

Prozac Paediatric Indication

Arbitration Procedure No: EMEA/H/A-6(12)/671

**Lilly Response to Questions from EMEA in Document
EMEA/CHMP/175191/05**

Eli Lilly and Company Ltd
Lilly Research Centre
Surrey GU20 6PH
England

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Table of Contents

Contents	Page
Table of Contents	2
1.Introduction.....	4
2.Responses to Questions 1 - 13	5
2.1.Non-Clinical.....	5
2.2. Clinical Efficacy.....	10
2.3.Clinical Safety	12

Contents	Page
Attachment 1. Additional Pre-Clinical Information	17
Attachment 2. Animal Studies Evaluated in Examining Juvenile versus Adult Sensitivity	20
Attachment 3. Briefing Document for Study HCLT	22
Attachment 4. Summary of Objectives: Study HCLS	56
Attachment 5. Growth Retardation and Delayed Sexual Maturation in Children and Adolescents Treated with Fluoxetine	57
Attachment 6. Reference List	83
Appendix 1. Analysis of Male Reproductive, Skeletal Muscle, Sexual Maturation, and Growth Effects of Fluoxetine and Norfluoxetine.....	86

1.Introduction

This document is to serve as Lilly's response to the letter from Dr Panos Tsintis dated 26 May 2005 and with reference to EMEA/174118/2005. It is being provided to the Rapporteur and Co-rapporteur with a copy to EMEA. Lilly has chosen to provide a single consolidated response and accordingly Letters of Representation were provided on 8 July 2005 to Ms Palmi Reig at EMEA.

2. Lilly Responses to Questions 1 - 13

2.1. Non-Clinical

*The study on young rats for the assessment of the juvenile toxicity shows a **very unfavourable profile to support the paediatric indication of fluoxetine hydrochloride**. Severe effects were observed on body weight gain, sexual maturation in males and females, testes, skeletal muscles, sperm concentration at the dose of 30 mg/kg/day, some of these effects occurring at 10 mg/kg/day.*

*The adverse effects may be due to exaggerated pharmacological effects (modification of GnRH, neuroendocrine and immunological parameters). However, **the effects are severe and they appear with no or low safety margins. Notably the effects on testes were not reversible** and reproductive performances were affected at the top dose. Some effects (delayed growth and delayed puberty) have been reported in humans. The safety margins are lower than those calculated by the MAH, because the MAH based its calculation on LOAELs instead of NOAELs. For example, the NOAEL of 3 mg/kg/day corresponds to an absence of safety margin (less than 1, based on systemic exposure). The reversibility or non-reversibility of the observed effects is a concern, as the clinical observations from clinical studies and from pharmacovigilance database. Therefore **the provided data are not currently acceptable for the agreement of a paediatric indication of fluoxetine hydrochloride**.*

*Question 1: **Further explanations and studies are necessary** to better define the mechanism of each adverse effect observed in juvenile rats, the reversibility of the effects for reproductive toxicity, the effects on the hormonal status, the role of the metabolites (taking into account potential differences in norfluoxetine formation in adults and children, when doing interspecies comparisons) and the rate of metabolization. The interspecies toxicity, especially for testes lesions and sexual maturation should be documented in prospect of the clinical relevance for young human.*

Lilly Response:

The document "Analysis of male reproductive, skeletal muscle, sexual maturation, and growth effects of fluoxetine and norfluoxetine" contains a detailed review of the concerns outlined above and was included in the March 18th response to the AFSSAPS Final Assessment Report (Appendix 1). The overall risk assessment takes into account margins of safety and other factors of equal or greater significance, including the relative sensitivity of monitorable and poorly monitorable (eg testicular toxicity) changes. The current data package is considered acceptable in assessing clinical risk; however, to understand the hormonal status surrounding the time of sexual maturation, an additional rat study is planned.

In summary, no toxicities were observed that were unique to the juvenile rats except for the slight delay in sexual maturation, which is an endpoint unique to development and therefore would not be expected to be affected in adults. Subtle delays in the onset of puberty were observed in the juvenile rat study with R,S-fluoxetine. The

effects were greater at exposures that exceeded the maximum tolerated dose (MTD); however, interpreting these data is confounded by the clinical condition of the animals. Although maturation delays were observed at the mid- and high-doses, all rats ultimately reached sexual maturity prior to the cessation of treatment. The clinical relevance of delayed sexual maturation in rats is unclear but is a monitorable event in human subjects. **Hormones were not measured in this study; however, other studies examining the neuroendocrine effects of serotonergic compounds suggest that perturbation of GnRH secretion is a possible cause.**

Lilly recognizes the low margins of safety based on plasma drug exposures. The table in Attachment 1 summarizes the margins of safety for fluoxetine and norfluoxetine; preadolescents and adolescents, including ranges for individual subjects; and single dose and steady-state values. For the endpoints in the juvenile R,S-fluoxetine study that were only affected at exposures above the MTD (testes and skeletal muscle pathology and femur length), individual margins of safety ranged from 0.4 to 23. For the endpoints that were affected at a lower exposure (body weight gain and sexual maturation), individual margins of safety ranged from 0.1 to 2.1. While the margins of safety based on this rat study are low, dose-response relationships in the rat study suggest that the clinical risk of these events is low. While this rat study might predict an effect on body weight gain or a slight delay in sexual maturation at therapeutic exposures, these are monitorable effects. Any profound toxicity (eg irreversible testicular toxicity) occurred only in conjunction with other clinically observable signs of toxicity (eg extreme decreases in body weight gain) and at an exposure that is not tolerated chronically in the rat. Current pediatric doses are well-tolerated upon repeated administration and are considered below the pharmacologic challenge required to produce the unwanted high-dose effects described.

Question 2: The MAH argues that norfluoxetine is implicated in the testicular toxicity. According to the toxicokinetic data, it appears that norfluoxetine exposure at day 21 is approximately 6 to 7 times less than the exposure at day 90. Nevertheless, the testicular toxicity may occur before the day 90, where exposure to norfluoxetine in the rat is lower and, thus, safety margins are lower.

The MAH indicates that the development of testicular pathology in rodents was observed when animals were dosed beginning at 3 weeks of age (R, S-

fluoxetine juvenile study) (Lilly research laboratories). In the juvenile study, IGS CD rats (3 weeks of age at initiation) were treated by gavage with 30 mg/kg/day for approximately 70 days. Seminiferous tubule degeneration was observed histologically in 7 of 10 males; however, no gross observations were made. In the one-month study with S-norfluoxetine, dietary exposures resulting in doses of approximately 30 mg/kg/day caused testicular degeneration in 6 of 15 rats. In both studies, the effect doses caused other concomitant clinical signs of toxicity.

As in both studies animals were exposed to S-norfluoxetine, it is considered that S-norfluoxetine is sufficient to induce testicular toxicity. Although the testicular toxicity may be linked to the pharmacological activity of fluoxetine and derivatives, these studies do not demonstrate that S-norfluoxetine is not necessary. A clear characterisation of the testicular toxicity should be investigated with the available data. (see also Q9)

Lilly Response:

Characterisation of the testicular toxicity has been included in previous submissions. Briefly, **testicular effects were observed in the rat and the mouse, but not in the dog.** The testicular findings in the rat and the mouse have been variably described across the studies but all are considered outcomes of the same pathogenesis. The lesion in the 3-month mouse study was described as focal hypospermatogenesis. Across the repeat-dose rat studies, the effects were described as seminiferous degeneration and testicular degeneration. The infrequent and minimal testicular findings in the dog with R,S-fluoxetine or S-norfluoxetine were consistent with background findings (Rehm 2000; Foley 2001) and were not regarded as treatment-related.

Question 3: General toxicity profile comparison adult – juvenile animals: One aim with juvenile toxicity studies is to assess whether young animals are more sensitive to an effect of a compound than adult animals. Such comparison appears to be lacking. The MAH should present comparisons of the toxicity profile in adult and juvenile rats. Moreover, these profiles should be discussed relative to exposure margins in adults and children, and thereby provide an evaluation whether toxicity profiles are similar in adult and young animals as well as whether there are differences in sensitivity.

Lilly Response:

The relative sensitivity of adult and juvenile rats for the most prominent toxicities observed in animal studies was discussed in a document previously provided to the EU regulatory agencies (“Analysis of male reproductive organ, skeletal muscle, sexual maturation, and growth effects of fluoxetine and norfluoxetine”; dated 18 March 2005; see Appendix 1). The relevant discussion surrounding testicular toxicity, skeletal muscle toxicity, and effects on growth is excerpted below. The studies used in this analysis were conducted over a 28-year period and incorporated mice, three strains of rat, and the beagle dog. R,S-fluoxetine and S-norfluoxetine (two different salts) were studied via diet, gavage, or capsule (studies are listed in Attachment 2). Based on these data, it is apparent that the juvenile animals are not unusually sensitive to the primary toxicologic effects of fluoxetine on an exposure:response basis. This observation, coupled with similar pharmacokinetic profiles in juvenile and adult humans, suggests that a meaningful shift in margin of safety is not expected when considering the juvenile population, compared to adult populations. Of note, the margins of safety that have been calculated for this submission are based on juvenile animal data and juvenile human exposure information.

Testicular Toxicity

Important age-related differences in sensitivity are not apparent for testicular toxicity. The development of testicular pathology in rodents has been observed when animals were dosed beginning at 3 weeks of age (R,S-fluoxetine juvenile study) or 6 to 7 weeks of age (S-norfluoxetine one-month study) (Beck 2004; Vodcnik and Roesner 1990). In the juvenile study, IGS CD rats (3 weeks of age at initiation) were treated by gavage with 30 mg/kg/day for approximately 70 days. Seminiferous tubule degeneration was observed histologically in 7 of 10 males; however, no macroscopic observations were made. In the one-month study with S-norfluoxetine, dietary exposures resulting in doses of approximately 30 mg/kg/day caused testicular degeneration in 6 of 15 rats. In both studies, the effect doses caused other concomitant clinical signs of toxicity. The only other rat study conducted at this or greater dose was a 3-month study conducted via dietary administration in 4 to 5 weeks of age Harlan-Wistar rats (Wold et al. 1976). All rats receiving approximately 75 mg/kg/day died by Week 9. Minimal testicular immaturity was described in 1 of 10 rats (an early death animal). While the date of the study (reported in 1976), the dietary route, and the lack of plasma exposure data make it difficult to compare to the other studies above, it seems clear that particular sensitivity to testicular pathology was not observed in these 4 to 5 weeks of age rats.

Skeletal Muscle Toxicity

The development of skeletal muscle pathology is not unique to the juvenile rat and there does not appear to be a particular sensitivity in immature animals. In the juvenile R,S-fluoxetine rat study where 3 weeks of age rats were administered R,S-fluoxetine daily for 70 days, a mean plasma exposure of 3.677 µg/mL (fluoxetine plus norfluoxetine) resulted in 19 of 20 male and female rats having skeletal muscle degeneration and necrosis (Beck 2004). In the mid-dose group where exposures were approximately 1.4 µg/mL, serum CK values in females were slightly increased but no

myopathy was observed. In contrast, myopathy was observed with high frequency in a series of studies with S-norfluoxetine in 6 to 7 weeks of age rats with exposure of approximately 1 µg/mL (Vodicnik and Roesner, 1990; Vodicnik and Snyder, 1990). Examining the effect of age on the development of myopathy is confounded by different strains of rats and different test materials among the studies conducted.

Growth Effects

The effects of fluoxetine on juvenile and adult body weight appear comparable on an exposure:response basis. While skeletal growth was only measured in the juvenile rat so that comparison to adults is not possible, it would be expected that effects on the lengthening of long bones would be most prominent during the rapid growth phase in rodents.

Question 4: Effects on bone accrual and the reversibility of these effects, need to be addressed. This should include a review of available non-clinical and clinical data. Further non-clinical and/or clinical investigations should be proposed.

Lilly Response:

Effects of fluoxetine on bone mineral accrual have not been studied preclinically by Lilly but the reviewers may be aware of a report in 4 weeks of age mice demonstrating an effect of fluoxetine on bone mineral content in the weight-bearing, but not non-weight bearing bone (Warden et al. 2005). Based on this distribution, hypoactivity in the affected mice may have contributed to mineral density changes in this group. The literature also contains preliminary reports suggesting an effect of selective serotonin reuptake inhibitors on bone mineral density in adult humans (Diem et al. 2004; Haney et al. 2004). However, other reports indicate that depression may be an independent risk factor associated with decreased bone mineral density or osteoporosis (Michelson et al. 1996; Schweiger et al. 1994). It is Lilly's position that further animal studies will not meaningfully contribute to the risk assessment of skeletal health in humans and are not warranted. **Fundamental differences in bone physiology between rodents and humans (Kimmel 1996) limit the ability of rodent studies to accurately predict the response in the human skeleton. Human skeletal health is monitorable in the clinic and remains a focus of clinical investigation.** Information regarding a study which is currently being developed to investigate the effects of fluoxetine treatment in pediatric patients (HCLT) can be found in the Lilly's response to Question 10. Lilly has demonstrated that fluoxetine, at a dose exceeding the MTD, decreased femur length in a juvenile rat study (Beck, 2004). The decreased femur length suggests an effect on longitudinal bone growth; however, this effect was likely reflective of decreased growth secondary to the decreased nutritional status of the animals. While direct or neurohormonal influences on skeletal growth cannot be ruled out, the concurrent decreases in food consumption and body weight are sufficient to be causative. **At the dose where a 4 to 6% decrease in femur length was observed, body weights were decreased 24 to 27% relative to controls.** Food consumption was also decreased in this group by approximately 25 to 34%. In dietary restriction studies (no fluoxetine treatment), weanling male Wistar rats had decreased femur lengths when their feed was restricted by 20% relative to ad libitum-fed

Bullshit. The kids become smaller also if "monitored"

controls (Boyer et al. 2000). Similarly, male Sprague-Dawley rats subjected to 40% food restriction had decreased femur length (Anugwa and Pond 1989).

Question 5: Effects on emotional behaviour and the reversibility of effects, need to be addressed. The MAH should, taking into account all available non-clinical and clinical data, discuss whether potential effects on brain development and function are adequately addressed, or whether further data can be obtained.

Lilly Response:

Lilly considers the current nonclinical data package acceptable for the assessment of potential effects on brain development and function. The juvenile rat study included a comprehensive evaluation of brain development and function designed to investigate potential effects on CNS development during human childhood through adolescence. Evaluations included sensory and motor functions, learning and memory in a complex water maze, and brain histopathology. Although subtle decreases in startle amplitude were noted 2 weeks after completion of fluoxetine treatment, there were no differences when rats were retested 4 weeks later. There were also no changes in latency to respond to auditory startle at either evaluation. Nonreversible changes in startle and learning (females only) only occurred in conjunction with severe systemic toxicity, and thus, the persistent effects on startle are confounded by the clinical condition of the animals (Beck 2004).

Although a recent study reported long lasting behavioral changes after fluoxetine treatment in 5-HTT+/+ and 5-HTT+/- mice (Ansorge et al 2004), the clinical relevance of these findings for childhood exposure is questionable. In that study, 5-HTT+/+, 5-HTT+/-, and 5-HTT-/- mice were administered saline or fluoxetine from postnatal day (PND) 4 through 21. This period of brain development is considered equivalent to a human third trimester fetus through a 2-year old child (Anderson 2003; Bayer et al. 1993; Kimmel and Buelke-Sam 2001; Rice and Barone 2000; Rodier 1980) and does not replicate the recommended age range for fluoxetine administration. Information regarding a study which is currently being developed to investigate the effects of fluoxetine treatment in pediatric patients (HCLT) can be found in Lilly's response to Question 10.

