CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

18-936/SE5-064

MEDICAL REVIEW

REVIEW AND EVALUATION OF CLINICAL DATA

NDA 18-936
SPONSOR: LILLY
DRUG: FLUOXETINE HYDROCHLORIDE (PROZAC)
MATERIAL SUBMITTED: RESPONSE TO APPROVABLE LETTER FOR PEDIATRIC EXCLUSIVITY SUPPLEMENT (SE5-064 AZ)
DATE SUBMITTED: 10-4-01
DATE RECEIVED: 10-5-01
USER FEE GOAL DATE: 4-5-02

Our approvable letter dated 7-12-01 for this pediatric supplement, in addition to proposing labeling, also requested additional information regarding several issues: re-analysis of growth data from the long term controlled trial, justification for the sponsor's re-analysis of ECG data on QT interval changes, and a literature update. We also asked the sponsor to conduct a Phase IV pediatric pharmacokinetic study, and informed the sponsor that Dr. Emslie's clinical trial site would be inspected.[1]

Herein I will review the sponsor's responses by topic.

Growth velocity

The approvable letter made the following request:

"We have included the findings on growth velocity for height and weight, along with the reduced levels of alkaline phosphatase, into the PRECAUTIONS-Pediatric Use section of labeling. Additionally, we are requesting that you reanalyze these data using age and gender adjusted height and weight percentiles and submit this report prior to approval of this application. Further, you should determine if the reduction in alkaline phosphatase is related to decreased bone growth. In addition, there may be other evaluations necessary to further examine the effects of Prozac on growth and development. Based upon the results of this reanalysis, we may request that you commit to conducting, as a Phase 4 agreement, a long-term study (e.g., 52 weeks) to assess the growth and development of Prozac in the pediatric population."

The data from the original submission are shown below. These data are for the 19-week endpoint of study HCJE.

Treatment group	Fluoxetine	Placebo	p-value
Mean change in height (cm)	+1.0	+2.0	0.008
Mean change in weight (kg)	+1.2	+2.3	0.008

In this submission, Lilly reports the data in terms of height and weight Z-scores, calculated for age and gender according to the National Center for Health Statistics method. A Z-score equal to zero is the population median. Z-score data for the same 19-week endpoint are shown below. The data shown are last-observation-carried-forward.

[1] This inspection has been completed; please refer to the 11-5-01 Clinical Inspection Summary from Dr. Khin of the Division of Scientific Investigations. DSI finds Dr. Emslie's data acceptable

Treatment group (LOCF)	Fluoxetine (n=88)	Placebo (n=75)	p-value (ANOVA)
Mean baseline height (Z-score)	0.51	0.33	0.269
Mean change in height (Z-score)	-0.10	+0.07	0.001
Mean baseline weight (Z-score)	1.03	1.01	0.908
Mean change in weight (Z-score)	-0.05	+0.03	0.027

Note that the majority of subjects in both groups were above the median on height and weight, and that at baseline the placebo group was somewhat shorter, although this did not reach statistical significance.

The sponsor also analyzed the median change in height Z-scores by ANOVA on rank-transformed data, and the results were similar (median change –0.06 for fluoxetine and –0.02 for placebo, p-value = 0.007).
In terms of percentiles, the placebo group mean height percentile was 63rd at baseline and 66th at endpoint, while the corresponding percentiles for the fluoxetine group were 69th (baseline) and 66th (endpoint).

For patients who completed all 19 weeks of treatment, the results were similar, and are shown below.

Treatment group (completers)	Fluoxetine (n=51)	Placebo (n=47)	p-value (ANOVA)
Mean baseline height (Z-score)	0.45	0.35	0.630
Mean change in height (Z-score)	-0.12	+0.07	0.003
Mean baseline weight (Z-score)	1.16	0.94	0.308
Mean change in weight (Z-score)	-0.06	+0.04	0.023

Fluoxetine-placebo contrasts for height and weight during the relapse prevention phase of the trial were not statistically significant, but the sample sizes were much smaller than at the 19-week visit.

An analysis of change in height versus change in alkaline phosphatase failed to find a statistically significant correlation between the two.

Lilly has declined to conduct a one-year study as a Phase IV commitment.

Lilly indicates that there was likely some inaccuracy in the height data, as evidenced by the observation that 15 fluoxetine and 2 placebo patients had negative changes in height. The practice of rounding to the nearest inch may have contributed.

Comment: Nineteen weeks of fluoxetine treatment was associated with reduced growth velocity relative to placebo. This finding holds under analysis of raw changes in height and weight, and also under analysis of age- and gender-normed data. In a randomized, blinded trial, variability in measurements would be anticipated to work against finding an effect of drug treatment, and not to produce an effect by artifact. Lilly has pointed out that in the shorter duration pediatric trials no growth decrements were observed; however, in my opinion, the longer duration exposure in HCJE is of more utility for assessing height and weight changes. On balance, I believe that this trial provides evidence of reduced growth velocity with fluoxetine treatment, and I believe the

labeling should reflect the finding. In my opinion, the sponsor has not provided an adequate rationale for declining to do a one-year study as we requested in the approvable letter.

QTc data analyses

The approvable letter included the following request.

"Justification of Cardiac Data:
We note that in your initial analysis of QTc (cube root corrected) data for the baseline to 19 week comparison in HCJE, there was a statistically significant greater increase of 7.4 msec for fluoxetine vs 0.2 msec for placebo. Subsequent reanalyses by 2 different consulting groups contracted by Lilly yielded no statistically significant differences. QTc data from the PK study (HCIU), as analyzed by [redacted] actually showed a decrease for fluoxetine vs placebo. These discrepant QTc results, dependent upon which consultant was used, need explanation. Please provide a better rationale for why the Agency should accept the results of the later analysis."

Lilly's response: Lilly argues that the statistically significant increase in mean QTc found with the initial analysis is the product of random variability. The initial readings of the ECGs were performed by adult cardiologists at the [redacted] using hand-held ECG calipers. This was the analysis that yielded the positive finding. Following this, Lilly consulted [redacted] reading also employed hand-held ECG calipers. Next, Lilly obtained a third ECG reading from the [redacted] organization. Their method employed computer scans of the tracings with intervals determined by technicians using electronic calipers. In addition, the [redacted] technicians assessed the degree of sinus arrhythmia present, and if it was significant averaged the RR and QT intervals over 5 heartbeats (if there was little sinus arrhythmia, the intervals were averaged over 3 heartbeats).

In order to fully evaluate Lilly's arguments it is necessary to compare the data from the three different methods. Attached to this review are a table summarizing the QTc data from all three cardiology consultant groups, and graphic displays of selected parameters. It will be seen that [redacted] analyses yielded higher baseline mean QTc values than [redacted] for both the correction methods. It will also be noted that the largest mean increase in QTc with fluoxetine was observed in the [redacted] data, and that this was statistically significant versus placebo (p-value for Fridericia = 0.009, for Bazett = 0.034). With respect to the variance of the measurements, in general the standard deviations were lowest for the [redacted] data, intermediate for [redacted] and highest for the [redacted] data. Of course, in these analyses the observed standard deviation reflects both the standard deviation of the "true" values in the sample and the variability introduced in the process of measuring the QT interval.

Overall, Lilly has concluded that the absence of an increase in QTc in the pharmacokinetic study HCIU, and in the second and third readings of the ECGs from study HCJE, is persuasive. The apparent finding from the initial reading of the ECGs in study HCJE is, in their view, an artifact of sinus arrhythmia that was not accounted for by [redacted] methodology.

Comment: While these QTc data are inconsistent, they are unfortunately all that are available. Personally, I would not weigh the uncontrolled data from study HCIU very heavily. With respect to study HCJE, I am not persuaded that the finding from the initial reading is an artifact of variability attributable to sinus arrhythmia. There would have to be some reason why this factor would affect the QT intervals of fluoxetine and placebo patients differently. The finding of an

increase with fluoxetine was especially robust with the Fridericia correction (p-value = 0.009); such p-values are by definition unlikely to be produced by random variability. Overall, I tend to view the —— analysis not as manifesting more random variability, but rather as having more sensitivity to a drug effect.

Thus, I feel that the most likely explanation for QTc interval prolongation in the —— dataset is that this is a true drug effect, and not an artifact of random variability. In part I suspect this is a true finding because the r-isomer of fluoxetine is known to prolong the QT interval in adults. Unfortunately, there is no enantiomer-specific pharmacokinetic data for pediatric patients, so it is not known whether exposure to the r-isomer is affected by age. It should be recalled that the majority of these data are from subjects receiving 20 mg/day, although the labeling will recommend higher doses (up to 60 mg for adolescents with OCD). We have asked Lilly to provide us with a subgroup analysis of QT interval data for those subjects receiving doses above 20 mg (this is likely to be a small subgroup, however).

Literature Update

We asked Lilly to conduct a literature search regarding focusing on safety of fluoxetine use in the pediatric population. Lilly searched various biomedical electronic literature databases for the period January 2000 through July 2001. Their search disclosed several publications describing the clinical trials submitted in this supplement. Additionally, there were articles describing two open label clinical trials, and one article describing outcome data in a naturalistic drug utilization study. Lastly, there were two published case reports, one noting worsening of eating symptoms in a child with Prader-Willi syndrome, and one noting decreased awareness of hypoglycemia in a diabetic boy.

