PK not done.
	Placebo	303	14	PK not done.
	Placebo	306	11	PK not done.
	Placebo	309	15	PK not done.
	Flx	313	9	PK not done.
	Flx	318	8	PK not done.
	Placebo	323	10	PK not done.
	Placebo	330	11	PK not done.
	Placebo	335	15	PK not done.
	Placebo	336	15	PK not done.
	Placebo	339	10	PK not done.
	Placebo	343	12	PK not done.
	Placebo	350	15	PK not done.
	Placebo	352	9	PK not done.
	Placebo	407	13	PK not done.
	Placebo	412	15	PK not done.
	Placebo	417	9	PK not done.

Type of Violation	Therapy	Patient Number	Visit Number	Comments
	Flx	419	11	PK not done.
	Placebo	425	15	PK not done.
	Placebo	427	8	PK not done.
	Placebo	432	7	PK not done.
	Flx	441	8	PK not done.
	Placebo	601	5	PK not done.
	Placebo	806	8	PK not done.
	Placebo	808	12	PK not done.
	Placebo	905	9	PK not done.
	Placebo	916	12	PK not done.
	Placebo	919	11	PK not done.
	Placebo	1102	9	PK not done.
	Placebo	1107	14	PK not done.
	Placebo	1120	15	PK not done.
	Placebo	1121	15	PK not done.
	Flx	1131	12	PK not done.
	Flx	1141	12	PK not done.
	Flx	1152	8	PK not done.
	Placebo	1201	13	PK not done.
	Flx	1203	11	PK not done.
	Placebo	1206	10	PK not done.
	Flx	1211	12	PK not done.
	Flx	1215	7	PK not done.
	Flx	1217	11	PK not done.
	Placebo	1222	15	PK not done.
	Placebo	1223	12	PK not done.
	Placebo	1308	13	PK not done.
	Placebo	1309	10	PK not done.
	Placebo	1310	1	PK not done.
	Placebo	1311	6	PK not done.
	Placebo	1501	15	PK not done.
	Placebo	1504	9	PK not done.
	Placebo	1513	9	PK not done.
	Flx	1515	12	PK not done.
	Flx	1606	12	PK not done.
	Placebo	1608	6	PK not done.
	Placebo	1653	8	PK not done.
	Placebo	1669	12	PK not done.
	Placebo	1707	15	PK not done.
	Placebo	1901	15	PK not done.
	Placebo	1903	9	PK not done.
	Flx	1904	11	PK not done.
	Placebo	1907	13	PK not done.
	Flx	1915	12	PK not done.

Type of Violation	Therapy	Patient Number	Visit Number	Comments
	Placebo	1925	15	PK not done.
	Placebo	2201	6	PK not done.
	Flx	2204	15	PK not done.
	Flx	2205	15	PK not done.
	Placebo	2210	8	PK not done.
	Placebo	2213	10	PK not done.
	Placebo	2221	10	PK not done.
Missing Study Procedures- MADRS				
	Placebo	135	7	MADRS not done.
	Flx	139	15	MADRS not done.
	Placebo	140	7	MADRS not done.
	Placebo	143	6	MADRS not done.
	Placebo	201	5	MADRS not done.
	Placebo	210	14	MADRS not done.
	Placebo	306	11	MADRS not done.
	Flx	313	9	MADRS not done.
	Flx	318	8	MADRS not done.
	Placebo	323	10	MADRS not done.
	Placebo	417	9	MADRS not done.
	Flx	419	11	MADRS not done.
	Placebo	427	8	MADRS not done.
	Placebo	432	7	MADRS not done.
	Placebo	806	8	MADRS not done.
	Placebo	808	12	MADRS not done.
	Flx	813	13	MADRS not done.
	Placebo	905	9	MADRS not done.
	Flx	913	12	MADRS not done.
	Placebo	919	11	MADRS not done.
	Placebo	1120	15	MADRS not done.
	Placebo	1121	15	MADRS not done.
	Placebo	1134	7	MADRS not done.
	Flx	1152	8	MADRS not done.
	Placebo	1206	10	MADRS not done.
	Flx	1211	12	MADRS not done.
	Flx	1215	7	MADRS not done.
	Flx	1217	11	MADRS not done.
	Placebo	1223	12	MADRS not done.
	Placebo	1308	13	MADRS not done.
	Placebo	1309	10	MADRS not done.
	Placebo	1311	6	MADRS not done.
	Placebo	1513	9	MADRS not done.