2.2. Clinical Efficacy

Question 6: The proposed posology is not sufficiently supported by the submitted documentation. The following concerns should be addressed by the MAH:

- **The minimal effective dose has not been established. A lower dose may be equally effective. This may be of particular concern in slow metabolisers. The MAH should discuss and propose ways to study this further.**

- *The maximum recommended dose should be specified.*

Lilly Response:

Minimal Effective Dose: In a recent study to evaluate the pharmacokinetic profile of fluoxetine and its major metabolite norfluoxetine, children who were given 20 mg of fluoxetine had twice the serum level of fluoxetine and norfluoxetine compared to adolescents, a difference largely accounted for by weight. Children and adolescents had similar pharmacokinetic profiles for fluoxetine and norfluoxetine relative to historical data in adults. These data suggest that initiating fluoxetine dosing at 10 mg/day in prepubertal children and 20 mg/day in adolescents may be considered in future trials (Wilens et al, 2002).

Maximum Effective Dose: The following SPC wording is proposed:

*“Children and adolescents aged 8 years and above:
Treatment should be initiated and monitored under specialist supervision. The starting dose is 10 mg/day given as 2.5 ml of the Prozac liquid formulation. Dose adjustments should be made carefully, on an individual basis, to maintain the patient at the lowest effective dose. After one week, the dose may be increased to 20 mg/day. Clinical trial experience with daily doses greater than 20 mg is minimal.”*

Lilly considers that a starting dose of 10 mg/day represents a conservative dose to initiate therapy in this age group. The dosage recommendation allows for dose increase to a known efficacious dose on an individual response basis and emphasises the need to maintain the patient at the lowest effective dose. It is also clearly indicated that experience with doses above 20mg is minimal.

Question 7: Efficacy has not been formally established for prolonged treatment duration, in particular due to the high number of withdrawals after 9 weeks of treatment. Results on maintenance of efficacy can only be considered as exploratory, due to the small number of patients (about 75) and the dual definition of relapse criteria. The MAH should comment.

Lilly Response:

The following SPC wording is proposed:

“There is only limited data on treatment beyond 9 weeks.”

Question 8: The patients in the pivotal studies were highly selected. The placebo-run-in phase in study HCJE led to the exclusion of 50% of the initially recruited patients. This raises concern with regard to the external validity of the results. The MAH should comment.

Lilly Response:

In Study B1Y-MC-HCJE, there was a 2-week diagnostic evaluation period (no study drug) followed by a 1-week, single-blind, placebo wash-out period. Four hundred and twenty patients entered the study. Of these, 201 patients either decided not to participate in the study or were considered screen failures. Of the 201, only 8 patients were excluded as a placebo-responder during the placebo washout period.

Thus, the vast majority of patients were excluded due to not meeting inclusion/exclusion criteria (eg, meeting inclusion criteria for nonpsychotic MDD, CDRS-R total score >40, CGI-Severity rating of moderate or greater) at 3 different independent evaluations (Visits 1, 2, and 3). For the 219 patients randomized, the mean CDRS-R total score was 56.2 and the range was 32 to 94. Thus, the randomized patients do represent a wide range of severity levels. (Of note, the patient with baseline CDRS-R total score of 32 was inadvertently randomized.)

The restriction proposed by one concerned member state to limit the indication to “patients who failed to respond to psychosocial interventions” is not reflective of the population evaluated in this study. The fluoxetine paediatric studies did not contain specific psychosocial interventions during the screening period. Lilly believes that the results of this study are generalizable to all children and adolescents diagnosed with major depressive disorder.

In summary, Lilly believes that the results of this study are generalizable to the broad spectrum of children and adolescents diagnosed with major depressive disorder.

2.3.Clinical Safety

Question 9: According to the MAH, the nor-fluoxetine metabolite is implicated in testicular toxicity in young rats. Furthermore, there may be differences in metabolism (e.g. norfluoxetine formation) in adults and children. The MAH should discuss this in relation to the benefit/risk in this population. Additional studies should be proposed in order to explore the risk of testicular toxicity in young humans.

Lilly Response:

Regarding the request for Lilly to propose additional studies to explore the risk of testicular toxicity in young humans, it is not considered feasible to perform such a study for the following reasons:

1. Informed Consent: Although basic physical examinations are a commonly accepted part of paediatric psychopharmacology studies, specialized exams to assess sexual maturation are not expected in psychopharmacology studies, especially if the exam includes a manual exam to estimate a testicular volume. It is anticipated that parents may not be very willing to enroll their children in a study of this nature. In addition, the current climate of public concern and warnings about suicidal thoughts and behaviours (“suicidality”) in children and adolescents who are exposed to antidepressant medications, coupled with the notion that parents must consider that these medications may also impair their child’s growth and/or reproductive function, would likely hinder recruitment for the study and bias the sample.

Bullshit

Even worse
bullshit

2. Logistics: Investigators who are psychiatrists may be reluctant to perform these types of exams out of concern for crossing interpersonal boundaries. It is possible that these exams might be delegated to another practitioner, such as a paediatrician with specialized training; however, this is inconvenient in that it would require the family and patient an additional visit to another office. In addition, the type of tests required would be invasive and would not answer the questions that the European agencies would like answered. Such tests require assessment of testicular function in young males that have not yet developed hormone levels that are amenable to testing (i.e. they are not stabilized enough to warrant “assessment” as they may fluctuate in value, regardless of the medications being given).
3. Other ethical concerns: The overall philosophy of this type of clinical trial would be unlikely to pass review by most Ethical Review Boards due to the nature of the trial (ie sperm count assessment for purposes of testicular toxicity testing and exposing children in a randomized way to one of a class of medications that have a putative association with suicidality and potential impact on growth and maturation).

It is amazing how they argue to avoid producing results that would scrap their drug entirely

Question 10: It is considered that the clinical relevance of toxicological data from study in juvenile rats cannot be established at this time. However, some effects (delayed growth and delayed puberty) have been reported in humans: During clinical trials conducted with fluoxetine in children and adolescents, statistically significant differences in height gain and/or weight gain have been observed between treatment groups, with a smaller gain in fluoxetine-treated patients compared to placebo-treated patients. In addition, the examination of all spontaneous reports from MAH database regarding Prozac use in the paediatric population shows 16 cases of growth retardation, 6 cases of delay in puberty (associated in 4 cases with growth retardation), 18 cases of menstrual disorders and 4 cases of sexual disorders. Even though the responsibility of fluoxetine is difficult to assess with accuracy in some cases, in particular due to the lack of information on the outcome, other cases (suggestive chronologies, positive dechallenges) suggest that fluoxetine may have consequences on growth/puberty in treated children and adolescents. These data are representing a signal which cannot be ignored. The MAH should comment.

Lilly Response:

Protocol HCLT is being developed as a **Phase IV commitment** with the United States Food and Drug Administration (FDA) to investigate the effects of fluoxetine treatment on height and weight in paediatric patients. As this protocol is still under development with the FDA, one of the discussion points is with respect to the feasibility of undertaking and completing this study as proposed due to the considerable recruitment challenges arising out of recent public discussion regarding the use of SSRIs in the child and adolescent population. This concern over recruitment challenges makes the manner and timeframe for this study uncertain. The MHRA was presented the first draft and has indicated that additional investigations are required by their advisory body (CSM), mainly with respect to the fertility status of the patients. Lilly has incorporated several of the proposed investigations in the current draft of Protocol HCLT, these include height, weight, Tanner breast/genital Staging (including testicular volumes), hand and wrist X-rays, and gonadotrophins assessments (lutening hormone and follicle stimulating hormone, testosterone in boys and estradiol in girls). The briefing document regarding HCLT, which was submitted to the MHRA and the FDA in March of 2005, can be found in Attachment 3.

I am pretty sure Lilly never did what they promised

Meanwhile Lilly has conducted a retrospective study (HCLS) to compare growth in children who used fluoxetine for at least 12 months with those who did not receive psychopharmacologic treatment. Results of this study will be submitted as soon as they are finalized. A summary of the study objectives can be found in Attachment 4.

Don't think they ever did the study

A search of the Eli Lilly and Company post-marketing adverse event database (Clintrace) was previously conducted for 41 different events indicating delayed sexual maturation or sexual dysfunction occurring in patients 18 years of age or younger. During the 21-year time period covered by the Clintrace search, a total of 26 such events were reported for this age group. The results from this search were submitted in April 2004; however, a full report was not provided. For the purposes of this response, a search and review of Clintrace covering a 5-year time period was conducted to evaluate case reports suggesting growth retardation or delayed sexual maturation in children and adolescents. A full report of the results of this search can be found in Attachment 5.

A search and review of Clintrace covering a 22-year time period will be conducted to evaluate case reports suggesting growth retardation or delayed sexual maturation in children and adolescents. A full report of the results from this search will be included in the Period Safety Update Report (PSUR) which will be submitted in November 2005.

Finally, it should be noted that the following statement was agreed for inclusion in the fluoxetine SPC following the recent Article 31 referral:

'In addition, long-term safety data in children and adolescents concerning growth, maturation, and cognitive and behavioural development are lacking'.

Question 11: Effects on reproductive organs: The MAH should assess the level of endocrine disruption in the clinical setting. The MAH is asked to compile available clinical data, and, if insufficient further data should be obtained.

Lilly Response:

Please refer to the response to Question 10 above for information regarding this request.

Question 12: Request for data on long term safety in children and adolescents was part of a FDA post-authorisation commitment. The MAH should provide the study protocol for review. Furthermore, an update of the status of the clinical trial including information on the discussions with the FDA should also be given.

Lilly Response:

Please refer to the response to Question 10 above for information regarding this request.

Question 13: The suicidality results in TADS indicate an increased risk of suicidality with fluoxetine, which is in line with other SSRIs. In addition to the outcome of the art 31 referral, the suicidality results in TADS should be included in the SPC.

See also Q4 and Q5 in the non-clinical section, where both non-clinical and clinical data should be addressed.

Lilly Response:

Lilly would agree with the authors of TADS in their conclusion that “The combination of fluoxetine with CBT offered the most favourable trade-off between benefit and risk for adolescents with major depressive disorder”, and that patients in all four treatment groups improved significantly in the area of “suicidal thinking”. It is important to note that, while 7 of 439 patients in the study did attempt suicide, none were completed suicides. The rate of response for fluoxetine alone was 60.6%; the rate of response for fluoxetine treatment in combination with CBT was 71%. Lilly agrees with the authors of TADS that combined therapy is more effective than either therapy alone.

The following SPC class wording was agreed upon by the CHMP following the review of all fluoxetine data, including the TADS study, and we believe this is appropriate information for prescribers:

‘Suicide-related behaviours (suicide attempts and suicidal thoughts), and hostility (predominantly aggression, oppositional behaviour and anger), were more frequently observed in clinical trials among children and adolescents treated with antidepressants compared to those treated with placebo. If, based on clinical need, a decision to treat is nevertheless taken, the patient should be carefully monitored for the appearance of suicidal symptoms.’

Lilly recommends that wording similar to that found in the US Label be added to the SPC (see below). Doing so will address the TADS data results, as well as point out that the results mentioned in the US Label were based on “pooled analyses” of 24 trials of 9 antidepressant drugs (including fluoxetine) involving over 4400 patients.

Current wording from US Label:

Suicidality in Children and Adolescents – Antidepressants increased the risk of suicidal thinking and behavior (suicidality) in short-term studies in children and adolescents with major depressive disorder (MDD) and other psychiatric disorders. Anyone considering the use of Prozac or any other antidepressant in a child or adolescent must balance this risk with the clinical need. Patients who are started on therapy should be observed closely for clinical worsening, suicidality, or unusual changes in behavior. Families and caregivers should be advised of the need for close observation and communication with the prescriber.

Pooled analyses of short-term (4 to 16 weeks) placebo-controlled trials of 9 antidepressant drugs (SSRIs and others) in children and adolescents with major depressive disorder (MDD), obsessive compulsive disorder (OCD), or other psychiatric disorders (a total of 24 trials involving over 4400 patients) have revealed a greater risk of adverse events representing suicidal thinking or behavior (suicidality) during the first few months of treatment in those receiving antidepressants. The average risk of such events in patients receiving antidepressants was 4%, twice the placebo risk of 2%. No suicides occurred in these trials.

Attachment 1.
Additional Pre-Clinical Information

Margins of Safety: Fluoxetine and Norfluoxetine Plasma Exposures in Preadolescents (6-12 yrs) and Adolescents (13-18 yrs) relative to Juvenile Rats in Study WIL353039

	Daily dose	Fluoxetine				Norfluoxetine			
		Single dose AUC	EM ^a	Steady State AUC	EM ^a	Single dose AUC	EM ^a	Steady State AUC	EM ^a
Human – Preadolescents									
Therapeutic dose	20 mg	NA	NA	4,102 ^b (672-7,488)	NA	NA	NA	4,680 ^b (1,632-7,440)	NA
Rat – Juvenile ^c NOAEL	3 mg/kg	446	0.1 (0.1-0.7)	333	0.1 (.04-0.5)	1,355	0.3 (0.2-0.8)	2,428	0.5 (0.3-1.5)
Minimally toxic dose	10 mg/kg	3,359	0.8 (0.4-5.0)	5,922	1.4 (0.8-8.8)	4,935	1.1 (0.7-3.0)	26,680	5.7 (3.6-16.3)
Exceeding MTD	30 mg/kg	17,575	4.3 (2.3-26.2)	19,764	4.8 (2.6-29.4)	10,254	2.2 (1.4-6.3)	68,474	14.6 (9.2-42)
Human – Adolescents									
Therapeutic dose	20 mg	NA	NA	2,071 ^b (720-4,872)	NA	NA	NA	2,700 ^b (1,152-3,912)	NA
Rat – Juvenile ^c NOAEL	3 mg/kg	446	0.2 (0.1-0.6)	333	0.2 (0.1-0.5)	1,355	0.5 (0.3-1.2)	2,428	0.9 (0.6-2.1)
Minimally toxic dose	10 mg/kg	3,359	1.6 (0.7-4.7)	5,922	2.9 (1.2-8.2)	4,935	1.8 (1.3-4.3)	26,680	9.9 (6.8-23.2)
Exceeding MTD	30 mg/kg	17,575	8.5 (3.6-24.4)	19,764	9.5 (4.1-27.5)	10,254	3.8 (2.6-8.9)	68,474	25.4 (17.5-59.4)

Abbreviations: AUC = area under the curve (ng•hr/mL), EM = exposure multiple, NA = not applicable, NOAEL = no-observed-adverse-effect-level, MTD = maximum tolerated dose.

- a. Single-dose exposure multiple = single dose rat AUC/steady state clinical AUC; Steady-state exposure multiple = steady state rat AUC/steady state clinical AUC.
- b. Data from Study B1Y-MC-HCIU. Only single timepoints were collected in this study, so AUCs were approximated by plasma concentration at steady state times 24 hrs. Presented as mean (minimum – maximum) values.
- c. Data from study WIL 353039. Adverse changes at the “minimally toxic dose” limited to decreased body weight gain (females only), delayed sexual maturation, and increased serum activity of creatine kinase (females only). Adverse changes observed above the MTD include convulsion, hypersensitivity to touch, hard muscle tone, decreased body weights (25% relative to control) and food consumption, delays in sexual maturation, increased serum activity of creatine kinase, aspartate aminotransferase, and alanine aminotransferase, degeneration and necrosis of skeletal muscle and testes, epididymal vacuolation, immaturity and inactivity of the female reproductive tract, and decreased femur length (relative to control).