Comment: On balance, there is no new information from the literature search that would materially affect the assessment of fluoxetine's safety in this population.

Postmarketing Safety Update

The approvable letter included the following request: "Please provide a worldwide updated search of the postmarketing adverse events database regarding fluoxetine in pediatric use...This should include an updated estimate of use for drug marketed in other countries, and English translations of current approved foreign labeling in the pediatric patient population."

This submission includes a compilation of all adverse events for patients aged 6-17 years inclusive from Lilly's "Clintrace" worldwide safety database. The Clintrace database includes all postmarketing spontaneous reports (serious and non-serious), and all serious clinical trial adverse events. Note that Lilly has recently converted all reports from COSTART to MedDRA terminology. The database was searched from launch (date not specified) to 8-27-01.[2] The submission provides a statistical summary but does not include descriptions of individual reports.

This search yielded a total of 3815 separate adverse events (a patient may have had more than one event). In comparison, there were 155,974 adverse events among patients who were not 6-17 years of age. (Note that this group included not only adults, but also any patients younger than 6 years old, and those with no age specified.) Lilly summed the number of reports of specific adverse events for each age group, and then calculated its percentage of the total number of

[2] The submission refers to a previous search of pediatric postmarketing reports, dated 5-11-00, but to my knowledge this was not submitted with the supplement, and so may have been for Lilly's internal use only.

adverse event reports for that age group. The following events represented more than 1% of the total adverse events in the 6-17 year age group, and were also proportionately more common for the 6-17 year age group than for the remaining age group: dermatitis NOS, overdose NOS, agitation, aggression, suicide attempt, somnolence, convulsions NOS, urticaria NOS, vomiting NOS. With respect to the question of prolonged cardiac repolarization, in the 6-17 year old group there were 6 reports of prolonged QT interval, one report of prolonged QTc interval, 3 reports of cardiac arrest, 1 sudden unexplained death, and 1 ventricular fibrillation. There was also one report each for aplastic anemia, liver transplant, agranulocytosis, hepatic necrosis, and Stevens-Johnson syndrome.

No information on estimated exposure domestically or overseas in this population was provided. The submission does not include any foreign labeling for pediatric use (presumably there is none).

Comment: Overall, the postmarketing surveillance data provided by Lilly does not point to a unique risk in the younger population.

Clinical Pharmacology and Biopharmaceutics Phase IV commitment

The approvable letter included the following request:

[redacted]

Labeling

Lilly has suggested the following amendments to the proposed labeling in our approvable letter. (Many other changes proposed by Lilly are of a very minor editorial nature, and I will not review them here.)

1. In the paragraphs concerning growth under "Pediatric Use"

As with other SSRIs, decreased weight gain has been observed in association with the use of fluoxetine in children and adolescent patients. After 19 weeks of treatment in a clinical trial, pediatric subjects treated with fluoxetine gained an average of 1 cm less in height (p=0.0[redacted]) and 1.1 kg less in weight (p=0.008) than subjects treated with placebo ~~(p=0.008)~~. In addition, fluoxetine treatment was associated with a decrease in alkaline phosphatase levels[redacted]

[redacted] The safety of fluoxetine treatment for pediatric patients has not been systematically assessed for chronic treatment longer than several months in duration. In particular, there are no studies that directly evaluate the longer-term effects of fluoxetine on the

growth, development, and maturation of children and adolescent patients. Therefore, height and weight should be monitored periodically in pediatric patients receiving fluoxetine.

The safety of fluoxetine treatment for pediatric patients has not been systematically assessed for chronic treatment longer than several months in duration. In particular, there are no studies that directly evaluate the longer-term effects of fluoxetine on the growth, development and maturation of children and adolescent patients.

Comment: I believe that our original language is superior and reflects the available data. I also believe that clinicians may be more apt to monitor growth if the language is stronger, as in our proposal. We may wish to delete the comment here regarding decreased alkaline phosphatase, although this finding remains unexplained.

2. Under Dosage and Administration/Major Depressive Disorder/Initial Treatment/Pediatric (Children and Adolescents)

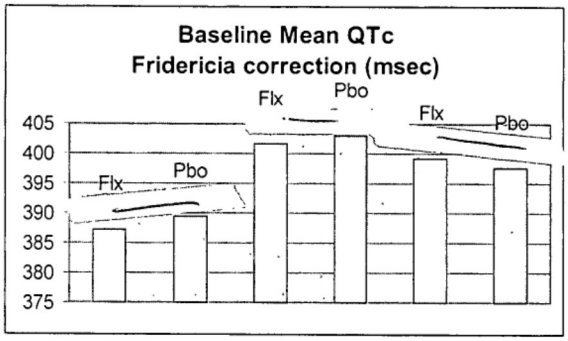
Pediatric (Children and Adolescents)—In the short-term (8- to 9-week) controlled clinical trials of fluoxetine supporting its effectiveness in the treatment of major depressive disorder, patients were administered fluoxetine doses of 10 to 20 mg/day (*see* Clinical Trials *under* CLINICAL PHARMACOLOGY).

Treatment should be initiated with a dose of 10 or 20 mg/day. After 1 week at 10 mg/day, the dose should be increased to 20 mg/day.

However, due to higher plasma levels in lower weight children, the starting and target dose in this group may be 10 mg/day. A dose increase to 20 mg/day may be considered after several weeks if insufficient clinical improvement is observed.

Comment: I agree with Lilly's revisions.

Andrew D. Mosholder, M.D., M.P.H.
Medical Officer, HFD-120


Baseline Mean QTc
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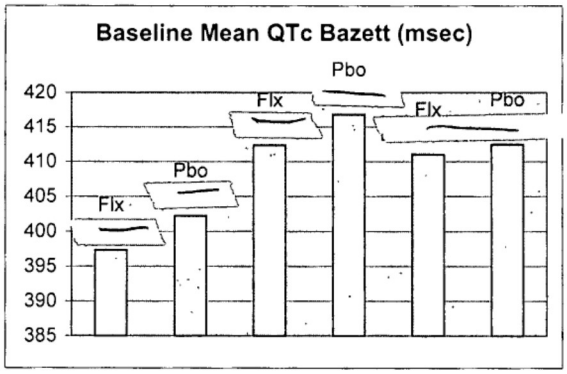
400
395
390
385
380
375
Flx
Pbo
Flx
Pbo
Flx
Pbo


Baseline Mean QTc Bazett (msec)
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415
410
405
400
395
390
385
Flx
Pbo
Flx
Pbo
Flx
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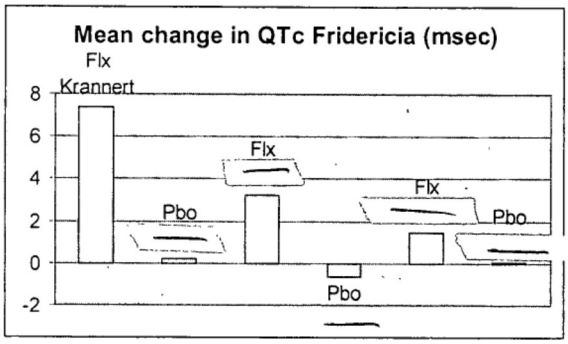
Mean change in QTc Fridericia (msec)
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Krannert
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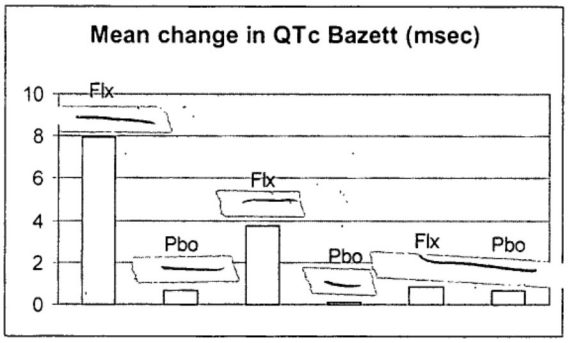
6
4
2
0
-2
Flx
Pbo
Flx
Pbo
Pbo


Mean change in QTc Bazett (msec)
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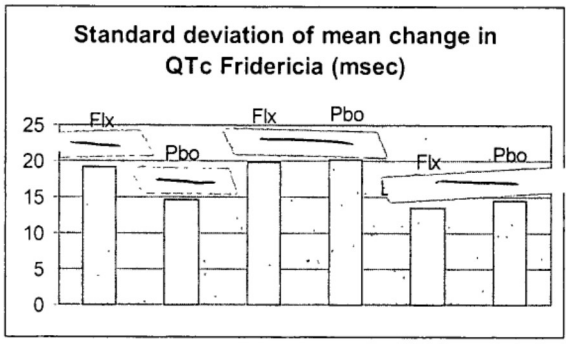
8
6
4
2
0
Flx
Flx
Pbo
Pbo
Flx
Pbo