Type of Violation	Therapy	Patient Number	Visit Number	Comments
	Flx	1515	12	MADRS not done.
	Flx	1606	12	MADRS not done.
	Placebo	1903	9	MADRS not done.
	Flx	1905	3	MADRS not done.
	Flx	1915	12	MADRS not done.
	Placebo	2201	6	MADRS not done.
	Placebo	2221	10	MADRS not done.
Missing Study Procedures- ECG				
	Placebo	135	7	ECG not done.
	Placebo	140	7	ECG not done.
	Placebo	143	6	ECG not done.
	Placebo	201	5	ECG not done.
	Flx	204	14	ECG not done.
	Placebo	210	14	ECG not done.
	Placebo	301	8	ECG not done.
	Flx	313	9	ECG not done.
	Flx	318	8	ECG not done.
	Placebo	323	10	ECG not done.
	Placebo	407	13	ECG not done.
	Flx	419	11	ECG not done.
	Placebo	427	8	ECG not done.
	Placebo	432	7	ECG not done.
	Placebo	806	8	ECG not done.
	Placebo	808	12	ECG not done.
	Flx	901	14	ECG not done.
	Placebo	905	9	ECG not done.
	Placebo	919	11	ECG not done.
	Placebo	1107	14	ECG not done.
	Flx	1118	10	ECG not done.
	Placebo	1139	4	ECG not done.
	Flx	1152	8	ECG not done.
	Flx	1203	11	ECG not done.
	Flx	1204	10	ECG not done.
	Placebo	1206	10	ECG not done.
	Flx	1217	11	ECG not done.
	Placebo	1223	12	ECG not done.
	Placebo	1308	13	ECG not done.
	Placebo	1309	10	ECG not done.
	Placebo	1311	6	ECG not done.
	Placebo	1513	9	ECG not done.
	Flx	1515	12	ECG not done.

Type of Violation	Therapy	Patient Number	Visit Number	Comments
	Flx	1606	12	ECG not done.
	Placebo	1903	9	ECG not done.
	Flx	1915	12	ECG not done.
	Flx	1919	15	ECG not done.
	Placebo	2201	6	ECG not done.
	Placebo	2210	1	ECG not done.
	Placebo	2210	8	ECG not done.
	Placebo	2221	10	ECG not done.
Missing Study Procedures- Physical Exam				
	Placebo	107	1	Physical Exam not done.
	Placebo	112	1	Physical Exam not done.
	Placebo	113	1	Physical Exam not done.
	Flx	114	1	Physical Exam not done.
	Placebo	119	1	Physical Exam not done.
	Flx	127	11	Physical Exam not done.
	Placebo	131	12	Physical Exam not done.
	Placebo	135	7	Physical Exam not done.
	Flx	139	15	Physical Exam not done.
	Placebo	140	1	Physical Exam not done.
	Placebo	140	7	Physical Exam not done.
	Flx	142	15	Physical Exam not done.
	Placebo	143	6	Physical Exam not done.
	Placebo	210	14	Physical Exam not done.
	Flx	313	9	Physical Exam not done.
	Flx	318	8	Physical Exam not done.
	Placebo	323	10	Physical Exam not done.
	Flx	334	15	Physical Exam not done.
	Flx	346	1	Physical Exam not done.
	Placebo	350	1	Physical Exam not done.
	Placebo	350	15	Physical Exam not done.
	Flx	401	12	Physical Exam not done.
	Placebo	407	13	Physical Exam not done.
	Placebo	412	1	Physical Exam not done.
	Flx	413	1	Physical Exam not done.
	Flx	419	11	Physical Exam not done.
	Flx	422	15	Physical Exam not done.
	Placebo	427	8	Physical Exam not done.
	Placebo	432	7	Physical Exam not done.
	Placebo	806	8	Physical Exam not done.
	Placebo	808	12	Physical Exam not done.
	Placebo	905	9	Physical Exam not done.