Attachment 2.
**Animal Studies Evaluated in Examining Juvenile
versus Adult Sensitivity**

Definitive repeat-dose toxicity studies were examined in order to determine juvenile versus adult susceptibility in the development of testicular and skeletal muscle toxicity and the effects on growth. The studies were conducted between 1976 and 2004 and incorporated mice, three strains of rat, and the beagle dog. R,S-fluoxetine and S-norfluoxetine (two different salts) were studied via diet, gavage, or capsule.

Repeat-Dose Toxicity Studies: Fluoxetine and Norfluoxetine

Species Strain Animals/sex/group	Age at Study Initiation	Study Duration	Doses (mg/kg/day) Route	Testing Facility (reference)
RS-fluoxetine				
Mouse B6C3F ₁ 15 (5 for reversibility)	5-6 weeks	3 month with 1 month reversibility	0, 0.001, 0.0045, 0.02% diet (~1.6, 6.9, 31 mg/kg/day)	Lilly Research Greenfield, IN (Brophy et al. 1983)
Rat Crl:CD(IGS) 10 (+20/group for functional evaluation)	3 weeks	10 wk with approx. 11 wk post treatment	0, 3, 10, 30 mg/kg/day, gavage	WIL Research Ashland, OH (Beck 2004)
Rat Harlan-Wistar 10	4-5 weeks	3 months	0, 0.01, 0.03, 0.09% diet (~9, 25, 75 mg/kg/day)	Lilly Research Greenfield, IN (Wold et al.1976)
Rat Fischer 344 25 (5 for reversibility)	5-6 weeks	1 year with 2 month reversibility	0, 0.001, 0.0045, 0.02% diet (~0.5, 2.3, 10.7 mg/kg/day)	Lilly Research Greenfield, IN (Brophy et al. 1982)
Dog Beagle 4 – 5 (2 for reversibility)	adult	1 year with 2 month reversibility	0, 1, 4.5, 20/10 mg/kg/day (dose lowered at 180 days) Oral capsule	Lilly Research Greenfield, IN (Brophy and Lake, 1982)
S-Norfluoxetine				
Rat Fischer-344 15	6-7 weeks	1 month	0, 0.005, 0.02, 0.04, 0.06% diet (~4.1, 16.4, 28.7, 30.7 mg/kg/day for males, ~4.5, 18.0, 31.8, or 31.6 mg/kg/day for females) maleate hemihydrate salt	Lilly Research Greenfield, IN (Vodicnik and Roesner, 1990)
Rat Fischer-344 21-25 (females only)	6-7 weeks	1 month + 1 month reversibility	0, 4, 16, 25 mg/kg/day gavage maleate hemihydrate salt	Lilly Research Greenfield, IN (Vodicnik and Snyder, 1990)
Rat Fischer-344 5 (females only)	6-7 weeks	1 month	0, 25 (maleate hemihydrate), 25 (HCl) mg/kg/day gavage	Lilly Research Greenfield, IN (Vodicnik et al., 1990)
Rat Fischer-344 15	5-6 weeks	6 months	0, 0.5, 2.5, 10 mg/kg/day gavage HCl	Lilly Research Greenfield, IN (Vodicnik et al., 1991)

**Attachment 3.
Briefing Document for Study HCLT**

Confidential Information

The information contained in this document is confidential and is intended for the use of the US Food & Drug Administration (FDA). 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)

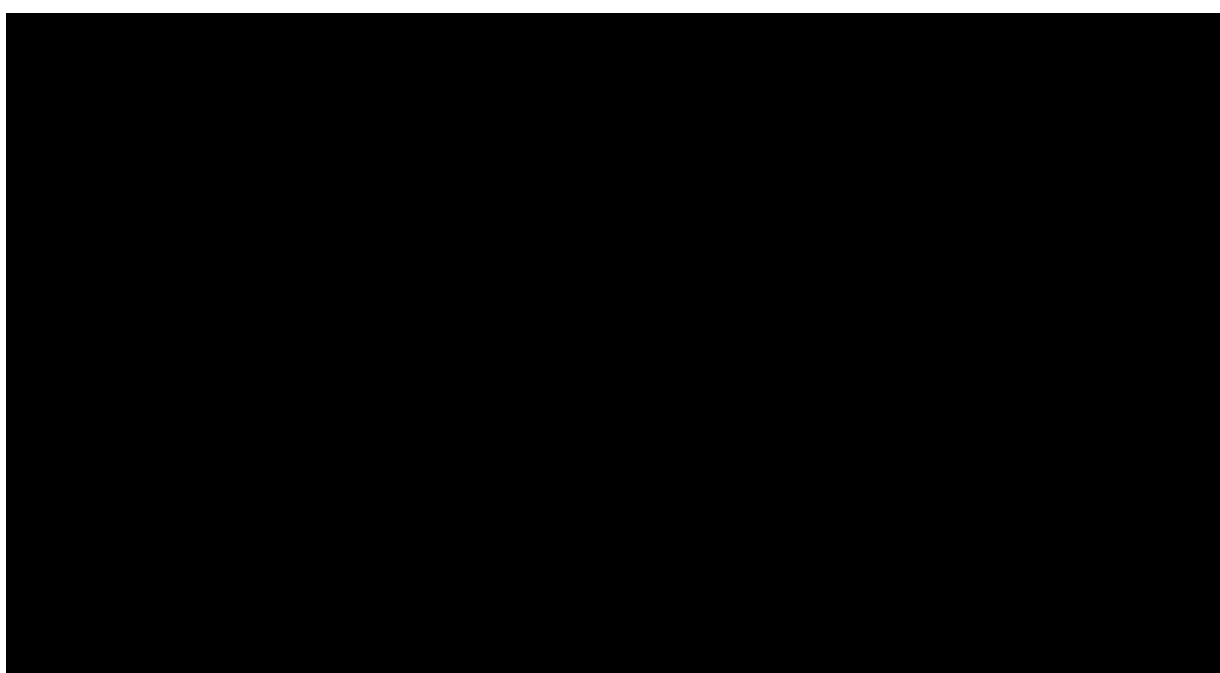
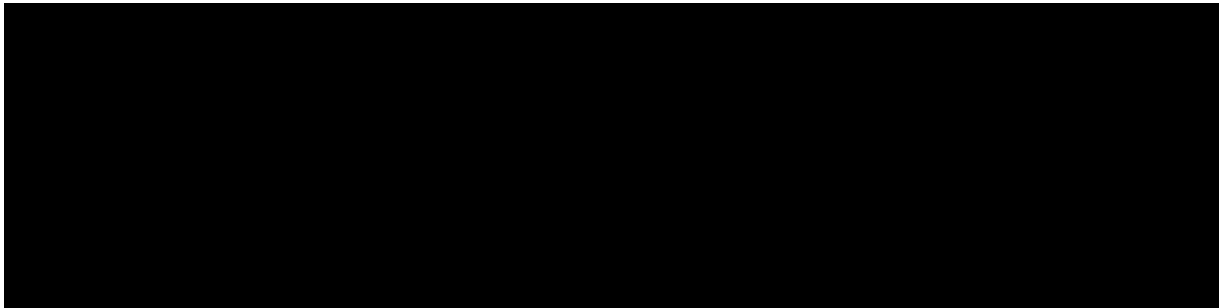
Briefing Document: Pediatric Plan

**Eli Lilly and Company
Indianapolis, IN 46285**

1. Purpose

Protocol B1Y-MC-HCLT (Protocol HCLT) is proposed to comply with the postmarketing commitment to conduct a prospective longer-term trial to assess the effect of fluoxetine hydrochloride (hereafter referred to as fluoxetine) treatment on **growth in pediatric patients, as requested in the approval letter received from the FDA in January 2003**. This request was made based on the results of a pediatric clinical trial with fluoxetine (Nilsson et al. 2004). Furthermore, studies in adults have reported decreased growth hormone response to pharmacologic therapy (O'Flynn et al. 1991; Coplan et al. 1995; Dinan 1998; Lerer et al. 1999), and a case study looked at decreased growth during therapy with selective serotonin reuptake inhibitors (SSRIs) (Weintrob et al. 2002).

This briefing document provides an updated version of our previous briefing document, submitted 07 October 2003, which outlined a proposal to investigate the potential effect of fluoxetine and duloxetine hydrochloride (LY248686) treatment on growth in pediatric patients, within the same protocol. At this time, Lilly is not pursuing the intent to investigate the long-term effect of duloxetine and fluoxetine concurrently in pediatric patients.



1.2. Background

1.2.1. Correspondence with FDA

Following the submission of the first briefing document, Lilly received safety-related comments regarding the protocol from the FDA on 05 February 2004, via e-mail from Paul David. Following the first advisory committee meeting on suicidality on 02 February 2004, the FDA requested that Lilly propose parameters regarding how to capture suicidality in the growth trial.

On 22 April 2004, Lilly submitted an IND Safety Report regarding toxicological findings in a juvenile animal study (rats), followed by an informational update on 14 July 2004 and the final study report on 01 September 2004.

In an e-mail dated 23 June 2004, the FDA suggested the following:

- Tanner breast/genital staging should be performed at baseline and every 6 months thereafter
- CPK should be measured at baseline and regularly throughout the trial to coincide with the blood draws.

In addition, the FDA requested that patients receive:

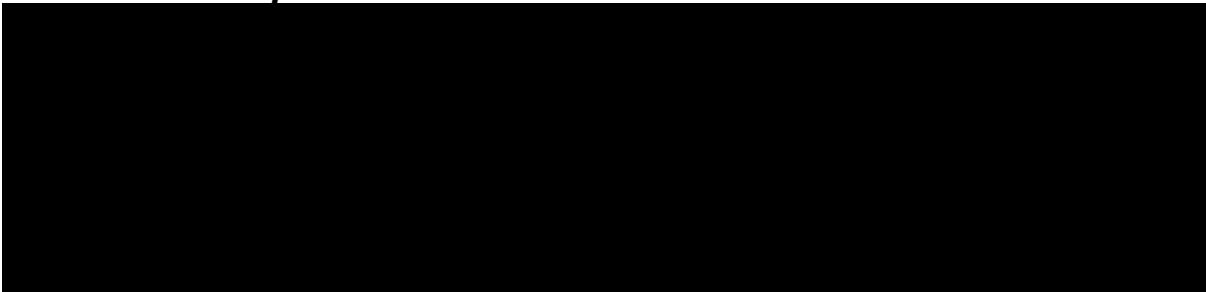
- assessment of suicidality

- baseline and treatment electrocardiograms (ECGs) with measurement of QT in lead II for the primary analysis and in one of the precordial leads.

The FDA also requested additional information regarding:

- statistical analysis plan
- measurement of height and weight
- handling of discontinuations
- data analyses methods during the 52-week, non-interventional, naturalistic observational phase in the event that a new antidepressant treatment (other than fluoxetine) is started during this time.

1.2.2. Correspondence with MHRA



On 18 January 2005, Lilly received a list of parameters from MHRA (based on consultation with the CSM working group) to be included in the pediatric long-term study. The parameters are as follows:

- height, weight, and Tanner breast/genital staging (including testicular volumes) at 3-month intervals
- hand and wrist X-ray to determine skeletal maturation at yearly intervals
- serial measurements of the gonadotrophins LH and FSH, along with testosterone in boys and estradiol in girls, on 9:00 am (± 2 hours) blood samples at 6-month intervals
- pelvic ultrasound examination in girls at yearly intervals
- inhibin B (in both sexes) and anti-mullerian hormone (AMH) (in boys) to evaluate the effect of a particular agent on the Sertoli cell population in boys at 6-month intervals
- consideration of the effect of delayed puberty and low sex steroids on bone mineral density, as assessed by a DXA scan at yearly intervals.

Rationale for inclusion or non-inclusion of each parameter in the protocol is outlined in Section 3 and Section 4 of this document.

2. Study Design

2.1. Overview

Study B1Y-MC-HCLT is a multicenter, randomized, double-blind, parallel, placebo-controlled trial consisting of four study periods, including a non-interventional, naturalistic observational phase. Approximately 440 children and adolescents with major depressive disorder (MDD) will be enrolled with a 1:1 randomization scheme of fluoxetine:placebo stratified by initial height percentile. In addition to pharmacologic therapy, all patients will be offered optional psychotherapy.

This study is comprised of four treatment periods, described below.

- Screening Phase (Study Period I): Visit 1 through Visit 3. The purpose of the screening phase is to evaluate eligibility. A diagnostic interview (Schedule for Affective Disorders and Schizophrenia for School Aged Children Present and Lifetime Version [K-SADS-PL]) and review will be conducted during Study Period I. Visit 2 will occur 1 week (visit interval 5 to 9 days) after Visit 1. Visit 3 will occur at least 5 days after Visit 2, but no more than 30 days following Visit 1. Patients who meet all inclusion and no exclusion criteria will be enrolled and randomly assigned at Visit 3 to one of two treatment groups: fluoxetine daily treatment or placebo.
- Acute Therapy Phase (Study Period II): Visit 4 through Visit 8. This is an 8-week, double-blind treatment phase designed to assess growth, safety, and efficacy of fluoxetine daily treatment in children and adolescents with at least moderate MDD. Optional psychotherapy will be available to all patients during this study period. Patients will be assessed weekly (5- to 9-day visit interval) from Visit 3 to Visit 5, and every 2 weeks (14 ± 4 -day visit interval) from Visit 5 to Visit 8.

Patients and investigators will remain blinded to the treatment assignment throughout the course of the study.

Dose titration of study drug will occur in a blinded manner as follows: patients will begin treatment with study drug at Dose Level 1 (fluoxetine 10 mg daily or matching placebo) at Visit 3, with the option to increase to Dose Level 2 (fluoxetine 20 mg daily or matching placebo) beginning at Visit 4. All patients must be taking Dose Level 2 by the end of 2 weeks (Visit 5). Patients who cannot tolerate Dose Level 2 may have a dose reduction to Dose Level 1. Patients who cannot tolerate a dose of at least Dose Level 1 will be discontinued from the study.

Dose increases are allowed based on investigator judgment to maximize efficacy. Investigators may increase the dose to Dose Level 3 (fluoxetine 40 mg daily or matching placebo) as early as Visit 6, and from Dose Level 3 to Dose Level 4 (fluoxetine 60 mg daily or matching placebo) as early as Visit 7. Dose Level increases may occur only at a study visit, and only after the patient has received the previous Dose Level for at least one visit interval. Those patients unable to tolerate the increased Dose Level of study drug may return to the previously tolerated Dose Level of study drug at any time between visits during this phase. Dose reductions between study visits may occur if the patient contacts the investigator, who, at his/her discretion, may instruct the patient to reduce his/her current dose to the next lower Dose Level by taking one less capsule until the patient's next scheduled study visit.

Only one dosage reduction will be allowed between any study visits, unless additional reductions are needed for safety reasons. Patients requiring more than one Dose Level reduction between scheduled visits must be seen for an unscheduled visit prior to making any additional reductions.

Note: a 1- to 2-week titration phase from fluoxetine 10 mg daily to fluoxetine 20 mg daily was incorporated at a dose lower than that used successfully in the Emslie and colleagues study (1997) or in adult studies due to results from prior studies suggesting a relationship between rate of dose escalation and susceptibility to adverse events (Riddle et al. 1991).

- Extension Therapy Phase (Study Period III): Visit 9 through Visit 19. This is a 44-week, double-blind treatment phase for patients who have a partial or better response at Visit 8 (defined as a Clinical Global Impressions of Improvement [CGI-Improvement] score of 1, 2, or 3) to determine if there is any effect on height and weight and to assess safety and efficacy of long-term fluoxetine daily treatment versus placebo. Optional psychotherapy will be available to all patients during this study phase.