Standard deviation of mean change in
QTc Fridericia (msec)
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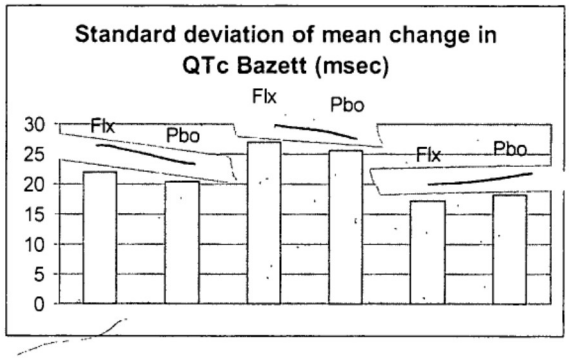
20
15
10
5
0
Flx
Pbo
Flx
Pbo
Flx
Pbo


Standard deviation of mean change in
QTc Bazett (msec)
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25
20
15
10
5
0
Flx
Pbo
Flx
Pbo
Flx
Pbo

QTc data from study HCJE, 19-week endpoint

Consultant	QTc correction	Treatment	N	Baseline QTc		Change from BL		p-value
				Mean	SD	Mean	SD	
[redacted]	Fridericia	Flx	88	387.25	15.98	7.38	19.12	0.009
		Pbo	73	389.43	13.09	0.21	14.64	
	Bazett	Flx	88	397.27	17.66	7.93	22.04	0.034
		Pbo	73	402.20	18.55	0.70	20.35	
[redacted]	Fridericia	Flx	89	401.69	18.97	3.20	19.76	0.228
		Pbo	73	402.96	19.76	-0.61	20.11	
	Bazett	Flx	89	412.38	21.69	3.74	27.02	0.385
		Pbo	73	416.78	23.35	0.12	25.52	
[redacted]	Fridiericia	Flx	87	399.14	14.47	1.44	13.45	0.535
		Pbo	68	397.70	14.43	0.04	14.42	
	Bazett	Flx	87	411.01	16.90	0.86	17.11	0.943
		Pbo	68	412.46	17.32	0.66	18.11	

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Andy Mosholder
2/19/02 10:19:29 AM
MEDICAL OFFICER

Thomas Laughren
3/12/02 08:40:06 AM
MEDICAL OFFICER
We have decided to issue a second approvable letter, given that more data are needed regarding the QTc changes; see memo to file for more detailed comments.--TPL

REVIEW AND EVALUATION OF CLINICAL DATA

APPLICATION INFORMATION
NDA: 18-936
Supplement: SE5-064
Sponsor: Eli Lilly and Company
Drug: Fluoxetine HCl (PROZAC)
Material submitted: Pediatric Study Reports for Pediatric Exclusivity
Date submitted: September 14, 2000
User fee due date: July 15, 2001
Medical officer: Andrew D. Mosholder, M.D.
Completion Date: June 25, 2001

Contents

1.0 Material Reviewed

This supplement was submitted September 14, 2000. Additional information was submitted on January 15, 2001: a report on the long-term treatment phase of study HCJE, which was not available at the time of the original submission, and additional analyses of ECG data. On January 30, 2001, Lilly submitted photocopies of the original study protocols, and some additional safety analyses. Finally, on May 23, Lilly submitted ECG analyses for study HCIU.

2.0 Background

Administrative history: On April 12, 1999, the agency issued a pediatric Written Request (WR) for studies of fluoxetine in children and adolescents; FDA amended this WR May 19, 1999. The agency's WR included two indications, pediatric depression and pediatric obsessive-compulsive disorder (OCD). This supplement is Lilly's response to the WR. On November 15, 2000, CDER's Pediatric Exclusivity Board granted Lilly pediatric exclusivity for fluoxetine based on this submission.

Proposed directions for use: The sponsor's proposed pediatric labeling recommends a starting dose of either 10 or 20 mg/day for depression, with titration to 20 mg/day after one week for patients starting on 10 mg/day. For OCD, a slightly different regimen is recommended, with a starting dose of 10 mg/day and titration to 20 mg/day after 2 weeks. For both indications, the recommended maximum dose is 60 mg/day.

Financial disclosure: Pursuant to 21 CFR 54, Lilly provided statements to the effect that their clinical investigators did not receive payment in return for particular results. One subinvestigator in study HCJE, [redacted] owned equity in Eli Lilly and Company [redacted] Note that two of these trials, X065 and [redacted] were completed prior to implementation of the financial disclosure regulations in February 1999.

3.0 Chemistry: There are no chemistry issues relevant to this supplement.

4.0 Preclinical: There are no preclinical data in this supplement.

5.0 Clinical Data Sources

The following is a listing of the studies submitted.

Study HCJE: Multicenter, randomized, double blind, placebo controlled, parallel group trial, n=219 children and adolescents with major depressive disorder. Acute treatment phase was 9 weeks in duration, compared fluoxetine 20 mg/d to placebo. Stabilization phase: 10 weeks in duration. Nonresponders from the acute treatment phase randomized to either continued treatment at same dose, or to increased dose (40 or 60 mg/day). Responders continued their double blind treatment. Relapse prevention phase: At the end of 10 week stabilization phase, fluoxetine responders were randomized to 32 weeks of either continued fluoxetine or placebo (placebo responders continued on placebo).

Study X065: (Emslie trial) Single center, randomized, double blind, placebo controlled, parallel group trial, n=96 children and adolescents with major depressive disorder, fluoxetine 20 mg/d versus placebo for 8 weeks.

Study HCJW: Multicenter, randomized, double blind, placebo controlled, parallel group trial; n=103 children and adolescents with obsessive-compulsive disorder, fluoxetine 10-60 mg/day versus placebo X 13 wks

Study HCIU: Open label pharmacokinetic study; n=22 children and adolescents with various diagnoses, fluoxetine 20 mg/d X 2 months

Study [redacted] Single center, randomized, double blind, placebo controlled, parallel group trial; n= 40 adolescents with major depressive disorder; fluoxetine [redacted] versus placebo X 6 weeks, followed by open label fluoxetine treatment. Study discontinued due to slow patient recruitment.

[redacted]

Demographics

The demographic characteristics for all patients in studies HCJE, HCJW, HCIU and X065 are summarized below (source: ISS).

Characteristic	Fluoxetine patients (N=250)	Placebo patients (N=190)
Ethinicity (%)		
Afro-American	5.2	6.3
Caucasian	84.4	80.0
Asian	0.4	0.5
Hispanic	6.8	7.9
Other	3.2	5.3
Age (yrs)		
Mean	12	12
Range	6-18	7-18
Age category (n)		
Children (6-12)	148	109
Adolescents (13-18)	102	81
Gender		
Male (n)	129	97
Female (n)	121	93

Extent of exposure: The total duration of exposure to fluoxetine by fluoxetine dose was only provided by the sponsor for the acute treatment phase of the three randomized controlled trials. These data are shown below. The number of subjects is the number who received the indicated dose as their final dose in the acute treatment phase.

Fluoxetine dose	n	Total person-years
10 mg/day	5	4.8
20 mg/day	214	34.2
40 mg/day	16	2.7
60 mg/day	15	1.6
All doses	250	43.4

Thus, the majority of safety data was obtained for 20 mg daily. Only 31 subjects in this development program received a final dose above 20 mg/day.

6.0 Pharmacokinetics

Pharmacokinetic blood samples were collected in study HCIU, a pharmacokinetic trial, and in study HCJE, an efficacy trial in depression.

The following is taken from the sponsor's proposed labeling, and describes the results from the pharmacokinetic study HCIU and from population pharmacokinetic sampling in study HCJE:

"Fluoxetine pharmacokinetics were evaluated in 21 pediatric patients (10 children ages 6 to <13, 11 adolescents ages 13 to <18) diagnosed with depression or obsessive compulsive disorder. Fluoxetine 20 mg/day was administered for up to 62 days. The average steady-state concentrations of fluoxetine in these children and adolescents were 171 ng/mL and 86 ng/mL, respectively. The average norfluoxetine steady-state concentrations in these children — adolescents were 195 ng/mL and 113 ng/mL, respectively. No gender-associated difference in fluoxetine pharmacokinetics was observed. ——— similar ranges of fluoxetine and norfluoxetine plasma concentrations were observed in 94 pediatric patients (ages 8 to <18) diagnosed with major depressive disorder...As in adults, fluoxetine and norfluoxetine accumulated extensively following multiple oral dosing; steady-state concentrations were achieved within 3 to 4 weeks of daily dosing."

There are no pharmacokinetic data in this submission for doses other than 20 mg/day. In addition, no data are available regarding concentrations of the r- and s- enantiomers of fluoxetine and norfluoxetine, which in adults have different pharmacokinetic properties.

7.0 Efficacy

7.1 Obsessive-Compulsive Disorder: Study HCJW

7.1.1 Investigators/sites

The following investigators participated in this study:

7.1.2 Objective: The primary objective of the trial, as stated in the protocol, was to test the efficacy of fluoxetine compared to placebo in the treatment of children and adolescents with OCD.