Type of Violation	Therapy	Patient Number	Visit Number	Comments
	Flx	906	15	Physical Exam not done.
	Placebo	919	11	Physical Exam not done.
	Placebo	1120	15	Physical Exam not done.
	Placebo	1121	15	Physical Exam not done.
	Flx	1137	15	Physical Exam not done.
	Flx	1152	8	Physical Exam not done.
	Flx	1153	15	Physical Exam not done.
	Flx	1204	10	Physical Exam not done.
	Placebo	1206	10	Physical Exam not done.
	Flx	1208	15	Physical Exam not done.
	Flx	1217	11	Physical Exam not done.
	Placebo	1222	15	Physical Exam not done.
	Placebo	1223	12	Physical Exam not done.
	Placebo	1301	15	Physical Exam not done.
	Flx	1305	15	Physical Exam not done.
	Placebo	1307	15	Physical Exam not done.
	Placebo	1308	13	Physical Exam not done.
	Placebo	1309	10	Physical Exam not done.
	Placebo	1311	6	Physical Exam not done.
	Placebo	1513	9	Physical Exam not done.
	Flx	1515	12	Physical Exam not done.
	Flx	1606	12	Physical Exam not done.
	Placebo	1901	15	Physical Exam not done.
	Flx	1915	12	Physical Exam not done.
	Flx	1919	15	Physical Exam not done.
	Placebo	1925	15	Physical Exam not done.
	Placebo	2201	6	Physical Exam not done.
	Flx	2220	14	Physical Exam not done.
	Placebo	2221	10	Physical Exam not done.
Laboratory Procedure Violations or Missing Laboratory Assessments				
	Placebo	135	7	Laboratory Assessments not done.
	Flx	139	1	Site used wrong lab kit and the plasma was omitted.
	Placebo	140	7	Laboratory Assessments not done.
	Placebo	143	6	Laboratory Assessments not done.
	Placebo	149	1	Labs were attempted but the technician was unable to drawl samples.

Type of Violation	Therapy	Patient Number	Visit Number	Comments
	Placebo	203	10	End of study hematology received beyond stability.
	Placebo	210	14	Laboratory Assessments not done.
	Flx	313	9	Laboratory Assessments not done.
	Flx	318	8	Laboratory Assessments not done.
	Placebo	323	10	Laboratory Assessments not done.
	Placebo	352	1	Urine drug screen not done.
	Flx	419	11	Laboratory Assessments not done.
	NR	421	10	Did not have plasma draw; will draw again at Visit 15 if child is resistant.
	NR	423	1	Urine drug screen not completed because patient was not able to provide enough sample.
	Placebo	427	8	Laboratory Assessments not done.
	Placebo	432	7	Laboratory Assessments not done.
	Placebo	806	8	Laboratory Assessments not done.
	Placebo	808	12	Laboratory Assessments not done.
	Flx	813	13	Patient could not void and specimen was not obtained.
	Placebo	905	9	Laboratory Assessments not done.
	NR	917	1	Patient was unable to provide urine specimen and discontinued at the next visit.

Type of Violation	Therapy	Patient Number	Visit Number	Comments
	Placebo	919	11	Laboratory Assessments not done.
	Flx	1141	12	Laboratory Assessments not done.
	Flx	1152	8	Laboratory Assessments not done.
	Flx	1203	11	Laboratory Assessments not done.
	Placebo	1206	10	Laboratory Assessments not done.
	Flx	1211	12	Laboratory Assessments not done.
	Flx	1217	11	Laboratory Assessments not done.
	Placebo	1223	12	Laboratory Assessments not done.
	Placebo	1308	13	Laboratory Assessments not done.
	Placebo	1309	10	Laboratory Assessments not done.
	Placebo	1311	6	Laboratory Assessments not done.
	Placebo	1513	9	Laboratory Assessments not done.
	Flx	1515	12	Laboratory Assessments not done.
	Flx	1606	12	Laboratory Assessments not done.
	Placebo	1903	9	Laboratory Assessments not done.
	Flx	1915	12	Laboratory Assessments not done.
	Placebo	1925	15	Laboratory Assessments not done.
	Placebo	2201	6	Laboratory Assessments not done.
	Placebo	2203	15	Not enough blood obtained at visit 15 to perform analysis.
	Flx	2205	15	Patient unable to give urine sample.
	NR	2211	1	Patient's lab results came back and there was not enough blood to complete the T-3 lab.