Patients will be assessed every 2 weeks (14 ± 4 -day visit interval) from Visit 8 to Visit 9, once every 4 weeks (28 ± 5 -day visit interval) from Visit 9 to Visit 15, and from Visit 16 to Visit 18, and once every 5 weeks (35 ± 5 -day visit interval) from Visit 15 to Visit 16, and from Visit 18 to Visit 19.

Patients and investigators will remain blinded to the treatment assignment throughout the course of the study.

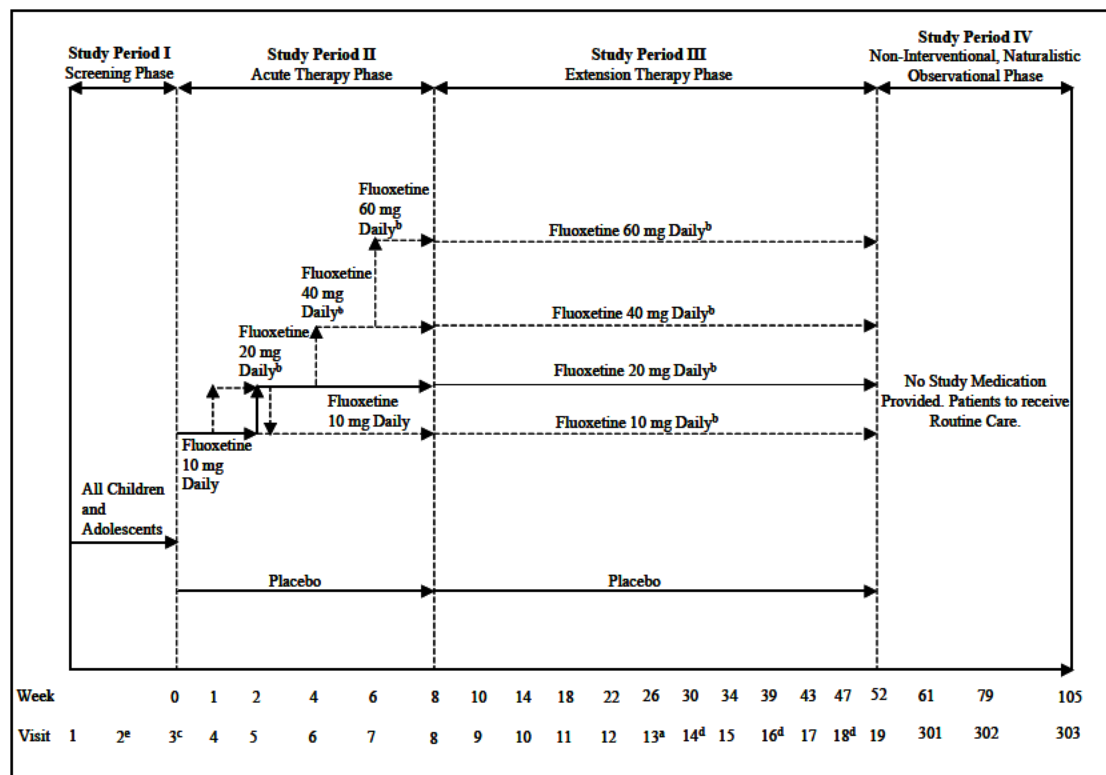
During Study Period III, patients will remain in the same treatment group to which they were randomly assigned in Study Period II (at Visit 3). Patients may have their dose increased or decreased, to a minimum of Dose Level 1 and to a maximum of Dose Level 4, at scheduled study visits based on the investigator's discretion. Patients may have their Dose Level reduced between scheduled study visits by contacting the investigator, who, at his/her discretion, may instruct the patient to reduce his/her current dose to the next lower Dose Level by taking one less capsule until the patient's next scheduled study visit.

Only one dosage reduction will be allowed between any study visits, unless additional reductions are needed for safety reasons. Patients requiring more than one Dose Level reduction between scheduled visits must be seen for an unscheduled visit prior to making any additional reductions.

- Non-Interventional, Naturalistic Observational Phase (Study Period IV): Visit 301 through Visit 303. This is a 52-week, non-interventional, naturalistic observational phase for patients who completed at least 6 months (Visit 13) of treatment. All patients who are exposed to study medication for a minimum of 6 months will be evaluated at 2, 6, and 12 months (\pm 14-day visit interval) to assess growth (height, weight, and Tanner breast/genital staging) and safety, and to record concomitant medications. There are no treatments or interventions provided during this study period. This study period is designed to assess the degree to which treatment-related changes in growth are reversed after study drug is discontinued. During Study Period IV, patients can be taking any commercially available medications for MDD or other psychiatric disorders and/or any other alternative treatments.

2.2. Preliminary Study Design Figure

Figure 1 illustrates the proposed study design.



- a If patient discontinues after Visit 13, the patient may enter Study Period IV.
- b Dose increases are allowed based on investigator judgment to maximize efficacy. If patient is unable to tolerate the higher dose, a dose reduction, to a minimum of 10 mg daily, is possible.
- c Patients are eligible to receive optional psychotherapy at the investigator's discretion beginning after Visit 3 through Visit 19.
- d Visit 14, Visit 16, and Visit 18 may be conducted by phone interview.
- e Visit 2 will occur 1 week (visit interval 5-9 days) after Visit 1.

Figure 1. Illustration of Study Design for Protocol B1Y-MC-HCLT.

2.3. Primary Objective

The primary objective of this study is to determine the effect on height and weight of fluoxetine up to 60 mg daily compared with placebo for 52 weeks in children and adolescents with at least moderate MDD, as measured by the change in height and weight z-scores from baseline to endpoint.

2.4. Secondary Objectives

2.4.1. Secondary Objectives of the 52-Week Therapy Period

- To evaluate the effect of treatment with fluoxetine up to 60 mg daily compared with placebo on height and weight velocity from baseline (randomization) to endpoint (1 year postrandomization).
- To evaluate the effect of treatment with fluoxetine up to 60 mg daily compared with placebo on body mass index (BMI) from baseline (randomization) to endpoint (1 year postrandomization).
- To evaluate the effect of treatment with fluoxetine up to 60 mg daily compared with placebo at endpoint (1 year postrandomization), on sexual maturation as assessed by change in the Tanner breast/genital stage.
- To evaluate the effect of treatment with fluoxetine up to 60 mg daily compared with placebo on QT intervals from baseline to endpoint (1 year postrandomization).
- To assess suicidality during treatment with fluoxetine up to 60 mg daily for up to 52 weeks compared with placebo, as measured by solicited and non-solicited suicidal-related or self-injurious events.
- To evaluate the effect of fluoxetine up to 60 mg daily on bone age at endpoint (1 year postrandomization), as measured by hand/wrist X-ray.
- To evaluate the safety of treatment with fluoxetine up to 60 mg daily compared with placebo at endpoint (1 year postrandomization), using information on discontinuation rates, treatment-emergent adverse events (TEAEs), vital signs, and electrocardiograms (ECGs).
- To evaluate the efficacy of treatment with fluoxetine up to 60 mg daily plus optional psychotherapy compared with placebo plus optional psychotherapy, as measured by change from baseline to endpoint in Children's Depression Rating Scale-Revised (CDRS-R) scores during the 8-week acute therapy phase.

- To evaluate the efficacy of treatment with fluoxetine up to 60 mg daily plus optional psychotherapy compared with placebo plus optional psychotherapy at endpoint (1 year postrandomization), as measured by change from baseline to endpoint in CDRS-R scores.

2.4.2. Secondary Objectives of the 52-Week, Non-Interventional, Naturalistic Observational Phase

- To evaluate the effect, after discontinuation, of treatment with fluoxetine up to 60 mg daily compared with placebo:
- To evaluate the effect, after discontinuation, of treatment with fluoxetine up to 60 mg daily compared with placebo on height and weight velocity from baseline to endpoint (2 years postrandomization).
- To evaluate the effect, after discontinuation, of treatment with fluoxetine up to 60 mg daily compared with placebo on BMI from baseline to endpoint (2 years postrandomization).
- To evaluate the effect, after discontinuation, of treatment with fluoxetine up to 60 mg daily compared with placebo at endpoint (2 years postrandomization), on sexual maturation as assessed by change in the Tanner breast/genital stage.
- To assess suicidality during the 52-week, non-interventional, naturalistic observational phase, as measured by solicited and non-solicited suicidal-related or self-injurious events.
- To evaluate the effect, after discontinuation, of treatment with fluoxetine up to 60 mg daily at endpoint (2 years postrandomization) on bone age, as measured by hand/wrist X-ray.

2.5. Measurements

2.5.1. Primary Safety Measure

- The primary measures of safety are standing height and weight. These will be measured at each visit throughout the study, preferably at the same time of day. All measurements will be made without shoes and any heavy items (such as large jewelry, wallets, coats) will be removed. Patients should face away from the reading portion of the instrument so that the patient cannot observe the reading. Standing measurements should be made with a standard wall-mounted stadiometer provided by the Sponsor. The stadiometer should be calibrated using a standard calibration rod, to be provided by the Sponsor, at the start of the study and approximately every 3 months thereafter. The scale for weighing should be calibrated using a standard weight, to be provided by the Sponsor, at the start of the study and approximately every 3 months thereafter. Instrument calibration should be documented in the appropriate log. Preferably, the same observer should measure the patients throughout the study, using the same instruments. Any change of instrument during the study should be documented, and cross-calibration between the two instruments should be performed by measurement of the standardized calibration rod or weight. Measurement of height and weight will be performed only by a Lilly-trained and approved person throughout the study.
- Baseline-to-1-year change in height and weight standard deviation score, using the height of United States (US) males and females at various chronological ages as the reference standard. A standard deviation score for a given variable is derived by subtracting the age- and sex-matched population mean value for that variable from the patient's value. The value obtained is then divided by the age- and sex-matched population's standard deviation (Kuczmarski et al. 2000).

The secondary safety variables used to assess safety are:

- First-year growth velocity, defined as 1-year height or weight minus baseline height or weight, divided by the exact elapsed time in years (365.25 days per year will be assumed throughout).
- Growth velocities from randomization through the second year.

2.5.2. Adverse Events

Lilly has standards for reporting adverse events that are to be followed regardless of applicable regulatory requirements that may be less stringent. For purposes of collecting and evaluating all information about Lilly drugs used in clinical trials, a clinical trial adverse event is any untoward medical occurrence in a patient administered a pharmaceutical product, without regard to the possibility of a causal relationship. Lack

of drug effect is not an adverse event in clinical trials because the purpose of the clinical trial is to establish drug effect.

Cases of pregnancy that occur during maternal or paternal exposures to study drug should be reported for tracking purposes. Data on fetal outcome and breast-feeding are collected for regulatory reporting and drug safety evaluation.

During the study, site personnel will record any change in the condition(s) and the occurrence and nature of any adverse events. If a patient never receives study drug but experiences an adverse event after the informed consent document (ICD) is signed, **ONLY** events that the investigator believes may have been caused by a protocol procedure will be reported to Lilly or its designee via case report form (CRF).

All adverse events occurring after enrollment must be reported to Lilly or its designee by CRF. Investigators will be instructed to report to Lilly or its designee the assessment of potential relatedness of each adverse event to the study drug via CRF.

Prior to enrollment, study site personnel will note the occurrence and nature of each patient's preexisting condition(s) in the appropriate section of the CRF.

In addition, study site personnel must report to Lilly or its designee immediately of the occurrence and nature of any **serious** adverse event or any instance where the investigator **unblinds** a patient's treatment group assignment for any other reason.

If a patient's dosage is reduced or treatment is discontinued as a result of an adverse event, study site personnel must clearly document the circumstances and data leading to any such dosage reduction or discontinuation of treatment, via CRF.

If clinically significant abnormal ECGs or laboratory values lead to, or are associated with, clinical symptom(s), the diagnosis should be reported as an adverse event.

In cases where the investigator notices an unanticipated benefit to the patient, study site personnel should report "unexpected benefit" with the actual event term to Lilly or its designee via CRF (for example, the complete actual term would be "unexpected benefit—sleeping longer").

2.5.3. Serious Adverse Events

Study site personnel must alert Lilly or its designee immediately, by the designated transmission method, to any adverse event from this study that results in one of the following outcomes, or is significant for any other reason:

- death
- initial or prolonged inpatient hospitalization
- a life-threatening experience (that is, immediate risk of dying)
- persistent or significant disability/incapacity

- congenital anomaly/birth defect.

Lilly or its designee will be alerted to serious adverse events occurring after a patient is discontinued from the study only if the investigator believes that the event may have been caused by the study drug or a protocol procedure.

2.5.4. Laboratory Tests

Standard laboratory tests including chemistry and hematology panels, urine drug screen, and urinalysis panels will be performed at the times specified in the Study Schedule (Section 2.8). Gonadotrophins (LH, FSH, testosterone [in boys], and estradiol [in girls]) will be analyzed from samples obtained at 9:00 am (± 2 hours). A urine pregnancy test (if applicable) will be performed at the investigative site. Other clinical laboratory tests will be analyzed by a central laboratory.

2.5.5. Other Safety Measures

Tanner breast/genital staging, testicular volumes, and a hand/wrist X-ray will be performed according to the Study Schedule (Section 2.8). There are two components of Tanner staging (breast genital and pubic hair stage) described for each sex, rated separately on a scale of five, where stage one is prepuberty and stage five is adult maturity. For the purposes of this study, only Tanner breast/genital staging will be used. For girls, staging will be based on breast maturation; for boys staging will be based on penis and testes development.

Bone age will be measured using a hand/wrist X-ray.

Twelve-lead ECGs, with measurement of QT in lead II for the primary analysis (and in one of the precordial leads as an additional safety analysis), will be obtained according to the Study Schedule (Section 2.8). Presence or absence of juvenile T waves will be recorded.

The ECGs will be interpreted by a qualified physician (the investigator or qualified designee) at the site as soon after the time of ECG collection as possible, and ideally while the patient is still present, for immediate patient management and to determine whether the patient meets entry criteria. If a clinically significant increase in the QTc interval from baseline is present, then the investigator should assess the patient for symptoms (such as palpitations or syncope).

The ECGs will subsequently be sent for analysis to the centralized ECG vendor designated by Lilly. ECGs will be interpreted by the ECG vendor pediatric cardiologist for data analysis and report writing purposes.

2.5.6. Suicidal-Related Events

The safety monitoring in this trial includes investigating incidents of suicidal ideation or self-injury using a prespecified self-harm CRF. At each visit, patients will be queried for any adverse events, and then specifically for potential thoughts or actions that may be

related to self-harm. Any adverse events or events related to self-harm will be recorded on a self-harm CRF, even if there are no potential thoughts or actions. If there is a potential thought or action that may be related to self-directed harm, additional information will be solicited and recorded on the self-harm CRF. This additional information will be used to categorize the event. The events will be categorized by Lilly personnel using the Columbia categorization method.

When a patient has an event related to suicidal ideation or self-injurious behavior and/or a CDRS-R Item 13 score of 3 or more, the investigator or designee will complete the Risk Assessment Tool.

The Risk Assessment Tool is based on the manuals for managing suicidality in the Treatment of Adolescent Suicide Attempters (TASA) and Treatment for Adolescents with Depression (TADS) studies and contains various questions to determine the patient's risk for self-harm, including intent, severity/strength, efforts to conceal, specific plans, lethality, motivation, previous attempts, access to lethal means, and ability of family to provide a safe environment.