7.1.3 Population: Subjects were to be children and adolescents with OCD, aged 7-17 years, with a pre-randomization CGI-severity score of at least 4, an NIMH Global OCD scale score of at least 7, and a Children's Yale-Brown Obsessive Compulsive scale (CYBOCS) score of at least 16. In addition, the subject's baseline Child Depression Rating Scale (CDRS) score could not be over 40. The following were grounds for exclusion: pregnancy, lactation, other significant psychiatric disorders, psychosis, suicidality, seizures, substance abuse, use of other psychotropic medications, medical illnesses, and having a first degree relative with bipolar disorder. One hundred patients were to be randomized, at a ratio of 2:1 for fluoxetine:placebo.

7.1.4 Design: This was a multicenter, randomized, double blind, parallel group, placebo controlled study. The screening assessments included a physical exam, medical history, ECG, clinical laboratories, pregnancy testing if needed, CYBOCS, CDRS and NIMH Global OCD. Eligible patients were to be randomized to 13 weeks of treatment with either fluoxetine or corresponding placebo (as noted, with a 2:1 randomization ratio for fluoxetine:placebo). The initial dose was 10 mg/day for two weeks, with titration to 20 mg/d for the next two weeks, and further titration up to a maximum of 60 mg if needed thereafter. Subjects were to have clinic visits every 1-3 weeks throughout the trial, with the efficacy assessments and safety monitoring to include vital signs, weight, and repeated height and clinical laboratories at the end of treatment. There was no particular follow up treatment specified in the protocol.

The protocol was amended once (amendment a), but the changes involved revisions for clarity, and did not affect the design of the study.

7.1.5 Analysis plan: The protocol specified the change from baseline to endpoint in the CYBOCS

total score as the primary outcome measure. The specified analysis method was ANOVA with treatment, investigator, and treatment X investigator as factors.

7.1.6 Results

A total of 148 subjects were screened, and of these 103 were considered eligible subjects and were randomized.

Demographics

The following tables summarize the study sample according to randomized treatment, age group and gender. (I derived this table from the sponsor's electronic dataset describing patient characteristics.) The subjects were mostly children under 13 years of age.

FLUOXETINE	Male	Female	Total
Children (<13 years)	24	27	51
Adolescents (≥ 13 years)	10	10	20
Total	34	37	71

PLACEBO	Male	Female	Total
Children (<13 years)	12	12	24
Adolescents (≥ 13 years)	3	5	8
Total	15	17	32

The table below summarizes the baseline patient characteristics for all randomized patients. Note that the subjects were predominantly Caucasian, with relatively few comorbid disorders.

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Characteristic	Fluoxetine (N=71)	Placebo (N=32)
Age (yrs) Mean Range	 11 7-17	 11 7-17
Ethnic origin (n) Caucasian Asian African-American Hispanic Other	 62 0 2 4 3	 27 1 0 3 1
Comorbidity (n) Major depressive disorder ADHD	 4 2	 1 0
Median duration of OCD prior to trial (yrs)	4.1	5.8
No psychotropic drug use in past year (n)	53	21
CYBOCS mean total score (p-value=0.13)	24.5	26.3

Patient disposition

The table below summarizes the disposition of subjects in each treatment group.

Reason for discontinuation	Fluoxetine (N=71)	Placebo (N=32)
Completed study	49 (69.0%)	20 (62.5%)
Adverse event	6 (8.5%)	2 (6.3%)
Lack of efficacy	10 (14.1%)	8 (25%)
Patient decision	3 (4.2%)	0
Other	3 (4.2%)	2 (6.3%)

A higher proportion of placebo patients discontinued for lack of efficacy; otherwise the reasons for discontinuing from the study were comparable between treatment groups.

Disposition by week: The numbers of patients completing each week of the trial is shown below.

	Week 0	Week 1	Week 2	Week 3	Week 4	Week 5	Week 7	Week 9	Week 13
Fluoxetine	71	71	67	66	65	64	57	52	49
Placebo	32	31	29	28	28	24	20	20	20

Dosage: Among the 71 fluoxetine treated patients, the final dose received was 10 mg for 5 patients, 20 mg for 35 patients, 40 mg for 16 patients, and 60 mg for 15 patients.

Concomitant medications: The most commonly used concomitant medications were ibuprofen, acetaminophen, and salbutamol. The greatest discrepancy in concomitant medication use was observed for loratadine, used by 12.5% of placebo patients and 1.4% of fluoxetine patients.

Efficacy measures

The mean change from baseline to endpoint in the CYBOCS, which was designated the primary outcome measure, was greater for fluoxetine than placebo:

Treament	N	CYBOCS-total	
		mean change	SD
Fluoxetine	71	-9.5	9.2
Placebo	32	-5.2	7.4

p-value = 0.026 (ANOVA)

With respect to secondary outcome measures, the CGI severity score also demonstrated superiority for fluoxetine over placebo:

Treament	N	CGI-S	
		mean change	SD
Fluoxetine	71	-1.3	1.3
Placebo	32	-0.6	1.0

p-value = 0.009 (ANOVA)

Likewise, the NIMH Global OCD scale also showed greater improvement for fluoxetine than placebo:

Treament	N	NIMH Global OCD scale	
		mean change	SD
Fluoxetine	71	-3.1	3.0
Placebo	32	-1.3	2.2

p-value = 0.003 (ANOVA)

On the Childhood Depression Rating Scale-revised (CDRS-R), the fluoxetine group had a slightly greater mean improvement than the placebo group (-1.6 versus +0.5) but this did not reach statistical significance (p-value = 0.12).

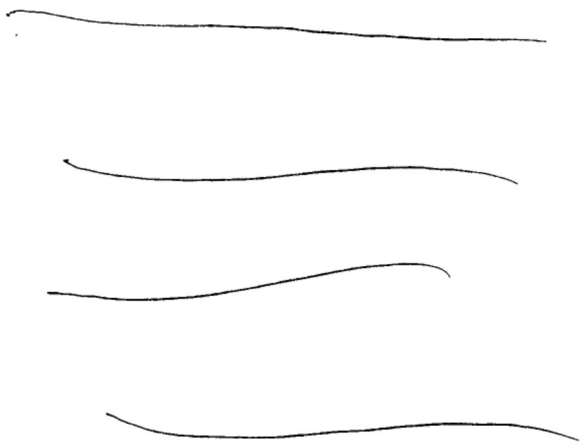
On the primary outcome measure (mean change in CYBOCS total score), there was not a statistically significant treatment X age or treatment X gender effect.

7.1.7 Conclusions: This trial provides evidence that fluoxetine is effective in the treatment of pediatric OCD.

7.2 Depression: Study HCJE

7.2.1 Investigators/sites

The following investigators participated in this study:



7.2.2 Objective: The principle objective of this trial was to evaluate the efficacy of 9 weeks of treatment with fluoxetine, compared to placebo, in children and adolescents with major depression.

7.2.3 Population: The study sample included male and female outpatients, aged 8-17 years, with non-psychotic major depressive disorder. Subjects were to have a minimum score of 40 on the Childhood Depression Rating Scale-Revised (CDRS-R) and a CGI Severity score of 4 or higher.

Among the exclusion criteria were the following: pregnancy, lactation, unprotected sexual intercourse for females, significant medical illnesses, seizures, thyroid disease, bipolar disorder, eating disorders, substance abuse, borderline personality disorder, suicidality, treatment refractory depression, drug allergies, previous fluoxetine treatment.

7.2.4 Design

The first study period was to be a 2-week evaluation, with three separate diagnostic interviews by three different clinicians. The patient's diagnosis was to be determined by consensus. Structured diagnostic interviews (Missouri Assessment of Genetics Interview for Children (MAGIC), Diagnostic Interview for Children and Adolescents (DICA), Family History Research Diagnostic Criteria (FHRDC), K-SADS) were to supplement the clinical interviews. Other scheduled baseline assessments included physical examination, clinical laboratories, CDRS-R, CGI, MADRS, and HAMA.

Following this, eligible patients were to receive one week of single blind placebo treatment. At the end of single blind placebo treatment, eligible subjects were to be randomized to fluoxetine or placebo; fluoxetine dosage was to be 10 mg daily for one week and then 20 mg/day for 8 weeks. The dose could be reduced back to 10 mg/day at the investigator's discretion.

At the end of this acute treatment phase, subjects who were considered responders to fluoxetine were to continue fluoxetine 20 mg/day. Those considered nonresponders were to be randomized to either continued treatment with 20 mg/day or titration to 40-60 mg/day. The duration of treatment in this phase of the study was to be 10 weeks. Placebo patients were to continue on placebo.

The final phase of the trial was an 8-month relapse prevention study. In this phase, patients who had responded to fluoxetine treatment were to be randomized to either placebo treatment or continued treatment with fluoxetine. Relapse was defined as a CDRS-R score > 40 plus 2 weeks of "clinical deterioration."

Subjects were not to use other psychiatric drugs for 2 weeks prior to the study (and were not permitted to use MAOIs for 6 weeks after the study). The protocol allowed only supportive psychotherapy as concomitant treatment.

The protocol included the following efficacy measures: CDRS-R, K-SADS, CGI, MADRS, Beck Depression Inventory, HAMA, Children's Depression Inventory. Safety assessments included vital signs, adverse event reporting, and repeat ECG, height and weight prior to the relapse prevention re-randomization.