Type of Violation	Therapy	Patient Number	Visit Number	Comments
	Placebo	2212	1	Specimen tubes were missed labeled and collected specimens had to be canceled, by[redacted]

Type of Violation	Therapy	Patient Number	Visit Number	Comments
	Placebo	2221	10	Laboratory Assessments not done.
Missing Study Procedures- KSADS				
	Placebo	135	7	KSADS not done.
	Flx	139	15	KSADS not done.
	Placebo	140	7	KSADS not done.
	Placebo	143	6	KSADS not done.
	Placebo	201	5	KSADS not done.
	Placebo	210	14	KSADS not done.
	Placebo	306	11	KSADS not done.
	Flx	313	9	KSADS not done.
	Flx	318	8	KSADS not done.
	Placebo	323	10	KSADS not done.
	Placebo	343	12	KSADS not done.
	Flx	401	12	KSADS not done.
	Placebo	407	13	KSADS not done.
	Flx	419	11	KSADS not done.
	Placebo	425	15	KSADS not done.
	Placebo	427	8	KSADS not done.
	Placebo	432	7	KSADS not done.
	Placebo	806	8	KSADS not done.
	Placebo	808	12	KSADS not done.
	Flx	814	13	KSADS not done.
	Placebo	905	9	KSADS not done.
	Placebo	919	11	KSADS not done.
	Flx	1118	10	KSADS not done.
	Placebo	1120	15	KSADS not done.
	Placebo	1121	15	KSADS not done.
	Flx	1137	15	KSADS not done.
	Flx	1141	12	KSADS not done.
	Flx	1152	8	KSADS not done.
	Placebo	1206	10	KSADS not done.
	Flx	1217	11	KSADS not done.
	Placebo	1223	12	KSADS not done.
	Placebo	1308	13	KSADS not done.
	Placebo	1309	10	KSADS not done.
	Placebo	1311	6	KSADS not done.
	Placebo	1513	9	KSADS not done.
	Flx	1514	7	KSADS not done.
	Flx	1515	12	KSADS not done.
	Flx	1606	12	KSADS not done.

Type of Violation	Therapy	Patient Number	Visit Number	Comments
	Placebo	1903	9	KSADS not done.
	Flx	1915	12	KSADS not done.
	Placebo	2201	6	KSADS not done.
	Flx	2220	14	KSADS not done.
	Placebo	2221	10	KSADS not done.

16.2.4.
Patients Excluded from the Efficacy Analysis

13:06 Mar 22, 2000 PAGE: 1

Listing of Patients Excluded from Primary Efficacy Analysis
All Randomized Patients
B1Y-MC-HCJE

Protocol: B1Y-MC-HCJE

Inv	Pat	Therapy Group	Visit	CDRSTL17
1	143	Placebo	4	65.00
2	201	Placebo	4	58.00
6	601	Placebo	4	43.00
8	807	Placebo	4	53.00
11	1139	Placebo	4	62.00
13	1310	Placebo	4	70.00
13	1311	Placebo	4	67.00

RMP.B1YP.JCLLIB2(MIL1JEMA)
RMP.B1YO.HCJEREP(MIL1JEMA)
XMIL0001

13:06 Mar 22, 2000 PAGE: 2

Listing of Patients Excluded from Primary Efficacy Analysis
All Randomized Patients
B1Y-MC-HCJE

Protocol: B1Y-MC-HCJE

Inv	Pat	Therapy Group	Visit	CDRSTL17
16	1657	Placebo	4	57.00
22	2201	Placebo	4	55.00

RMP.B1YP.JCLLIB2(MIL1JEMA)
RMP.B1YO.HCJEREP(MIL1JEMA)
XMIL0001

16.2.5.
Demographic Data

Please see SAS Transport file located in Item 11 of this submission.

16.2.6.
Compliance and/or Drug Concentration Data

Please see SAS Transport file located in Item 11 of this submission.

16.2.7.
Individual Efficacy Response Data

Please see SAS Transport file located in Item 11 of this submission.

16.2.8.
Listing of Individual Laboratory Measurements by Patient

Please see SAS Transport file located in Item 11 of this submission.

16.3.
Clinical Report Forms (CRFs)

Please refer to Item 12 of a US submission or Part 5 of a Canadian submission. These clinical report forms are available to other regulatory agencies upon request.

16.4.
Individual Patient Data Listings

16.4.1. Patients Excluded from Pharmacokinetic Analysis
16.4.2. Concomitant Medication
16.4.3. Vital Signs Listing
16.4.4. ECG Listing
16.4.5. Comments Listing

Please see SAS Transport file located in Item 11 of this submission.