The Risk Assessment Tool does not provide a score that would trigger automatic actions an investigator would follow. Rather, it is a tool to help gather information systematically to make a sound clinical judgment. The investigators chosen for this study will be experienced child and adolescent psychiatrists and this kind of assessment is not unusual. Based on the investigators' assessment of the situation, one of several possible interventions will be elected and documented in the final section of the Risk Assessment Tool. The possible interventions include, but are not limited to: no change/continue to monitor, start/restart CBT, medication adjustment, or remove from study for other intervention.

2.5.7. Safety Monitoring

The Lilly clinical research physician will monitor safety data throughout the course of the study.

The Lilly clinical research physician will review serious adverse events within time frames mandated by company procedures and will review trends, laboratory analytes, and adverse events at periodic intervals.

2.5.8. Secondary Efficacy Measures

The following secondary efficacy measures will be collected at the times shown in the Study Schedule (Section 2.8).

- The **Children’s Depression Rating Scale-Revised (CDRS-R)** (Poznanski et al. 1983; 1984; 1985) is a clinician-rated instrument designed to measure the presence and severity of depression in children. The scale was modeled after the Hamilton Depression Rating Scale for adults (Hamilton 1960) 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.

Five subtotals of the CDRS-R will also be evaluated (Guo Y, Nilsson M, Heiligenstein J, Emslie G. An Exploratory Factor Analysis of the Children’s Depression Rating Scale-Revised [In progress]). The Observed Mood subtotal includes tempo of speech, hypoactive, and depressed affect. The Anhedonia subtotal includes social withdrawal and capacity to have fun. The Morbid Thoughts subtotal includes morbid ideation and suicide ideation. The Somatic Symptoms subtotal includes excessive fatigue, sleep, physical complaints, and schoolwork. The Reported Depressive Mood subtotal includes weeping, depressed feeling, and self-esteem.

- The **Clinical Global Impressions of Severity (CGI-Severity)** (Guy 1976) must be administered by a physician, in the presence of the patient, to record the severity of illness at the time of assessment. 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.”
- The **Clinical Global Impressions of Improvement (CGI-Improvement)** (Guy 1976) must be administered by a physician, in the presence of the patient, to record the degree of the patient’s improvement at the time of assessment since starting the study medication. 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.”

2.6. Determination of Sample Size

There will be approximately 440 children and adolescents randomly assigned in this protocol (220 per treatment group). If 108 patients (54 per treatment group) complete 52 weeks, there is 80% power to detect a difference of 0.3 in standardized height or weight (z-scores) from baseline to endpoint between treatments, assuming a standard deviation of 0.55 and no adjustment for multiple comparisons (fluoxetine versus placebo). If the retention rate from randomization (Visit 3) to 52 weeks appears to be lower than anticipated, more patients will be randomly assigned in order to obtain an estimated 108 patients at 52 weeks. For reference, a difference of 0.3 in standardized z-scores is

equivalent to changing from the 50th percentile to the 38th percentile. The estimate of the standard deviation was obtained from Study B1Y-MC-HCJE (height and weight tables). Also, for reference, with 108 patients (54 per arm), there is 80% power to detect a difference of 2.4 cm in height between treatments, assuming a standard deviation of 4.4.

The primary analysis will include all patients on study drug remaining in the study at least 6 months. Assuming that 216 (108 per treatment group) of the children and adolescents randomly assigned in this protocol remain in the study through 6 months, and the standard deviation is 0.55, there is a 91% power to detect a difference of 0.25 in standardized z-scores and a 75% power to detect a difference of 0.2. For reference, a difference of 0.25 in standardized z-scores is equivalent to changing from the 50th percentile to the 40th percentile, and a difference of 0.2 is equivalent to changing from the 50th percentile to the 42nd percentile.

2.7. Primary Outcome Methodology

Change in height and weight z-scores from baseline (Visit 3) to endpoint (Visit 19) will be compared between fluoxetine and placebo using an analysis of variance (ANOVA) (Type III sum-of-squares) with initial height standard deviation score (SDS) (as a continuous covariate), Tanner breast/genital stage, and treatment in the model. The primary population analyzed will be those patients who have 6 months or more of therapy. For purposes of meeting this 6-month criterion, 6 months of therapy will be defined as a patient continuing on therapy to at least Visit 13 (Week 26) as long as this visit occurs by the minimum time defined by the 6-month visit window. The last observation will be carried forward (LOCF) for the primary analysis.

Additional computations will be performed to aid in interpreting the observed changes in height and weight. The height and weight at baseline define SDS (z-score) values. Assuming these same SDS values at the endpoint, the expected height and weight will be computed along with the differences between the observed and expected height and weight. The expected heights and weights and the differences will be tabulated along with the SDS scores and changes from baseline of the SDS heights and weights. Also, the SDS scores will be used to compute mean height and weight percentiles, which will be tabulated with the SDS scores.

Adjustments for investigator effect will not be made.

2.7.1. Effect of Fluoxetine During the 52-Week Non-Interventional, Naturalistic Observational Phase

The effect (after discontinuation) of treatment with fluoxetine up to 60 mg daily from random assignment (Visit 3) through the non-interventional, naturalistic observational phase (up to 2 years postrandomization) will be assessed for change in height and weight z-scores from baseline using an ITT analysis. Height and weight velocity and Tanner breast/genital stage will be analyzed from randomization through the end of observation

in the non-interventional, naturalistic observational phase using the intent-to-treat (ITT) approach. The methods of analysis will be the same as for the 52-week analysis. Finally, suicidality will be summarized over the 2-year period. Summary statistics will be produced for the height and weight changes by original therapy and use of SSRIs and other antidepressants during the non-interventional, naturalistic observational phase of the study. Tanner breast/genital stage will be summarized in these same subgroups.

2.8. Preliminary Study Schedule

Study Schedule Protocol B1Y-MC-HCLT

	SP I Screening			SP II Acute Therapy					SP III Extension											SP IV NINO			ED ^c
	1	2 ^g	3	4	5	6	7	8	9	10	11	12	13 ^e	14 ^c	15	16 ^c	17	18 ^c	19	301	302	303	
CRF Visit No.:																							
Week No.:			0	1	2	4	6	8	10	14	18	22	26	30	34	39	43	47	52	61	79	105	
Procedure																							
Informed Consent ^h	X																						
Demographics	X																						
Family Pubertal History	X																						
Psychiatric/Depression History	X																						
K-SADS-PL	X	X ^a																					
Historical Diagnosis	X																						
Previous Drug/Non-Drug Therapy	X																						
Height	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Weight	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical Exam		X																					
Tanner breast/genital Staging		X								X			X				X		X	X	X	X	X
Testicular Volumes		X								X			X				X		X	X	X	X	X
Hand/Wrist X-Ray		X																	X			X	X ^d
Vital Signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
ECG	X	X											X						X			X	X
Pre-existing Conditions and Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Study Summary																			X			X	X

Study Schedule Protocol B1Y-MC-HCLT (Continued)

	SP I Screening			SP II Acute Therapy					SP III Extension											SP IV NINO			ED ^c
	1	2 ^g	3	4	5	6	7	8	9	10	11	12	13 ^e	14 ^c	15	16 ^c	17	18 ^c	19	301	302	303	
CRF Visit No.:			0	1	2	4	6	8	10	14	18	22	26	30	34	39	43	47	52	61	79	105	
Procedure																							
Efficacy Measurements																							
CDRS-R	X	X	X	X	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	X	X			X	X
CGI-Improvement				X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			X	X
Laboratory Tests																							
Chemistry and Electrolytes ^b	X																						
Gonadotrophins	X												X						X			X	X
Hematology ^b	X																						
Urinalysis ^b	X																						
Urine Drug Screen ^b	X																						
Pregnancy Test (all females) ^b	X																						
Thyroid Panel	X																						

Study Schedule Protocol B1Y-MC-HCLT (Concluded)

	SP I Screening			SP II Acute Therapy					SP III Extension											SP IV NINO			ED ^c
CRF Visit No.:	1	2 ^g	3	4	5	6	7	8	9	10	11	12	13 ^e	14 ^c	15	16 ^c	17	18 ^c	19	301	302	303	
Week No.:			0	1	2	4	6	8	10	14	18	22	26	30	34	39	43	47	52	61	79	105	
Procedure																							
Study Drug and Concomitant Medications																							
Study Drug Dispensed			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X				
Study Drug Compliance				X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X				X
Date of Last Dose								X											X				X
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Safety Measurements																							
Self-Harm CRF				X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Risk Assessment Tool ^f																							

Abbreviations: CDRS-R = Children's Depression Rating Scale-Revised; CGI-Improvement = Clinical Global Impressions of Improvement; CGI-Severity = Clinical Global Impressions of Severity; CRF = case report form; ECG = electrocardiogram; ED = early discontinuation; K-SADS-PL = Schedule for Affective Disorders and Schizophrenia for School Aged Children Present and Lifetime Version; NINO = non-interventional naturalistic observational phase; No = number; SP = study period.

- a Review and confirm all sections that did not utilize the "Skip-Out" criteria.
- b Test can be repeated at the investigator's discretion.
- c Visit 14, Visit 16, and Visit 18 may be conducted by phone interview.
- d Test only performed at ED for patients having completed at least 6 months of trial.
- e Any patient discontinuing from the study at or after Visit 13 will proceed to the 52-week, non-interventional, naturalistic observational phase.
- f The Risk Assessment Tool should be completed any time potential thought or action is assessed to be possibly related to self-directed harm on the Self-Harm CRF.
- g Visit 2 will occur 1 week (visit interval 5-9 days) after Visit 1.
- h Parent or legal guardian and patient/Assent (Patient)

3. FDA Requests

- Assessment of suicidality.
- Tanner breast/genital staging performed every 6 months.
- Baseline and treatment electrocardiograms (ECGs) with measurement of QT in lead II for the primary analysis and in one of the precordial leads.
- Measurement of height and weight.
- Handling of discontinuations from the trial.
- Assessment of new antidepressant treatment during the 52-week, non-interventional, naturalistic observational phase.
- Statistical analysis plan
- Assessment of CPK at baseline with regular monitoring.

3.1. Questions for the FDA

Based upon our proposal in Section 3 and Section 4, Lilly has questions and would like clarification from the FDA:

1. Does the FDA believe the method of suicidality assessment proposed in Section 2.5.6 is adequate to assess suicidality and safeguard against it in these trials?
2. Does the FDA agree with the proposal to assess growth and development every 3 months using the Tanner staging assessment (Section 3.2.2)?
3. Does the FDA agree with the proposal to obtain ECGs at baseline as well as during treatment, with measurement of QT in lead II for the primary analysis and in one of the precordial leads (Section 3.2.3)?
4. Does the FDA agree with the proposal for measuring height and weight (Section 3.2.4)?
5. Does the FDA agree with the proposal for the handling of discontinuations from the trial (Section 3.2.5)?
6. Does the FDA agree with the proposed statistical analysis plan for the primary objective (Section 3.2.6)?
7. Does the FDA agree that the treatment period should be at least 6 months for those patients included in the primary population for analysis (Section 3.2.6)?
8. Does the FDA agree with the proposed data analysis methods during the non-interventional, naturalistic observational phase (Section 3.2.7)?

9. Does the FDA agree with the conclusion that assessment of CPK would not be useful to evaluate muscle lesions (Section 3.3.1)?
10. Does the FDA agree with the proposal to obtain hand/wrist x-rays to measure skeletal maturation (Section 4.1.2)?
11. Does the FDA agree with the proposal to assess gonadotrophins to measure the degree of sexual maturity and gonadal function (Section 4.1.3)?
12. Does the FDA agree with the conclusion that pelvic ultrasound examination in girls is unnecessary (Section 4.2.1)?
13. Does the FDA agree with the conclusion that the assessment of Inhibin B (both sexes) and Anti-Mullerian Hormone (AMH) (in boys) is unnecessary (Section 4.2.2)?
14. Does the FDA agree with the conclusion that the use of DXA scans is unnecessary (Section 4.2.3)?
15. Is the FDA in agreement that the proposal outlined in this document would fulfill our commitment to investigate the long-term effect of fluoxetine on growth in the pediatric population (Section 5)?

3.2. FDA Requests That Will Be Included

3.2.1. Assessment of Suicidality

Scientific Rationale

Due to the current issues regarding suicidality in pediatric patients treated with other antidepressants, Lilly proposes to include several methods to evaluate suicidality (see Section 2.5.6).

1. Does the FDA believe the method of suicidality assessment is adequate to assess suicidality and safeguard against it in these trials?

3.2.2. Tanner Breast/Genital Staging

Tanner breast/genital staging (including testicular volumes) will be performed every 3 months, according to the Study Schedule (Section 2.8).

Scientific Rationale

Assessment of growth and development is essential in the care of pediatric patients. In adolescents, this includes not only height and weight in a younger child, but also sexual maturity or pubertal growth. Lilly plans to use the Tanner staging of puberty, also known as the Sexual Maturity Rating (SMR), to obtain the most informative measure of an adolescent's pubertal development. There are two components of Tanner staging (breast/ genital and pubic hair stage) described for each sex, rated separately on a scale of five, where stage one is prepuberty and stage five is adult maturity. For the purposes of this study, only Tanner breast/genital staging will be

used. For girls, staging is based on breast maturation; for boys staging is based on penis and testes development.

Lilly also plans to conduct a measurement of testicular volumes as requested by the MHRA; however, Lilly believes that this requirement will have a significant negative effect on recruiting for this study. The measurement of testicular volume is fairly specialized and requires more training than that required for Tanner breast/genital staging. However, a series of Tanner breast/genital staging and testicular volume trainings, either virtual or presented at the start-up meeting, will be offered. To assess breast and penile development, training of study personnel performing assessments using pictures will occur. Lilly will also collect data regarding when female patients reach menarche.

2. *Does the FDA agree with the proposal to assess growth and development every 3 months using the Tanner staging assessment?*

3.2.3. Baseline and Treatment Electrocardiograms

Twelve-lead ECGs, with measurement of QT in lead II (for the primary analysis) and in one of the precordial leads, will be obtained according to the Study Schedule (Section 2.8).

Scientific Rationale

Lilly plans to obtain ECGs in order to accurately identify significant increases in the QTc interval from baseline, which would require the investigator to assess the patient for symptoms (such as palpitations or syncope).

Logistics

The ECGs will be interpreted by a qualified physician (the investigator or qualified designee) at the site as soon after the time of ECG collection as possible, and ideally while the patient is still present, for immediate patient management and to determine whether the patient meets entry criteria.

The ECGs will subsequently be sent for analysis to the centralized ECG vendor designated by Lilly. The ECGs will be interpreted by the ECG vendor pediatric cardiologist for data analysis and report writing purposes.

3. *Does the FDA agree with the proposal to obtain ECGs at baseline as well as during treatment, with measurement of QT in lead II (for the primary analysis) and in one of the precordial leads?*

3.2.4. Measurement of Height and Weight

A detailed description of the method for the measurement of height and weight was added to the protocol (see Section 2.4.1).

4. *Does the FDA agree with the proposal for measuring height and weight?*

3.2.5. Handling of Discontinuations from the Trial

Information regarding the handling of discontinuations from the trial is located in the protocol (sent as a separate pdf).

Patients who discontinue the study prior to having 6 months exposure to study medication (Visit 13) will have end-of-study procedures performed as shown in the Study Schedule (Section 2.8). Patients who discontinue after having six months exposure to study medication (Visit 13) will have end-of-therapy procedures performed as shown in the Study Schedule (Section 2.8) and proceed into Study Period IV. If discontinuation occurs during a phone interview, the patient must be seen in person to complete all end-of-therapy procedures.

5. Does the FDA agree with the proposal for the handling of discontinuations from the trial?

3.2.6. Statistical Analysis Plan

Additional information regarding the planned analyses is included in Section 8 of the protocol. Specifically, detailed information regarding all analyses methods is presented in the statistical analysis plan for this study. Section 2.7 describes the statistical analysis plan for the primary outcome measure.