7.2.5 Analysis

The primary outcome measure was defined as the proportion of patients achieving $\geq$ 30% reduction in their CDRS-R score at endpoint compared to baseline. To be included in the analysis subjects were required to have completed at least 2 weeks of fluoxetine treatment (with at leaset

one week at a dose of 20 mg/day). The titration of non-responders to higher fluoxetine doses was to be compared to continued fluoxetine treatment at 20 mg/day using the same definition of response.

For the relapse prevention phase, the time to relapse (as defined above) was the primary efficacy variable, and fluoxetine 10-60 mg/day was to be compared to placebo using a Kaplan-Meier survival analysis.

7.2.6 Results

Note that the relapse prevention phase was ongoing at the time of the original submission. The results for the relapse prevention portion of the study were submitted January 15, 2001.

Demographics and baseline characteristics

The following tables show the number of subjects according to randomized treatment, age group and gender. (I derived these tables from the sponsor's electronic dataset describing patient characteristics.) There was a slight preponderance of children versus adolescents; the ratio of male to female was close to unity.

FLUOXETINE	Male	Female	Total
Children (<13 years)	33	28	61
Adolescents (≥ 13 years)	22	26	48
Total	55	54	109

PLACEBO	Male	Female	Total
Children (<13 years)	33	28	61
Adolescents (≥ 13 years)	23	26	49
Total	56	54	110

With respect to ethnicity, 82% of the patients were Caucasian, 6% African-American, 6% Hispanic, 5% unspecified, and 1% Asian; the ethnic composition was comparable for the fluoxetine and placebo groups. The mean duration of the current episode of depression was approximately 61 weeks for both treatment groups; however, approximately 80% of subjects in both groups were naï ve to antidepressant drug treatment. Approximately 60% of subjects in both groups had a positive family history of depression.

The mean CDRS-R scores at baseline were 57.1 and 55.4 for the fluoxetine and placebo groups, respectively (p-value = 0.23, ANOVA).

Patient disposition: A total of 420 subjects were entered into the evaluation phase of the trial, and of these, 219 were considered eligible and were randomized to placebo (n=110) or fluoxetine (n=109).

The following table shows the numbers of patients remaining in the study at each visit during the acute treatment period, by randomized treatment.

Visit	Fluoxetine	Placebo
Randomized	109	110
Week 1	109	109
Week 2	109	104
Week 3	109	100
Week 5	106	96
Week 7	100	87
Week 9	94	77

Ninety-four fluoxetine subjects and 77 placebo subjects entered the nonresponder rerandomization phase, and of these, 40 fluoxetine subjects and 35 placebo subjects completed this phase.

The table below shows the numbers of subjects discontinuing prematurely during acute treatment, according to the specific reason for dropout.

Reason	Fluoxetine (n=109)	Placebo (n=110)
Adverse event	5	9
Lack of efficacy	5	12
Patient decision	3	11
Physician decision	1	0
Protocol requirement	4	3
Lost to follow-up	1	7
Total dropouts	19	42

There were considerably more dropouts from the placebo group than from the fluoxetine group. The pattern of dropouts for the placebo group was rather unusual, in that compared to fluoxetine, there were more dropouts for adverse events, patient decision and lost to follow up.

Concomitant medications: The most commonly used concomitant medications during the 9 week acute treatment period were acetaminophen and ibuprofen; more fluoxetine patients than placebo patients used acetaminophen (35% versus 21% for fluoxetine and placebo, respectively).

Efficacy results: As noted above, the primary endpoint was the proportion of patients achieving at least a 30% reduction in their baseline CDRS-R scores. The following table shows the results on this measure. As stipulated in the protocol, only patients who had completed at least week 2 of randomized treatment were analyzed.

Treatment group	Fluoxetine (n=109)	Placebo (n=101)
Responders	71 (65%)	54 (53%)
Nonresponders	38 (35%)	47 (47%)

p-value = 0.093, Fisher's exact, two tailed

Thus, the protocol specified primary outcome measure failed to show superiority of fluoxetine at the usual level of statistical significance. Subset analyses of the sample, according to gender, age category, and family history of depression, showed proportions of responders that were comparable to those in the complete sample.

The following shows the results for mean change on the CDRS-R:

Treatment group	Fluoxetine (n=109)	Placebo (n=105)
Baseline mean CDRS	57.1	55.1
Endpoint mean CDRS	35.1	40.2

p-value < 0.001 (ANOVA)

Similarly, the mean change results for the CGI-Severity and MADRS scores were statistically significant in favor of fluoxetine over placebo, but comparisons of the mean changes for the Beck Depression Inventory, the Children's Depression Inventory, and the HAMA were not statistically significant.

At the end of the acute treatment period, 29 fluoxetine non-responders were randomized to 10 weeks of either continued fluoxetine 20 mg/day (n=15) or fluoxetine 40-60 mg/day (n=14). Ten of the subjects who received a higher dose of fluoxetine became responders, compared to 5 of the subjects who continued on 20 mg/day (p-value = 0.13, Fisher's exact, two tailed). It is possible that had the sample size been larger, an advantage for titrating nonresponders to higher doses might have been demonstrated statistically.

Relapse prevention phase: At the end of the 10 week dose titration phase of the study (i.e., after 19 weeks of double blind treatment), fluoxetine patients who had a CDRS score $\leq$28 were re-randomized to either continue on their current fluoxetine treatment or to receive placebo. Placebo responders continued on placebo. The duration of this phase of the study was 8 months.

There were a total of 40 fluoxetine responders and 35 placebo responders. Of the 40 fluoxetine responders, all but 6 were receiving 20 mg/day (4 were receiving 40 mg/day and 2 were receiving 60 mg/day). Of the fluoxetine responders, 20 were randomized to placebo and 20 to continued fluoxetine. The fluoxetine subjects were older on average; the mean age for the 20 placebo subjects was 11.7 years, and for the 20 fluoxetine subjects was 13.5 (p-value = 0.025, ANOVA). There were 9 girls and 11 boys in the fluoxetine group, and 11 girls and 9 boys in the placebo group. There was an imbalance with respect to anxiety symptoms, however: 13 placebo patients

but only 5 fluoxetine patients had baseline HAM-A scores above the median.

A total of 10 fluoxetine subjects and 8 placebo subjects completed this 8-month portion of the trial. In the study report, Lilly designated the analysis using the protocol defined definition of relapse as a secondary analysis. However, I prefer to consider this as the primary analysis, and according to the protocol definition (see above), 9 placebo patients and 3 fluoxetine patients relapsed. The difference in time to relapse as determined by survival analysis was statistically significant in favor of fluoxetine (p-value = 0.032, log-rank). Using Lilly's preferred definition of relapse, which also included patients who were discontinued from the trial for lack of efficacy, there were 6 relapses in the fluoxetine group and 12 in the placebo group, and the difference in time to relapse was also statistically significant in favor of fluoxetine.

7.2.7 Conclusions: This study provides some evidence for an effect of fluoxetine on depressive symptoms, as measured by the change in the CDRS score, but failed to show statistically significant effect of fluoxetine according to the protocol specified primary outcome measure. The relapse prevention phase showed an advantage for fluoxetine over placebo in time to relapse; however, the sample size was relatively small even though statistical significance was demonstrated.

7.3 Depression: Study X065

Lilly did not sponsor this study, and the trial was not conducted under an IND. The investigator's NIMH grant proposal was submitted as part of the study report, in lieu of a study protocol. For some reason, it appears that the first 28 pages of this grant proposal are not included in the submission.

This study has been published.[1] According to the published paper, the study was supported by grants from NIMH.

7.3.1 Investigators/sites: There was a single principal investigator for this study, Graham Emslie, M.D., and one site, the University of Texas Southwestern Medical Center at Dallas. There were two other study physicians who served as the principle subinvestigators:

7.3.2 Objective: The grant proposal states that the following were the goals of the study: to assess sleep abnormalities and responses to the dexamethasone suppression test (DST) in depressed pediatric outpatients, to determine the effectiveness of fluoxetine in comparison to placebo in the treatment of pediatric outpatients with major depressive disorder (MDD), to determine if the response to fluoxetine differs between children and adolescents, to determine if reduced REM latency or DST response predicts response to fluoxetine, to assess the relationship between patient

1 Emslie GJ, Rush AJ, Weinberg WA, et al. A double-blind, randomized, placebo-controlled trial of fluoxetine in children and adolescents with depression. Arch Gen Psychiatry 1997; 54:1031-1037.

baseline characteristics and response, and to obtain pharmacokinetic samples for fluoxetine concentrations. Obviously, not all of these objectives are germane to Lilly's submission.

7.3.3 Population: The specified population was outpatients aged 8-18 years, with MDD as defined by DSM-III criteria. Half of the sample was to be children aged 8-12 years and half was to be adolescents aged 13-18 years. The sample size was to be 120 subjects, although the protocol states elsewhere that "the study continues until 80 subjects (40 children and 40 adolescents) have completed the protocol." Subjects were not to have psychotic features, and were to be of normal intelligence. Exclusion criteria included bipolar disorder, a family history of bipolar disorder, medical illnesses, previous fluoxetine treatment, sleep disorders, substance abuse, eating disorders, allergies to tricyclic antidepressants, and failure to use contraceptive measures. The subjects were to have a baseline Children's Depression Rating Scale-revised (CDRS) score of at least 40.