Height and weight velocity (defined as the difference between final and baseline value divided by time since baseline) and SDS/y (defined as the difference between final SDS value and baseline value divided by time since baseline) will be summarized by mean, standard deviation, and patient count for each visit using those patients completing the visit. In addition, a p-value for a t-test comparing study therapies will be reported for each visit.

6. Does the FDA agree with the proposed statistical analysis plan for the primary objective?

Currently, our primary population for analysis consists of those patients who have 6 months or more of therapy. For purposes of meeting this 6-month criterion, 6 months of therapy will be defined as a patient continuing therapy to at least Visit 13 (Week 26) as long as this visit occurs by the minimum time defined by the 6-month visit window.

7. Does the FDA agree that the treatment period should be at least 6 months for those patients included in the primary population for analysis?

3.2.7. Assessment of New Antidepressant Treatment During the 52-Week, Non-Interventional, Naturalistic Observational Phase

A description of data analysis methods that will be used if a new antidepressant treatment is initiated during the non-interventional, naturalistic observational phase has been added to the protocol (Section 2.7.1).

Logistics

Summary statistics will be produced for the height and weight changes by original therapy and use of selective serotonin reuptake inhibitors (SSRIs) and other antidepressants during the observational phase of the study. Tanner breast/genital stage data will be summarized in these same subgroups.

8. *Does the FDA agree with the proposed data analysis methods for the non-interventional, naturalistic observational phase?*

3.3. Rationale for FDA Requests Not Included

3.3.1. Assessment of CPK

Lilly does not believe that assessment of CPK will be useful to evaluate muscle lesions.

Scientific Rationale

According to toxicology results of a rat study, any detected CPK activity was related to muscle degeneration and necrosis (Warden et al. 2005). Therefore, one might consider assessment of CPK to evaluate possible lesions of the muscle. Since Lilly does not have an algorithm in human subjects, and particularly not in children, the assessment of CPK to evaluate muscle lesions is currently not an established and validated procedure. It is an unspecific measurement since children may experience muscle injury as detected by CPK during normal activities (for example, playground activities). Also, during 19 weeks of subchronic fluoxetine treatment in pediatric patients, there were modest mean increases in CPK in both the fluoxetine- and placebo-treated groups. There was no statistically significant difference between the two treatment groups. After further research, Lilly could not find any evidence that specific assessment of CPK would be necessary.

9. *Does the FDA agree with the conclusion that assessment of CPK would not be useful to evaluate muscle lesions?*

4. MHRA Requests

- Height, weight, and Tanner breast/genital staging (including testicular volumes) at 3-month intervals.
- Hand and wrist X-ray to determine skeletal maturation at yearly intervals.
- Serial measurements of the gonadotrophins LH and FSH along with testosterone in boys and estradiol in girls on 9:00 am (± 2 hours) blood samples at 6-month intervals.
- Pelvic ultrasound examination in girls at yearly intervals.
- Inhibin B (in both sexes) and Anti-Mullerian Hormone (AMH) (in boys) to get some idea of effects in boys of a particular agent on the Sertoli cell population at 6-month intervals.
- Consideration of the effect of delayed puberty and low sex steroids on bone mineral density as assessed by DXA scan at yearly intervals.

4.1. Rationale for MHRA Requests That Will Be Included

4.1.1. *Height, Weight, and Tanner Breast/Genital Staging (Including Testicular Volumes)*

Tanner breast/genital staging and measurement of height and weight will be conducted at 3-month intervals (see Section 3.2.2) and will include testicular volumes.

Effect on Recruitment

Although basic physical examinations are a commonly accepted part of pediatric psychopharmacology studies, specialized exams to assess sexual maturation are not expected in psychopharmacology studies, especially if the exam includes a manual exam to estimate testicular volume. Even though Lilly believes the addition of these exams is beneficial, as the sponsor, Lilly is concerned that this type of exam will be refused by families considering participation in the trial and that it will be upsetting to the patients undergoing the exams. Likewise, investigators who are psychiatrists may be reluctant to perform these types of exams out of concern for crossing interpersonal boundaries. It is possible that these exams might be delegated to another practitioner (for example, a pediatrician with specialized training); however, this is inconvenient in that it would require the family and patient an additional visit to another office. Lilly believes that this requirement will have a significant negative effect on recruiting for this study.

4.1.2. *Hand and Wrist X-Ray*

Hand and wrist X-rays will be conducted at yearly intervals.

Scientific Rationale

Hand and wrist X-rays are an accurate way of measuring skeletal and overall maturation, thus skeletal maturation can be compared to chronological age.

Logistics

The process is straightforward and can be done at any X-ray facility. Central readers will be used.

Effect on Recruitment

Although this type of exam is, in theory, uncomplicated, there are a few concerns regarding potential effects on recruiting. Certain families who are unfamiliar with the technology involved with this type of X-ray might refuse this type of exam due to fear of X-ray exposure. Also, this will be inconvenient for patients at some sites that are not immediately adjacent to an X-ray facility for outpatients. Lilly estimates that including this exam will have a mild to moderate negative effect on recruiting.

10. Does the FDA agree with the proposal to obtain hand/wrist X-rays to measure skeletal maturation?

4.1.3. Gonadotrophins: Lutenizing Hormone and Follicle Stimulating Hormone, Testosterone in Boys and Estradiol in Girls

Assessment of gonadotrophins will be conducted at 6-month intervals on 9:00 am (± 2 hours) blood samples.

Scientific Rationale

Measurements of the hormones can be used to evaluate degree of sexual maturity and gonadal function. Since serum testosterone and estradiol levels follow a diurnal rhythm and also change from pre- to late-puberty (Norjavaara et al. 1996; Ankarberg-Lindgren and Norjavaara 2004) it is necessary to standardize the time for patients to have blood drawn for these tests. Testosterone levels in boys can be used to evaluate ambiguous sex characteristics and precocious puberty. Estradiol is the most potent estrogen and can be used to evaluate sexual maturity in girls.

Literature reviews revealed a strong relationship between androgens and increase of growth, particularly in boys. Estrogen serves more as regulation. There is evidence that velocity seems to be related to levels of GH, estradiol, and androstendion (Delemarre van de Waal et al. 2001).

Logistics

These tests can be done without fasting to account for patients' schedules. Esoteric Lab in California has conducted this testing for other Lilly studies.

Effect on Recruitment

Collecting these tests is invasive, and will require a total of up to 3 blood draws (2 during the extension therapy phase and 1 during the non-interventional, naturalistic observational phase) in addition to the blood draw required at Visit 1. Increasing the

amount of blood drawn during the study may have an adverse effect on recruitment. In addition, obtaining 9:00 am (± 2 hours) samples may be an inconvenience for patients and adds expense, which may also negatively affect recruitment.

11. Does the FDA agree with the proposal to assess gonadotrophins to measure the degree of sexual maturity and gonadal function?

4.2. Rationale for MHRA Requests That Will Not Be Included

4.2.1. Pelvic Ultrasound Examination in Girls

Pelvic ultrasound examination in girls was requested to be conducted yearly.

Scientific Rationale

Pelvic ultrasounds would not contribute any additional clinical information than the information obtained from a good clinical exam combined with collection of hormonal levels.

Pelvic ultrasonography cannot always differentiate clearly between different stages of puberty. Even though pelvic ultrasound parameters increase progressively from birth to maturity, no clear cut-off values have been established between age ranges (Buzi et al. 1998).

Logistics

Lilly considers pelvis ultrasound to be excessive since this procedure is rarely conducted in a standard pediatric endocrinology work-up. Since the ultrasound will assess ovarian and uterine volume, this procedure will require a specialist in pediatric gynecologic radiology. There are very few of these specialists available, adding to the difficulty of conducting this assessment. Pelvic ultrasound requires that the child/adolescent have a full bladder during the test. This could be uncomfortable, and requires a significant amount of compliance from children/adolescents who may not want to participate in this assessment due to the physical discomfort.

Effect on Recruitment

Recruitment would most likely be severely impacted if pelvic ultrasounds were required for this study due to the assessment involving some discomfort and the need for the assessment to be conducted by a specialist at a separate facility.

12. Does the FDA agree with the conclusion that pelvic ultrasound examination in girls is unnecessary?

4.2.2. Inhibin B (both sexes) and Anti-Mullerian Hormone (AMH)(in boys)

Assessment of Inhibin B and AMH (in boys) was requested to occur at 6-month intervals to assess the effect of fluoxetine on the Sertoli cell population in boys (AMH).

Scientific Rationale

Sertoli cells are the site of Inhibin B production in males and account for the majority of testicular size. In females, Inhibin B is produced in the ovaries. Inhibin B can be analyzed to get some idea of effects of fluoxetine on the Sertoli cell population in boys and ovarian function in girls. There has not been a specific hypothesis regarding a particular problem with Sertoli cell development, and a review of studies with fluoxetine did not reveal any concerns with Sertoli cell development. The most recent fluoxetine animal toxicology study reveals that spermatogenesis appears to be normal except in animals given toxic doses of fluoxetine. Similarly, there is no evidence that fluoxetine impairs ovarian function in female animals.

AMH is produced in the testes of males and in the ovaries of females. AMH levels change at puberty in both males and females and thus are indicators of gonadal function. Considering the measures that already exist in the protocol for pubertal development (Tanner breast/genital staging) and gonadal function (testosterone and estradiol levels), these measures seem to be excessive. Also, there is the possibility of inter-batch variability in Inhibin assays that could make the interpretation of results from a large sample group difficult.

Effect on Recruitment

There does not appear to be a strong scientific rationale for performing an assessment of Inhibin B and AMH. Eliminating these tests from the study would minimize the amount of blood drawn. Increasing the amount of blood drawn during the study may have an adverse effect on recruitment.

13. Does the FDA agree with the conclusion that the assessment of Inhibin B (both sexes) and AMH (in boys) is unnecessary?

4.2.3. Dual-Energy X-Ray Absorptiometry (DXA) Scan

Dual-energy X-ray absorptiometry (DXA) scans were requested to occur yearly.

Scientific Rationale

Lilly intended to evaluate bone growth rather than bone density. The use of DXA is valuable, but there is currently no consensus on how to interpret the results. According to Horlick et al. (2004), there was a significant gender and ethnicity effect as well as height, weight, and pubertal stage effect. Since there are currently no guidelines for well-categorized groups of pediatric patients (compared to normal controls) available, the variance of bone density measurements (since children have not yet reached peak bone mass) are well recognized and do not serve the purpose of our study.

Lilly has no evidence in human studies that puberty is delayed during treatment with fluoxetine and performing DXA scans at this point would be premature.

If the results from this study suggest there are problems, then this assessment could be incorporated into a future study. Thus, there is not a strong, justifiable need to conduct DXA scans in this study.

Logistics

This measurement is approved by the FDA and established in clinical practice for bone mineral density measurements in children. However, radiologists are required to interpret DXA scans without proper guidelines, and the different types of software or scans used affects the outcome. Together with the lack of appropriate interpretation guidelines and the potential variability in outcome based on the tools used, DXA scans appear to be too complicated to provide a reliable interpretation of bone mineral density during a multisite clinical trial.

Effect on Recruitment

Recruitment would most likely be severely impacted if DXA scans were required for this study. There are few facilities capable of performing this assessment. Coordination of a patient's visit to the study site as well as separate visits to the DXA scan site would be difficult. In addition, traveling to an additional location, if required, would necessitate an additional commitment of time from patients/parents.

14. Does the FDA agree with the conclusion that the use of DXA scans is unnecessary?

5. Conclusion

Lilly proposes to assess the long-term effect of fluoxetine in children over a treatment period totaling 52 weeks and a non-interventional, naturalistic observational period of an additional 52 weeks.

15. Is the FDA in agreement that the proposal outlined in this document would fulfill our commitment to investigate the long-term effect of fluoxetine on growth in the pediatric population?

6. References

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Attachment 4. Summary of Objectives: Study HCLS

In its approval of the paediatric use of fluoxetine for patients with major depressive disorder and obsessive-compulsive disorder (January 2003), the Food and Drug Administration (FDA) asked Eli Lilly and Company (Lilly) to investigate the impact of fluoxetine on growth as part of Lilly's Phase IV commitment. A retrospective study was conducted to compare growth in children diagnosed with depression and/or OCD who used fluoxetine for at least 12 months (cases) to growth in children diagnosed with depression and/or OCD who did not receive psychopharmacologic treatment (controls).

Objectives

1. To determine whether fluoxetine decreases the rate of growth in children and adolescents who use fluoxetine for depression or OCD compared to otherwise similar children and adolescents who were not treated with psychotropic medications.
2. To examine growth subsequent to fluoxetine treatment in children and adolescents diagnosed with depression and/or OCD who discontinued pharmacologic treatment after at least 12 months on fluoxetine compared to otherwise similar children and adolescents who were never treated with psychotropic medications, in order to assess whether children and adolescents, whose growth may have been retarded while they were using fluoxetine, tend to "catch up" after they discontinue treatment until they reach age 18.

Methods

Clinical and administrative databases at Kaiser Permanente Medical Center in Northern California (KP) were used to obtain data on demographics, medical and psychiatric diagnoses, and use of medications. Data on height, weight, and race/ethnicity were abstracted from medical charts where growth measurements had been recorded.

Attachment 5.

Growth Retardation and Delayed Sexual Maturation in Children and Adolescents Treated with Fluoxetine

Background

A recent toxicology study conducted in juvenile rats revealed evidence of growth retardation including decreased weight gain, minor skeletal muscle degeneration, and decreased mean femur length, as well as delayed sexual maturation (eg delayed vaginal patency, and reduced testicular, epididymal, uterine, and ovarian weights). Plasma concentrations of fluoxetine achieved in these animals corresponded to plasma exposures (area under the curve) approximately 5 to 8 fold higher than that achieved in children administered fluoxetine 20 mg daily.

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 1.1 cm less in height ($p=0.004$) and 1.1 kg less in weight ($p=0.008$) than subjects treated with placebo (Hoog 2000). The safety of fluoxetine therapy in paediatric patients has not been systematically assessed for treatment periods longer than several months in duration. There are no studies that directly evaluate the longer-term effects of fluoxetine on the growth, development, and maturation of children and adolescent patients.

In response to the animal toxicology findings, a search of the Eli Lilly and Company postmarketing adverse event database (Clintrace) was conducted to evaluate case reports suggesting growth retardation or delayed sexual maturation in children and adolescents.

Methods

The Lilly postmarketing adverse event database was searched for a 5-year time period (04 March 2000 through 07 March 2005) for adverse drug events reported in association with fluoxetine administration consistent with growth retardation or delayed sexual maturation in children and adolescents 18 years of age and younger. A list of 59 MedDRA High Level terms was compiled which would indicate biochemical (e.g. Endocrine Abnormalities of Gonadal Function NEC, Reproductive Hormone Analyses) or physical (eg Physical Examination Procedures, Reproductive Tract Signs and Symptoms) evidence of deficient sexual maturation/function or reduced growth. A complete list of the search terms is provided in Appendix 1.

Results

For the same 5-year time period covered in this report, the Clintrace database contains reports of 885 patients 18 years of age and younger, who have experienced one or more adverse events associated with fluoxetine administration.

A total of 87 cases involving 101 adverse events were identified through the search. An initial review of these cases revealed 6 cases which were not pertinent to the issues under review (Respiratory Rate Increased: 2 cases, Body Temperature Increased: 2 cases, Body Temperature Decreased: 1 case, Abnormal Apgar Score: 1 case). The remaining 81 cases (95 events) were grouped into general categories: Weight Loss, Weight Gain, Breast Disorders, Growth Retardation, Penis Disorders, Menstrual Abnormalities, and Delayed Puberty. Individual cases may appear in more than one category based on the events under review.

Weight Loss

Seventeen cases were identified which were assigned the MedDRA preferred term of "Weight Decreased." Details of these 17 cases are provided in Table 1.

Table 1. Case Summaries for Children and Adolescents Experiencing Weight Loss During Fluoxetine Therapy

Case #	Age/Sex	MedDRA Preferred Terms	Daily Fluoxetine Dose	Duration of Fluoxetine	Concomitant Medications	Concomitant Disease States	Pertinent information
		Weight decreased	40 mg	2 years	Acne medication	QT prolongation	Weight loss of 25 lb after fluoxetine discontinued.
		Weight decreased; appetite decreased	20 mg	1 month	None listed	History of kidney surgery	Weight decreased from 104 lb to 92 lb (12 lb loss) in 3 weeks.
		Weight decreased; decreased appetite; growth retardation; delayed puberty	13 mg	21 months	Methylphenidate	Dysthymia; anxiety; ADHD	Reduced growth from 90 th to 50 th percentile; amount of weight loss not specified.
		Weight decreased	20 mg	8 months	None	Tourette's syndrome; bulimia; acid reflux	Patient overweight prior to fluoxetine; on diet and exercise program. Lost 31 pounds in 5 months.
		Weight decreased	30 mg	12 months	Mirtazapine; guanfacine; amphetamine/dextroamphetamine	Anxiety; depression	Amount of weight loss not specified; patient also developed gynecomastia.
		Weight decreased	20 mg	1 month	None listed	Reportedly extremely thin at baseline	Experienced "some" weight loss; amount not reported.

Table 1. Case Summaries for Children and Adolescents Experiencing Weight Loss During Fluoxetine Therapy (continued)

Case #	Age/Sex	MedDRA Preferred Terms	Daily Fluoxetine Dose	Duration of Fluoxetine	Concomitant Medications	Concomitant Disease States	Pertinent information
		Weight decreased	Placental	2nd & 3rd trimesters	Prenatal vitamins	None reported	1 lb (10%) weight loss over first week of life. Probable physiologic weight loss.
		Weight decreased; nausea; diarrhea	30 mg	3 months	None listed	Celiac disease	Daily nausea and diarrhea. Lost 10 lb.
		Weight decreased; decreased appetite; nausea	20 mg	1 month	Ranitidine	Nausea	Amount of weight loss not reported. Nausea and decreased appetite have resolved.
		Weight decreased	20 mg	1 month	Olanzapine	Psychosis	Lost 10 pounds over 1 year. Weight gain with olanzapine administration.
		Weight decreased	40 mg	1 month	Insulin	Type I diabetes mellitus; Hashimoto's thyroiditis	1.4 kg weight loss. 9 kg weight gain after fluoxetine discontinued.
		Weight decreased; nausea	40 mg	2 months	Atenolol, insulin	Diabetes, hypertension, s/p bypass surgery GE reflux; hiatal hernia	15 lb weight loss due to nausea.
		Weight decreased	15 mg	Unknown	Atomoxetine	ADHD; Tourette's disorder; Abdominal pain and nausea	4 lb weight loss possibly after atomoxetine started.

Table 1. Case Summaries for Children and Adolescents Experiencing Weight Loss During Fluoxetine Therapy (concluded)

Case #	Age/Sex	MedDRA Preferred Terms	Daily Fluoxetine Dose	Duration of Fluoxetine	Concomitant Medications	Concomitant Disease States	Pertinent information
		Weight decreased	Unknown	Unknown	None listed	Lymphoma in remission	Amount of weight loss not reported. Recent night sweats – possible lymphoma recurrence?
		Weight decreased	40 mg	Unknown	Potassium supplement	Bulimia	Lost 15 pounds in 3 weeks. Patient died from overdose.
		Weight decreased, viral infection; nausea; vomiting; diarrhea	20 mg	4 days	None listed	Unspecified viral infection (gastroenteritis?)	Lost 12 pounds in 4 days.
		Weight decreased, nausea; anorexia	20 mg	0.5 months	Analgesics; metoclopramide	Asthma; nightmares	Amount of weight loss not reported.

Confounding factors potentially contributing to weight loss can be identified in the majority of cases. In one case [REDACTED], the weight loss did not occur until after fluoxetine had been discontinued. Two patients [REDACTED] were receiving concomitant stimulant therapy (methylphenidate and amphetamine/dextroamphetamine), which has been associated with appetite suppression. A 4-pound weight loss occurring in one patient may have occurred after the initiation of atomoxetine therapy (USA040465156). One patient [REDACTED] was overweight at the start of fluoxetine therapy and was attempting weight loss through diet and exercise. In three patients [REDACTED], the reported weight loss may have represented fluid loss rather than loss of lean body mass.

Concomitant illnesses may have been contributing factors in three cases. One patient [REDACTED], reporting night sweats in combination with weight loss, may have been experiencing a recurrence of lymphoma, while weight loss reported in another patient [REDACTED] may be attributed to bulimia nervosa under treatment. A third patient suffered from celiac disease [REDACTED]. Nausea, vomiting, and diarrhea were factors contributing to weight loss in three patients [REDACTED]
[REDACTED]

Three cases did not contain obvious confounding factors. Case [REDACTED] was a 15-year-old [REDACTED] receiving fluoxetine 20 mg daily who experienced a 12-pound weight loss (104 lb to 92 lb) over a 3-week period. Case [REDACTED] was a 14 year-old [REDACTED] described as extremely thin prior to fluoxetine therapy, who experienced “some” weight loss, although the actual amount of weight loss was not reported. Case [REDACTED] was a 14 year-old [REDACTED] who lost 10 pounds over a one-year period during fluoxetine therapy. She subsequently experienced weight gain during olanzapine therapy.

Weight Gain

Twenty-five cases were identified which were assigned the MedDRA preferred term of “Weight Increased.” Details of these 25 cases are provided in Table 2.

Table 2. Case Summaries for Children and Adolescents Experiencing Weight Gain During Fluoxetine Therapy

Case #	Age/Sex	MedDRA Preferred Terms	Daily Fluoxetine Dose	Duration of Fluoxetine	Concomitant Medications	Concomitant Disease States	Pertinent information
		Weight increased, Growth retardation	20 mg	Unknown	Unknown	Unknown	"Mild" weight gain; amount not specified.
		Weight increased, hypothyroidism	Unknown	Unknown	Unknown	Hypothyroidism	Fluoxetine discontinued 5 years ago but weight gain has persisted. Amount of weight gain not reported.
		Weight increased	Unknown	12 months	Olanzapine	Anxiety; depression	Weight gain appears to have occurred after fluoxetine discontinued. Amount of weight gain not specified.
		Weight increased	20 mg	36 months	Risperidone, guanfacine, marijuana, alcohol	Pervasive developmental disorder	Gained 30-40 pounds in 3 months.
		Weight increased	20 mg	5 weeks	None indicated	Influenza, Guillain-Barre Syndrome	Weight gain of 20 lb (180 lbs increasing to 200 lbs)
		Weight increased; somnolence	Unknown	18 months	Olanzapine, paroxetine, alprazolam	von Willebrand's Disease	Gained 30 pounds in 4 months after starting olanzapine

Table 2. Case Summaries for Children and Adolescents Experiencing Weight Gain During Fluoxetine Therapy (continued)

Case #	Age/Sex	MedDRA Preferred Terms	Daily Fluoxetine Dose	Duration of Fluoxetine	Concomitant Medications	Concomitant Disease States	Pertinent information
		Weight increased	20 mg	12 months	Olanzapine, valproate, risperidone, oral contraceptives	Bipolar disorder	Gained 30 pounds in 3 months. History of 20 lb weight gain during previous olanzapine therapy.
		Weight increased	20 mg	2 months	None	None mentioned	Amount of weight gain not reported. Previous history of weight gain with fluoxetine therapy.
		Weight increased, fluid retention, somnolence	20 mg	5 months	Olanzapine	Bipolar disorder, self-mutilation	Gained 25 pounds in 6 weeks, described as being water retention.
		Weight increased	20 mg	8 months	Methylphenidate	Autism; obsessive-compulsive disorder	Gained 30 pounds in 8 months.
		Weight increased, appetite increased	10 mg	2 months	None listed	None mentioned	Gained 13 pounds in 2 months.
		Weight increased	10 mg	3 years	Olanzapine	Schizoaffective disorder, pervasive developmental disorder	Amount of weight gain not specified.
		Weight increased	50 mg	Unknown	Quetiapine	none mentioned	Amount of weight gain not reported.

Table 2. Case Summaries for Children and Adolescents Experiencing Weight Gain During Fluoxetine Therapy (continued)

Case #	Age/Sex	MedDRA Preferred Terms	Daily Fluoxetine Dose	Duration of Fluoxetine	Concomitant Medications	Concomitant Disease States	Pertinent information
		Weight increased	20 mg	Unknown	None indicated	Eating disorder	Patient described as grossly underweight at outset of fluoxetine therapy.
		Weight increased	10 mg	4 months	Atomoxetine, valproate; methylphenidate; clonidine	ADHD	Amount of weight gain unknown.
		Weight increased	30 mg	Unknown	Atomoxetine; oxcarbazepine; quetiapine; amphetamine/dextro-amphetamine	Autism; Asperger's Syndrome; ADHD	Amount of weight gain not reported.
		Weight increased	40 mg	12+ months	Olanzapine	Obsessive-compulsive disorder; trichotillomania	Gained 19 pounds in 2 months while taking fluoxetine and olanzapine. Switched to ziprasidone with subsequent weight loss.
		Weight increased	Unknown	Unknown	None listed	Dyslexia; anxiety disorder	Amount of weight gain not reported.
		Weight increased	Unknown	Unknown	None listed	None mentioned	Amount of weight gain not reported.

Table 2. Case Summaries for Children and Adolescents Experiencing Weight Gain During Fluoxetine Therapy (continued)

Case #	Age/Sex	MedDRA Preferred Terms	Daily Fluoxetine Dose	Duration of Fluoxetine	Concomitant Medications	Concomitant Disease States	Pertinent information
		Weight increased, increased appetite	20 mg	Unknown	Olanzapine, chlorpromazine, diphenhydramine	Bipolar disorder	Fluoxetine discontinued prior to weight gain. Gained 100 pounds in one year after switching to olanzapine.
		Weight increased	20 mg	Unknown	None listed	None mentioned	Gained 6 pounds
		Weight increased	40 mg	5 months	Mirtazapine, quetiapine	Bulimia, depression	History of 40 lb weight loss due to dieting and vomiting. Gained 7 kg (15.43 pounds) in 2 months, attributed to resolution of bulimic symptoms.
		Weight increased	60 mg	5 months	Olanzapine	None mentioned	Gained 15 kg (33 pounds) in 5 months on fluoxetine. Further weight gain with olanzapine therapy.

Table 2. Case Summaries for Children and Adolescents Experiencing Weight Gain During Fluoxetine Therapy (concluded)

Case #	Age/Sex	MedDRA Preferred Terms	Daily Fluoxetine Dose	Duration of Fluoxetine	Concomitant Medications	Concomitant Disease States	Pertinent information
		Weight increased	20 mg	15 months	None listed	None mentioned	Gained 30 kg (66 pounds) in 15 months.
		Weight increased, hyperphagia	20 mg	4 months	None listed	None mentioned	Gained 10 kg (22 pounds).

Confounding factors potentially contributing to weight gain can be identified in more than half of the cases. In one case [REDACTED], a young [REDACTED] diagnosed with hypothyroidism experienced weight gain that persisted for a period of 5 years following discontinuation of fluoxetine. In a second case [REDACTED], the patient was noted to be grossly underweight at the onset of fluoxetine therapy, and the reported weight gain may represent a return to a body weight appropriate for age. Twelve patients

[REDACTED] were noted to be receiving concomitant therapy with atypical antipsychotics, which may be associated with weight gain.

Twelve cases [REDACTED] did not contain obvious confounding factors. The amount of weight gained was reported for 7 patients and ranged from 6 pounds accumulated over an unspecified period of time to 66 pounds accumulated over a 15-month period.

Breast Disorders

Thirteen cases were identified which described some sort of breast disorder occurring in association with fluoxetine therapy. Details of these 13 cases are provided in Table 3.

Table 3. Case Summaries for Children and Adolescents Experiencing Breast Disorders During Fluoxetine Therapy

Case #	Age/Sex	MedDRA Preferred Terms	Daily Fluoxetine Dose	Duration of Fluoxetine	Concomitant Medications	Concomitant Disease States	Pertinent information
		Gynecomastia	30 mg	12 months	Mirtazapine; guanfacine; amphetamine/dextroamphetamine	Anxiety; depression	Patient going through puberty
		Gynecomastia	Unknown	Unknown	Olanzapine; topiramate	Tourette's Syndrome	Gynecomastia developed after starting olanzapine.
		Hypertrophy breast; hormone level abnormal	Unknown	Unknown	None listed	None mentioned	Low testosterone level. Hormone levels returned to normal after fluoxetine was discontinued.
		Breast disorder	Unknown	20 months	None listed	None mentioned	Breasts have not developed. Previous sertraline therapy.
		Breast disorder; growth retardation	Unknown	18 months	None listed	None mentioned	Patient stated that breasts "were not really developing" Similar to USA021224766.
		Breast discharge; blood prolactin increased	20 mg	8 months	None listed	None mentioned	Fluoxetine continued. Pituitary adenoma ruled out.
		Lactation disorder	Unknown	Unknown	None listed	None mentioned	

Table 3. Case Summaries for Children and Adolescents Experiencing Breast Disorders During Fluoxetine Therapy (concluded)

Case #	Age/Sex	MedDRA Preferred Terms	Daily Fluoxetine Dose	Duration of Fluoxetine	Concomitant Medications	Concomitant Disease States	Pertinent information
		Galactorrhea	20 mg	6 weeks	Medroxy-progesterone acetate	Hormonal problems	
		Galactorrhea; hyperprolactin-emia	20 mg	6 weeks	Pizotifen, sumatriptan, oral contraceptive, ibuprofen, co-codamol	Migraines	Serum prolactin mildly elevated.
		Galactorrhea	20 mg	1 month	None listed	None mentioned	Serum prolactin not determined.
		Galactorrhea	20 mg	2 months	None listed	None mentioned	Galactorrhea developed after fluoxetine was discontinued.
		Galactorrhea	20 mg	1 month	None listed	None mentioned	Serum prolactin not determined.
		Galactorrhea	20 mg	14 months	Venlafaxine	None mentioned	

Three adolescent males, 12 to 16 years of age, experienced gynecomastia during fluoxetine administration. Gynecomastia occurs in approximately one-third of normal males during early to mid-puberty (Jenkins 2000a), and the 12-year-old patient [REDACTED] was described as going through puberty. In a second case [REDACTED], the gynecomastia developed after the patient started olanzapine therapy. In the third case [REDACTED], the patient was noted to have low hormone levels, including testosterone, which returned to normal after fluoxetine was discontinued.

Two cases likely represent the same patient [REDACTED], a 16-year-old [REDACTED] who expressed concern over [REDACTED] lack of breast development. [REDACTED] had been receiving an unspecified dose of fluoxetine for a period of approximately 18 months. [REDACTED] past medical history indicates a 3-year period of sertraline therapy following [REDACTED] mother's death, but insufficient details regarding development of secondary sex characteristics are available to fully evaluate [REDACTED] case.