7.3.4 Design: Initial screening was to be by telephone call, after which the subject was to discontinue medications for at least 7 days prior to the initial evaluation. The screening procedures were scheduled over 3 weeks, with a structured interview of the child and caregiver using the Diagnostic Interview for Children and Adolescents (DICA) at the first visit. Additional assessments scheduled for the initial visit included a physical exam, clinical laboratories, family history, and CDRS, among others. The CDRS was to be completed by the clinician after interviewing the child and parent together. The next week's screening visit was to involve a clinical assessment by one of the investigators to confirm the diagnosis, along with another CDRS. Subjects also were to receive dexamethasone suppression testing (DST) and polysomnography. A third and final diagnostic assessment by a second investigator was to follow these procedures. If subjects met eligibility criteria on all three visits they were to enter the treatment phase of the study.

Following the informed consent process, subjects were to receive a one-week supply of single-blind placebo. At the end of this week, if their CDRS score was still at least 40, they were to be randomized to either fluoxetine 20 mg/d or placebo. Randomization was to be stratified on both age group (child versus adolescent) and gender. An ECG was also to be obtained at the end of the single blind placebo week. Subjects were to continue their study medication for 8 weeks, with weekly clinic visits and CDRS ratings. Other assessments were to include Bellevue Index of Depression, Weinberg Screening Affective Scale, Child Global Assessment Scale (C-GAS), Children's Depression Inventory or Beck's Depression Inventory, Clinical Global Improvement (CGI), and Brief Psychiatric Rating Scale. Safety monitoring was to include side effect checklists, clinical laboratories and ECGs. Pharmacokinetic blood sampling was also scheduled at several visits. In addition, provisions were made for a clinician unfamiliar with the patient to conduct independent assessments, at the end of the single blind placebo week and at the end of double blind treatment. Patients were not to receive concomitant psychotherapy. Patients could have their dosage reduced to every other day if indicated. After the study, patients who were considered responders could continue on their double blind medication, while nonresponders were to receive usual care; apparently the study medication was to be unblinded for a subject who relapsed.

7.3.5 Analysis

On page 47 of the grant proposal is the following statement: "The primary outcome variable of this experiment is the proportion of completing subjects in each group (placebo and drug) who recover, where recovery is defined as below 28 on the CDRS-R and a CGI of 1 or 2...A second way to measure outcome is to use the end-of-treatment scores on the weekly CDRS-R and CGAS." Elsewhere the grant proposal defines completers as subjects who received at least 4 weeks of medication.

Lilly arranged to acquire the raw data from Dr. Emslie and colleagues in 1997, as part of their pediatric development program for fluoxetine, but of course by this time the results of the study had been published. In reporting the trial for this submission, Lilly chose a different primary endpoint, the proportion of patients achieving a 30% reduction from baseline in their CDRS score.

7.3.6 Results

The study was conducted between April 1991 and February 1995.

Demographics and baseline characteristics: The following table shows the number of subjects according to randomized treatment, age group and gender. (I derived this table from the sponsor's electronic dataset describing patient characteristics.)

FLUOXETINE	Male	Female	Total
Children	14	10	24
Adolescents	12	12	24
Total	26	22	48

PLACEBO	Male	Female	Total
Children	15	9	24
Adolescents	11	13	24
Total	26	22	48

With respect to ethnic origin, 79% of the total sample was Caucasian, 10% Hispanic, and 8% African-American, and the fluoxetine and placebo groups were comparable. The most common comorbid diagnoses were ADHD (24%), anxiety (41%), oppositional/conduct disorders (29%) and dysthymia (35%). There was an imbalance at randomization between the fluoxetine and placebo groups with respect to comorbid anxiety disorders: 26 fluoxetine patients but only 13 placebo patients had comorbid anxiety disorders (p-value = 0.012).

The mean CDRS-R total scores for the fluoxetine and placebo groups at baseline were 58.9 and 57.5, respectively.

Patient disposition: One hundred and eight subjects entered the single blind placebo treatment period, and of these, 96 were still considered eligible at the end of the placebo run-in and were randomized (48 to placebo and fluoxetine each). One placebo patient had no post-randomization CDRS assessments and was therefor excluded from the efficacy analyses. Thirty-three fluoxetine patients and 25 placebo patients completed the study.

Initially, the pharmacy at the site formulated the placebo capsules by taking marketed Prozac capsules and replacing the contents with lactose powder. (Note that the two halves of the Prozac capsule must be re-aligned after such a procedure, otherwise the imprints on the two halves of the capsule will be mismatched and it will be obvious that the capsule has been opened.) The first 54 patients received either marketed Prozac or placebo made in this way. Subsequently, Lilly provided investigational fluoxetine capsules and matching placebo; apparently no subjects received both types of study drug.

Concomitant medications: Ibuprofen, acetaminophen and diphenydramine were the most frequently used concomitant medications. For no concomitant medication was there a statistically significant discrepancy between treatment groups in the proportion of patients receiving it.

Efficacy measures

For Lilly's definition of response (30% reduction in CDRS total score from baseline), the following table shows the proportion of patients achieving this outcome.

Treatment group	Fluoxetine (n=48)	Placebo (n=47)
Responders	28 (58.3%)	15 (31.9%)
Nonresponders	20 (41.7%)	32 (68.1%)

p-value = 0.013, Fisher's exact, two tailed

I was not able to locate an analysis of the primary outcome measure specified in the grant proposal (i.e., the proportion of completers in each group with a CDRS below 28 and a CGI of 1 or 2).

The following shows the results for mean CDRS scores:

Treatment group	Fluoxetine (n=48)	Placebo (n=47)
Baseline mean CDRS	58.9	57.5
Endpoint mean CDRS	38.7	47.0

p-value = 0.002 (ANOVA)

In addition, the CGI-Improvement mean endpoint scores were 2.5 and 3.2 for fluoxetine and placebo, respectively, indicating more improvement in the fluoxetine group (p-value = 0.015, ANOVA).

Subgroup analyses

Source of study medication: Lilly conducted a subgroup analysis based upon whether patients received study medication prepared on site or supplied by Lilly (see above). For site prepared study medication, the proportion of patients meeting Lilly's definition of response was 15/25 (60%) for fluoxetine and 8/29 (28%) for placebo. For Lilly supplied study medication, the proportion of responders was 13/23 (57%) for fluoxetine and 7/18 (39%) for placebo. Thus, the results were roughly comparable between the two types of medication (Breslow-Day test for homogeneity of odds ratio p-value = 0.4).

Comorbid anxiety:
As described above, there was an imbalance at randomization in the proportion of patients with comorbid anxiety disorders, with the fluoxetine group having significantly more such patients. Dr. ——— the Biometrics reviewer, performed a subgroup analysis based on presence or absence of comorbid anxiety:

Patients without comorbid anxiety

Treatment	Fluoxetine	Placebo
n	22	34
Responders	12	13
% responders	55%	38%

p-value = 0.28, Fisher's exact

Patients with comorbid anxiety

Treatment	Fluoxetine	Placebo
n	26	13
Responders	16	2
% responders	62%	15%

p-value = 0.008, Fisher's exact

Thus, the difference favoring fluoxetine over placebo in the proportion of responders was much greater in the subgroup of 39 patients with comorbid anxiety disorders.

——— also provided an analysis of mean change from baseline in CDRS scores for each subgroup:

Patients with comorbid anxiety
Fluoxetine –20.8
Placebo –4.6
p-value = 0.0016

Patients without comorbid anxiety
Fluoxetine = -19.5
Placebo = -12.7
p-value = 0.11

Note that the mean improvement with fluoxetine treatment was similar in each subgroup, but was much less with placebo for patients with comorbid anxiety.

Unblinding

The blind for the entire study was not broken until spring 1995; however, there appear to have been some isolated instances in which the blind was broken:

1. A nurse who had access to the randomization codes substituted as a clinician rater on two occasions (visit 2 for placebo patient 2013 and visit 3 for fluoxetine patient 2014).
2. Two subjects who attempted suicide may have had their blinded treatment revealed to a non-study physician who was not an investigator (fluoxetine patients 2051 and 2163).
3. For "less than ten" patients who received post-study treatment from one of the physician-investigators, the subject's treatment was unblinded for the purpose of planning follow up treatment.

In addition, Lilly reported that in their review of the primary source records it was not uncommon to see notations defining the patient's blinded treatment, or in some cases to find fluoxetine plasma concentration results. Apparently, however, the information about the patient's actual treatment was typically added to the charts retrospectively. Lilly states in the study report, "...very rarely did the [Lilly] team see evidence the site did, in fact, unblind the patient's assigned therapy..."

7.3.7 Conclusions

There were some difficulties in the conduct of the study, as described above, including some instances of unblinding, and the fact that placebo initially had to be formulated from marketed Prozac capsules. These problems would be unusual for an industry-sponsored Phase III trial, but of course this study was not overseen by Lilly. On balance I do not think these problems would have introduced enough systematic bias to invalidate the results.

As noted above, I was not able to locate an analysis of the primary outcome measure specified in the grant proposal (i.e., the proportion of completers in each group with CDRS < 28 and CGI $= 1$ or 2). However, there is enough consistency in the outcome measures that were provided in the study report to make this less of a concern. Furthermore, our Division has tended to favor analyses based on continuous measures (such as mean CDRS score) over such categorical outcomes with their somewhat arbitrary definitions of clinical response.

More problematic is the finding that the effect of the drug is most evident in the subgroup of patients with comorbid anxiety disorders. Although this was a post-hoc analysis, this finding should be viewed in the context of previous pediatric psychopharmacology trials, which have typically showed minimal efficacy in depression, but obvious benefits in OCD. In fact, Zoloft and Luvox are currently labeled for pediatric OCD, and a recent publication suggests that fluvoxamine

has effects in other pediatric anxiety disorders as well.[1] In fact, this supplement includes a positive clinical trial for fluoxetine in OCD. Thus, it is possible that the improved CDRS scores in this trial did not reflect amelioration of depression per se, but instead a non-specific overall improvement related to anxiolytic effects of fluoxetine.

On balance, this trial provides evidence for a benefit of fluoxetine treatment in pediatric depression, but the outcome may have been confounded by comorbid anxiety disorders.

7.4 Overall conclusions regarding efficacy: The evidence for efficacy in the treatment of OCD is convincing. The evidence for efficacy in the treatment of pediatric depression is not as robust, because one study was not positive on its designated primary outcome measure, and the other may have been confounded by an imbalance of patients with comorbid anxiety disorders. The relapse prevention protocol did show a difference in time to relapse favoring fluoxetine treatment, but the sample size was small, and there was again an imbalance in baseline anxiety symptoms between treatment groups. It is conceivable that the CDRS instrument is more sensitive to changes in anxiety than in depression. However, with respect to this, it is somewhat reassuring that the MADRS also showed a positive effect in study HCJE. On balance, I believe the trials provide evidence that fluoxetine benefits pediatric patients with depression.

8.0 Safety

8.1 Safety methods

The sponsor created an integrated safety data set using clinical data from studies HCJE, HCJW, HCIU and X065. This included a total of 250 fluoxetine treated subjects and 190 placebo treated subjects. Additionally, data from the three randomized trials (HCJE, HCJW, and X065) were pooled for analysis of events in the acute treatment portions of the randomized controlled trials; this excluded the extension phases of HCJE. Spontaneously reported adverse event data from studies HCJE, HCJW, and HCIU were pooled for analysis, while solicited adverse event data from the two studies employing the Side-Effects Checklist (HCJE and X065) were analyzed separately. Lilly states in the integrated safety summary (ISS) that "treatment-emergence" was unclear for the spontaneously reported adverse events in study X065, and so only solicited adverse event data from that trial were included in the integrated analysis.

Clinical laboratories were obtained at baseline and on treatment in all four studies noted above, as were vital signs, height and weight. (Please see table 1.1 in ISS, page 145). ECGs were obtained only in studies HCIU and HCJE.

Updated safety information from the relapse prevention phase of study HCJE was submitted January 15, 2001. As this phase of the study involved only 20 subjects who received fluoxetine, I did not attempt to integrate these data into the sponsor's ISS data, and I will describe these safety

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1 Research Unit on Pediatric Psychopharmacology Anxiety Study Group. Fluvoxamine for the treatment of anxiety disorders in children and adolescents. N Engl J Med 2001;334:1279-85

data separately. Also, the safety data from study [redacted] which was terminated early, were not included in the ISS, and will also be described separately.

8.2 Deaths: There were no deaths in these pediatric studies.

8.3 Assessment of dropouts

8.3.1 Overall pattern of dropouts

The following table shows the pattern of premature discontinuations for the randomized controlled trials, acute phase.

Reason for discontinuation	Fluoxetine (n=228)	Placebo (n=190)
Adverse event	7.0%	5.8%
Lack of efficacy	9.2%	20.5%
Patient decision	2.6%	6.8%
Protocol requirement	3.5%	2.6%
Lost to follow up	0.9%	4.2%
Discontinuation--any reason	24.5%	40.5%

The largest discrepancy between fluoxetine and placebo patients was in the percentage of dropouts for lack of efficacy.

8.3.2 Adverse Events Associated with Dropout

No patients discontinued for adverse events from the pharmacokinetic study HCIU.
Twenty-two of the 228 patients randomized to fluoxetine in the short term controlled trials discontinued for adverse events. The adverse events and numbers of patients discontinuing because of them are listed below. Not shown are events for which only placebo patients discontinued.

	Discontinuations	
Adverse event	Number of fluoxetine patients	Number of placebo patients
Manic reaction	4	0
Hyperkinesia	2	1
Rash	2	1
Personality disorder	2	0
Agitation	1	0
Constipation	1	0
Headache	1	1
LFT abnormal following acetaminophen overdose	1	0
Nervousness	1	1
Somnolence	1	0
Suicide attempt	1	0

Depression	1	0
Endometrial hyperplasia	1	0
Hostility	1	1
Euphoria	1	0
Migraine	1	0

8.4 Serious adverse events: No serious adverse events occurred in the pharmacokinetic study HCIU, or in the relapse prevention phase of study HCJE. In short term controlled trials, there were 3 serious adverse events prior to randomization (all involving psychiatric hospitalization of the patient, in depression study HCJE). The following serious adverse events occurred among fluoxetine treated patients during controlled trials HCJE, HCJW and X065: tonsillectomy, suicide attempt (2 subjects), hospitalization for suicidal ideation, acetaminophen overdose with hepatic toxicity.

Additionally, in the adolescent depression study that was terminated early and was not included in the ISS database (protocol ——— two fluoxetine treated subjects experienced serious adverse events: generalized rash, and hospitalization for suicidal ideation.

8.5 Other safety findings

8.5.1 Adverse event incidence

For spontaneously reported adverse events in the acute treatment studies HCJW and HCJE, the following were common, drug related adverse events (defined as events with an absolute incidence of at least 5% and a relative risk of at least 2):

Event	Fluoxetine incidence (%)	Placebo incidence (%)
Hyperkinesia	6.1	0.7
Rash	7.8	2.8

For the adverse events solicited by checklist in studies HCJE and X065, there were no common, drug related adverse events by the above definition.

8.5.2 Laboratory findings

Acute studies
Clinical laboratories were obtained routinely during study HCJW and to a lesser extent during study X065; clinical laboratories were not obtained during the acute treatment phase of study HCJE. Lilly analyzed the available laboratory data from HCJW and X065. Unfortunately the reference ranges for the clinical laboratories were not provided with the submission.

The only premature discontinuation in conjunction with a clinical laboratory abnormality involved the patient who took an overdose of acetaminophen and developed elevated liver enzymes (see under Serious Adverse Events above).

With respect to the incidence of laboratory values outside the normal range, there was no difference between fluoxetine and placebo. With respect to mean changes from baseline in laboratory values, the following differences were statistically significant:

Laboratory	Units	Fluoxetine mean change	Placebo mean change
Phosphorus	mmol/L	-0.05	+0.03
Cholesterol	mmol/L	+0.03	-0.30
Sodium	mEq/L	+0.19	+1.70
Chloride	mEq/L	-0.07	+1.60

Longer term treatment
In study HCJE, clinical laboratories were obtained at baseline and at week 19, prior to randomization for the relapse prevention phase. Differences in incidence of abnormal values were not statistically significant for any laboratory parameter between fluoxetine and placebo. However, the following differences in mean change from baseline were statistically significant when comparing fluoxetine and placebo:

Laboratory	Units	Fluoxetine mean change	Placebo mean change
Alkaline Phosphatase	U/L	-35	-5
Cholesterol	mmol/L	+0.09	-0.13

The only finding common to both acute and longer term treatment was the increase in mean cholesterol levels with fluoxetine.

8.5.3 Vital signs, height and weight

Data on mean changes in heart rate and blood pressure from the acute treatment clinical trials showed a decrease in mean heart rate for fluoxetine of 1.9 bpm compared to an increase of 0.6 bpm with placebo (p-value = 0.06). This is consistent with data in adults showing a slight decrease in mean heart rate.

Data on height and weight were available for the 19 week timepoint of study HCJE. These data are shown below:

Treatment group	Fluoxetine	Placebo	p-value
Mean change in height (cm)	+1.0	+2.0	0.008
Mean change in weight (kg)	+1.2	+2.3	0.008

Reduced mean weight and height gains for fluoxetine treated patients relative to placebo were found in both the child and adolescent subgroups, although the group differences were not statistically significant in the somewhat smaller adolescent subgroup. Lilly's examination of data from the few patients who received doses above 20 mg/day in this study suggested that the reduction in weight gain was dose related (but not the reduced increase in height).

There was also a smaller, but statistically significant, difference in weight gain between groups in the acute treatment trials, again indicating reduced weight gain with fluoxetine compared to placebo. There were no such differences in mean change in height in these trials.

8.5.4 Electrocardiograms

Background: Previous ECG findings regarding fluoxetine in adults

In the development program for r-fluoxetine, this isomer was found to produce dose-dependent prolongation of the corrected QT interval in adults. For example, in an 8 week depression trial, the high dose of 80 mg of r-fluoxetine daily produced a mean change in QTc of 9.8 msec, compared to –3.3 msec for placebo (p-value = 0.0001); the 40 mg daily dose was associated with a smaller mean increase. Also, in the original NDA for racemic fluoxetine, in placebo controlled trials fluoxetine treatment (various doses combined) was associated with a mean change in QTc of 5 msec compared to –2 msec for placebo (p-value = 0.012). Additionally, both r-fluoxetine and r-norfluoxetine have been shown to inhibit cardiac I_{kr} (HERG) channels, suggesting that the compounds may affect cardiac repolarization. I am not aware of any such preclinical data for the s-isomers. Previously, there have been few systematically collected data regarding the ECG effects of fluoxetine in pediatric patients.

Pediatric ECG data in this submission

ECGs were obtained during treatment in two studies: in the pharmacokinetic study HCIU, which had no placebo control group, and after 19 weeks of treatment in the depression study HCJE. Lilly submitted a revised analysis of the ECG data from study HCJE on January 15, 2001, and an analysis of the ECG data from study HCIU on May 22, 2001.

In study HCJE, baseline and on-treatment ECGs were available for 88 fluoxetine patients and 73 placebo patients. Mean changes in heart rate, PR interval, and QRS duration were not statistically significantly different between fluoxetine and placebo. The cube root corrected QT interval increased by a mean of 7.4 msec for fluoxetine patients compared to 0.2 msec for placebo patients (p-value = 0.009, ANOVA). Using the square root correction, the mean QT interval changes were 7.9 msec and 0.7 msec for fluoxetine and placebo, respectively (p-value = 0.034, ANOVA). Mean QTc increased with fluoxetine in both the child and adolescent subgroups (1/30/01 submission). With respect to the incidence of outliers for ECG parameters, there were no significant differences between fluoxetine and placebo.

The analyses summarized above were performed using blinded ECG readings provided by the [redacted]. As described in a February 2001 email from Dr. David Johnson at Lilly, this is a group that Lilly has used frequently in the past for ECG analyses. After receiving the [redacted] analyses, Lilly decided "based on some things we saw in those readings" to obtain two other readings of the same ECG tracings, a blinded reading by [redacted] of Medicine), and a computer reading by [redacted] using "electronic calipers." For the ECGs as read by [redacted] no differences between

fluoxetine and placebo on mean changes in any ECG parameter were statistically significant. Lilly argues that the electronically generated ECG data from [redacted] are the most precise and accurate.

Analysis of ECG data by [redacted] for the pharmacokinetic study HCIU revealed no statistically significant mean changes from baseline in any ECG parameter; in fact, the mean QTc interval actually decreased, by a margin that was not statistically significant.

8.5.5 Other safety topics

Safety data from relapse prevention phase of HCJE: This was submitted separately (January 15, 2001). There were 20 subjects who received fluoxetine throughout the double blind and relapse prevention phase, and 35 subjects who received only placebo during the entire trial. A third group of 20 subjects received fluoxetine initially, and were then randomized to placebo for the relapse prevention phase. These 3 groups of subjects are designated as fluoxetine/fluoxetine, placebo/placebo, and fluoxetine/placebo, respectively. The total duration of study treatment was up to 51 weeks from baseline.

There were no deaths or serious adverse events in the relapse prevention phase. One fluoxetine/fluoxetine patient discontinued with agitation; two placebo/placebo patients discontinued (one for ADHD, one for a viral illness).

Fluoxetine/fluoxetine patients had a mean height increase of 2.9 cm at endpoint from pre-study baseline, compared to 5.1 cm for placebo/placebo patients (p-value = 0.065). However, Lilly points out that the fluoxetine/fluoxetine patients were taller on average at baseline.

With respect to laboratory values, there were no statistically significant between group differences in the incidence of abnormal values; however, the following differences in mean values between fluoxetine/fluoxetine and placebo/placebo patients were statistically significant:

Laboratory	Units	Mean change flx/flx	Mean change pbo/pbo
Alk. Phos.	U/L	-39	-5
BUN	mmol/L	0.8	-0.1
Free T4 index	(none)	-0.14	0.09
Urine sp gr	(none)	0.01	0.00

With respect to alkaline phosphatase, a mean decrease with fluoxetine treatment was also observed with shorter duration treatment (see above). In addition, mean alkaline phosphatase for fluoxetine/placebo patients increased by 19 U/L during placebo treatment, following discontinuation of fluoxetine.

Safety data from study [redacted] The study included a 6-week double blind period, and open label treatment up to 52 weeks in duration. A total of 21 adolescent subjects were randomized to fluoxetine in this trial, which was terminated due to slow patient accrual. In addition, 21 subjects received open label fluoxetine (but I was unable to determine how many of these subjects were

first treated with placebo and were only exposed to fluoxetine in the open label period). There were 5 serious adverse events (none fatal) in the trial: one fluoxetine subject discontinued treatment with a generalized rash, one fluoxetine and one placebo patient each were hospitalized for suicidality, one subject took an overdose of placebo during the placebo lead in, and one fluoxetine subject took an overdose of 3 medications.

Literature review:
Lilly provided a literature review only with respect to efficacy in the pediatric population; they did not review the literature with respect to the pediatric safety profile for fluoxetine.

Attempted suicide:
Lilly searched the adverse event reports in this development program for events which represented attempted suicide. There were 3 suicide attempts among 228 fluoxetine treated patients, and 1 suicide attempt among 190 placebo treated patients (p-value = 0.6). In addition, one fluoxetine patient was hospitalized because of suicidality.

Mania:
Lilly reported that in the three controlled trials, 6 out of 228 (2.6%) fluoxetine treated patients, and none of 190 placebo treated patients, developed mania or hypomania. This difference in risk was statistically significant (p-value = 0.034). Four of the six subjects discontinued from their study prematurely because of this event.

8.6 Adequacy of safety assessment: I have the following comments.

1. Only 31 subjects in this development program received a final dose of fluoxetine higher than 20 mg/day. Additionally, there are no pharmacokinetic data available for any dose higher than 20 mg/day. I do not believe the data are adequate to label doses higher than 20 mg/day for pediatric use.

2. There are no pharmacokinetic data with respect to the r- and s- enantiomers of fluoxetine and norfluoxetine, which have different pharmacokinetic properties in adults.

3. Lilly did not search their postmarketing adverse event database for signals of any unusual adverse events in children and adolescents.

4. There is no dose-response data for any ECG parameters, which would have been especially relevant in assessing the effects on cardiac repolarization.

5. Lilly did not review the literature regarding safety in pediatric patients.

6. With respect to height and weight, Lilly did not assess these data in terms of growth percentiles for age and gender. This would have been more meaningful than simply pooling the height and weight data for all subjects.

8.7 Overall conclusions about safety

Mania and hypomania appear to be much more common with fluoxetine treatment in these trials than has been the case in adult clinical studies. Also, the available data indicate that fluoxetine reduces growth velocity, although a superior method of analysis would have been to determine the effect of treatment on height and weight percentiles, according to age and gender. Lilly may wish to perform such an analysis. With respect to the decrease in mean alkaline phosphatase among fluoxetine treated patients, this is of some concern given the finding of decreased height gain, because alkaline phosphatase levels reflect calcium deposition in bones. For example, alkaline phosphatase is decreased in prepubertal growth hormone deficiency.[1] Regarding the ECG analyses, clearly the findings vary according to the consulting group performing the analysis. My own bias is to place more weight on the initial analysis, which did show a mean increase in the QTc interval with fluoxetine. This finding is quite plausible, given the recent evidence that the r-isomer of fluoxetine prolongs the QTc interval in a dose dependent fashion, and blocks HERG potassium channels in vitro.

9.0 Overall Conclusions and Recommendations

The supplement is approvable, in my opinion.

I do not believe the data are adequate to label doses higher than 20 mg/day for pediatric use.

Lilly should search their postmarketing adverse event database for signals of any unusual adverse events in children and adolescents.

Lilly should conduct a pharmacokinetic-pharmacodynamic study to assess more completely the cardiac effects of fluoxetine in pediatric subjects, given the mean increase in QTc interval with 20 mg daily observed in study HCJE.

Lilly should review the literature regarding safety in pediatric patients.

With respect to height and weight, Lilly may wish to analyze the existing data from study HCJE in terms of growth percentiles for age and gender.

My suggestions for labeling are attached.

Andrew D. Mosholder, M.D.
Medical Officer, HFD-120

Cc: Laughren, David, Mosholder

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5 page(s) of
revised draft labeling
has been redacted
from this portion of
the review.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Andy Mosholder
6/25/01 10:45:38 AM
MEDICAL OFFICER

Thomas Laughren
7/3/01 02:21:29 PM
MEDICAL OFFICER
I agree that this supplement is approvable; see memo to file for more detailed comments.--TPL