Eight cases of galactorrhoea were reported during the course of fluoxetine therapy. Two patients [REDACTED] were receiving concomitant medications associated with galactorrhea (medroxyprogesterone acetate and an oral contraceptive). In 2 patients [REDACTED], the serum prolactin concentration was elevated, and pituitary adenoma was ruled out in one case [REDACTED]. The remaining patients received fluoxetine 20 mg daily for periods of 1 to 14 months; however, the case reports provide insufficient information for thorough evaluation.

Growth Retardation

Eight cases were identified which described some form of growth retardation. Details of these 8 cases are provided in Table 4.

Table 4. Case Summaries for Children and Adolescents Experiencing Growth Retardation During Fluoxetine Therapy

Case #	Age/Sex	MedDRA PT Term	Dose of Fluoxetine	Duration of Fluoxetine	Concomitant Medications	Concomitant Disease States	Pertinent information
		Growth retardation; weight increased	20 mg	Unknown	None	None mentioned	Reduced longitudinal growth, mild weight gain. Current height 143 cm (50 percentile).
		Growth retardation, delayed puberty, weight decreased, decreased appetite	13 mg	29 months	Methylphenidate	None mentioned	Reduced height from 90th to 50th percentile in height in span of 1 year.
		Growth retardation; body height below normal	60 mg	21 months	Risperidone	None mentioned	Reduced height from 75th to 25th percentile in height in span of 1 year. Current height 150 cm (45 percentile), current weight 48 kg (75 percentile).

Table 4. Case Summaries for Children and Adolescents Experiencing Growth Retardation During Fluoxetine Therapy (continued)

Case #	Age/Sex	MedDRA PT Term	Dose of Fluoxetine	Duration of Fluoxetine	Concomitant Medications	Concomitant Disease States	Pertinent information
		Growth retardation; delayed puberty, laboratory test abnormal	20 mg	12 months	Methylphenidate, fluvoxamine	ADHD	Fell from 50th percentile in height to 15th percentile in one year. Responded to somatropin therapy. Mother had history of delayed puberty.
		Developmental delay; body mass index decreased	Maternal dose unknown	Placental exposure: Weeks 0 to 5 and 16 to term	None listed	None mentioned	Child described as small, but no weight or length information provided.
		Weight gain poor; body height	20 mg	7 years	None listed	None mentioned	Patient's height and weight were 50th percentile at time of report. Concern about possible delayed puberty. Current height 155 cm (50 percentile), weight 46.8 kg (60 percentile).

Table 4. Case Summaries for Children and Adolescents Experiencing Growth Retardation During Fluoxetine Therapy (concluded)

Case #	Age/Sex	MedDRA PT Term	Dose of Fluoxetine	Duration of Fluoxetine	Concomitant Medications	Concomitant Disease States	Pertinent information
		Body height below normal; weight increased	20 mg	20 months	None listed	Eating disorder; grossly underweight prior to fluoxetine therapy.	Patient described as short in comparison to rest of family. Current height 152 cm (85 percentile).
		Breast disorder; growth retardation	Unknown	18 months	None listed	None mentioned	Current height 152 cm (5 %ile), weight 49 kg (25 percentile).

None of these cases provided sequential height or weight measurements, which prevents evaluation of growth patterns. Neither did any of the cases provide information about parental heights or weights, which further complicates assessment. Fluoxetine therapy was continued in 5 of the 8 cases, which precludes comparison of growth velocity during and after fluoxetine therapy.

Case [REDACTED] was a 14-month-old infant described as being “small”, but a lack of weight and length information precludes any further evaluation. The remaining 7 cases did provide height, and in some cases, weight information. Four of the 7 cases indicated a height measurement at the time of report that was greater than or equal to the 50th percentile of height for age, and a fifth patient was at the 45th percentile of height for age.

A limited amount of information was available in the reports and that which was provided was occasionally conflicting. For example, Case [REDACTED] was an 11-year-old [REDACTED] receiving fluoxetine for an unspecified eating disorder. [REDACTED] was described as being short compared to the rest of [REDACTED] family; however, [REDACTED] measured height of 152 cm represents the 85th percentile of height for [REDACTED] age. A second example of conflicting information was Case [REDACTED] which was a 12-year-old [REDACTED] receiving fluoxetine 60 mg daily who reportedly had dropped from the 75th percentile of

height to the 25th percentile over a 1-year time period. ■■■ height at the time of reporting; however, was 150 cm, which represents the 45th percentile of height for age.

Of note is Case ■■■■■■■■■■, a 16-year-old ■■■■■ who had received fluoxetine for a period of 18 months, preceded by a 3-year regimen of sertraline. ■■■ height at time of reporting was 152 cm (5th percentile for age) and her weight was 49 kg (25th percentile for age). There was no information in the case report to readily explain ■■■ modest stature.

Penis Disorders

Four cases were identified which described some form of penile disorder. Details of these 4 cases are provided in Table 5.

Table 5. Case Summaries for Children and Adolescents Experiencing Penile Disorders During Fluoxetine Therapy

Case #	Age/Sex	MedDRA PT Term	Dose of Fluoxetine	Duration of Fluoxetine	Concomitant Medications	Concomitant Disease States	Pertinent information
■■■■■	■■■■■	Erectile dysfunction	20 mg	Unknown	Olanzapine; divalproex	None mentioned	Patient experienced frequent painful erections.
■■■■■	■■■■■	Priapism	Unknown	2 weeks	None listed	None mentioned	Patient treated for OCD.
■■■■■	■■■■■	Priapism; erection increased	20 mg	2 weeks	Clonidine	None mentioned	
■■■■■	■■■■■	Hypospadias	Placental exposure	9 months placental exposure	None listed	None mentioned	Mother took fluoxetine during all three trimesters of pregnancy.

There is limited information in these cases supporting diagnoses of priapism; however, the Fluoxetine Core Data Sheet does identify priapism as an adverse event associated with fluoxetine administration. There was no information in these 3 cases to suggest that the event is more common or more severe in children or adolescents.

Menstrual Irregularities

Thirteen cases were identified which described some form of menstrual irregularity. Details of these 13 cases are provided in Table 6.

Table 6. Case Summaries for Children and Adolescents Experiencing Menstrual Irregularities During Fluoxetine Therapy

Case #	Age/Sex	MedDRA PT Term	Dose of Fluoxetine	Duration of Fluoxetine	Concomitant Medications	Concomitant Disease States	Pertinent Information
		Menorrhagia; metrorrhagia; menstrual disorder	20 mg	3 weeks	Amphetamine; dextro-amphetamine	Depression	Required hormonal therapy to terminate menstrual period.
		Menorrhagia; metrorrhagia	20 mg	1 day	Paracetamol; salbutamol	Asthma	Menarche at age 10 years. Metrorrhagia began first day of fluoxetine therapy.
		Menorrhagia	40 mg	7 weeks	None listed	Unknown	Unknown if fluoxetine continued.
		Meno-metrorrhagia	20 mg	2 weeks	None listed	None mentioned	Fluoxetine discontinued. History of vaginal bleeding with paroxetine.
		Menstruation irregular	20 mg	1 month	None listed	None mentioned	Fluoxetine continued.
		Menorrhagia; metrorrhagia	20 mg	2 months	Phentermine	Bulimia; obesity; mental insufficiency; chronic constipation	Family history of menstrual difficulties. Fluoxetine continued.
		Metrorrhagia	20 mg	7 months	Salbutamol; beclomethasone; alprazolam	Depression, asthma, anxiety	Unknown if fluoxetine continued.

Table 6. Case Summaries for Children and Adolescents Experiencing Menstrual Irregularities During Fluoxetine Therapy (concluded)

Case #	Age/Sex	MedDRA PT Term	Dose of Fluoxetine	Duration of Fluoxetine	Concomitant Medications	Concomitant Disease States	Pertinent Information
		Vaginal hemorrhage; rectal hemorrhage	20 mg	9 months	None listed	None mentioned	Fluoxetine continued. Patient experienced similar problems while taking paroxetine previously.
		Menstrual irregularities	20 mg	1 month	Olanzapine	Psychosis	Fluoxetine discontinued. Return to monthly cycle within 3 months.
		Premenstrual syndrome	30 mg	Several months	Oral contraceptive; gabapentin	Premenstrual dysphoric disorder	Event represents recurrence of PMDD symptoms.
		Premenstrual syndrome	Unknown	7.5 months	Methamphetamine; alcohol	Bipolar disorder	Occurred after fluoxetine discontinued.
		Amenorrhea	60 mg	5 months	Olanzapine	none mentioned	Amenorrhea developed after olanzapine started.
		Hypomenorrhea	20 mg	5 weeks	None listed	None mentioned	Single period with reduced flow. Returned to normal pattern with continued fluoxetine therapy.

No consistent pattern of menstrual irregularities can be determined from these cases. For the 2 cases of premenstrual syndrome [REDACTED] one case developed prior to fluoxetine administration, and the second most likely represented a recurrence of premenstrual dysphoric disorder symptoms. In one case [REDACTED], menstrual irregularities normalized within 3 months of fluoxetine discontinuation, while in another case [REDACTED] a return to a normal menstrual cycle occurred with continued fluoxetine therapy. At least one case of menorrhagia [REDACTED] occurred in a patient with a family history of menstrual irregularities.

Given that dysfunctional uterine bleeding is common in young females (Jenkins 2000b), the data presented above do not indicate conclusively that fluoxetine administration to young females imposes a greater risk of menstrual dysfunction than that normally observed in this population.

Delayed Puberty

Two cases were identified which were categorized as delayed puberty. Details of these 2 cases are provided in Table 7.

Table 7. Case Summaries for Children and Adolescents Experiencing Delayed Puberty During Fluoxetine Therapy

Case #	Age/Sex	MedDRA PT Term	Dose of Fluoxetine	Duration on medication	Concomitant Medications	Concomitant Disease States	Pertinent information
[REDACTED]	[REDACTED]	Growth retardation; delayed puberty, Laboratory test abnormal	20 mg	12 months	Methylphenidate; fluvoxamine	ADHD	Tanner 2 pubertal signs appeared at age 14 years; Tanner 4 at age 15 years.
[REDACTED]	[REDACTED]	Weight decreased; decreased appetite; growth retardation; delayed puberty	13 mg	21 months	Methylphenidate	Dysthymia; anxiety; ADHD	Reduced growth from 90 th to 50 th percentile. Amount of weight loss not specified.

Puberty is considered delayed in boys when there is no testicular enlargement by age 13.5 years, or no pubic hair by age 15 years. In girls, puberty is considered delayed if there is no breast development by age 13 years, no pubic hair by age 14 years, or no menstruation by age 16 years (Beers and Berkow 1999). In the two cases above, diagnoses of delayed puberty in a 12-year-old boy and an 11-year-old girl appear questionable given the children's ages.

Other Cases

Other cases identified in the adverse event database search were 1 case each of increased libido and anorgasmia in a ■■■-year-old girl and ■■■-year-old girl, respectively. There was one case of a ruptured ovarian cyst in a ■■■-year-old female. Erythrocytes were observed in the semen of a ■■■-year-old male. An ■■■-year old male experienced a low sperm count (value not reported) after a 2-year period of fluoxetine therapy. Finally, a case of elevated human chorionic gonadotropin concentration was observed in a ■■■-year-old female with a history of irregular menses.

Summary

A total of 87 cases involving 101 adverse events related to growth and sexual maturation were reviewed for potential relationships to fluoxetine therapy. Cases were classified into general categories: Weight Loss, Weight Gain, Breast Disorders, Growth Retardation, Penis Disorders, Menstrual Abnormalities, and Delayed Puberty.

Changes in body weight were the most frequently reported events with 17 cases of weight loss and 19 cases of weight gain. Results of clinical trials revealed that children receiving fluoxetine gained an average of 1.1 kg body weight less than children receiving placebo. Results of the current review suggest that nausea, vomiting, and diarrhea occurring with fluoxetine administration have been reported in conjunction with weight loss and may be contributing factors. Concomitant medications should also be considered as agents; for example, methylphenidate, amphetamine, and other stimulants may contribute to weight loss through appetite suppression. Weight gain was observed in a number of cases, however, the majority involved extenuating circumstances such as concomitant administration of atypical antipsychotics.

Three cases of gynecomastia were reported in adolescent males. For the most part, such cases may be attributed to endocrine changes occurring during puberty. At least one patient was also receiving concomitant olanzapine therapy, which has also been associated with gynecomastia. Galactorrhea was reported in 8 cases, two of which could be attributed to concomitant hormonal therapies (medroxyprogesterone and oral contraceptives). Undiagnosed pituitary adenoma must also be considered in these cases, as only one case specifically indicated that adenoma had been ruled out. The reporting rate of galactorrhea in adolescents for the 5-year reporting period (8/885 total reports; 0.9%) is approximately the same as that observed for adults for the same period (92/16,379 total reports; 0.56%).

Growth retardation was reported in 8 cases. Results of clinical trials revealed that children receiving fluoxetine gained an average of 1.1 cm less in height than children receiving placebo. It is noted that some cases in the current review reported significant reductions in growth velocity (eg from 75th percentile to 25th percentile). Evaluations of the height information reported in the cases, however, do not necessarily support the dramatic reductions described in the case narratives. Delayed puberty was described in two cases, however, the patients were relatively young (11 and 12 years old) to permit such a diagnosis.

Priapism was reported in 3 cases, and has been identified as an adverse event associated with fluoxetine administration. Menstrual irregularities were also reported in a number of patients; however, dysfunctional uterine bleeding is observed frequently in young, post-pubescent females. In either circumstance, there are no data to suggest that these events occurred more frequently or with greater severity in adolescents receiving fluoxetine than in older patients.

Conclusion

Growth retardation and delayed sexual maturity have been observed in toxicology studies conducted in juvenile rats receiving fluoxetine. Reduced weight gain and reduced growth velocity have been observed in children receiving fluoxetine in clinical trials. The current review of the postmarketing adverse event database was limited by the presence of potential confounding factors and incomplete information within many of the case reports. The results of the current review are inconclusive regarding an increased risk of delayed sexual maturity in children and adolescents.

References

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Appendix 1: List of MedDRA High Level Terms used for Growth Retardation and Delayed Sexual Maturation Clintrace Search

1. Adrenal Cortex Tests
2. Adrenal Disorders Congenital
3. Age-Related Issues
4. Breast Disorders NEC
5. Breast Signs and Symptoms
6. Cervix Disorders NEC
7. Disability Issues
8. Endocrine Abnormalities of Gonadal Function NEC
9. Endocrine Abnormalities of Puberty
10. Epiphyseal Disorders
11. Erection and Ejaculation Conditions and Disorders
12. External Female Genital Therapeutic Procedures
13. Female Gonadal Function Disorders
14. Female Reproductive Tract Disorders Congenital
15. Fertility Analyses
16. Fertility and Fertilisation Interventions Female
17. Fibrosis NEC
18. Gender Disorders
19. Hormonal Therapeutic Procedures NEC
20. Lactation Disorders
21. Male Gonadal Function Disorders
22. Male Reproductive Tract Disorders Congenital
23. Mass Conditions NEC
24. Menopausal Effects NEC
25. Menstruation and Uterine Bleeding NEC
26. Menstruation with Decreased Bleeding
27. Menstruation with Increased Bleeding
28. Orgasmic Disorders and Disturbances
29. Ovarian and Fallopian Tube Cysts and Neoplasms
30. Ovarian and Fallopian Tube Disorders NEC
31. Pelvic Prolapse Conditions
32. Pelvis and Broad Ligament Disorders NEC
33. Penile Disorders NEC
34. Penile Therapeutic Procedures
35. Physical Examination Procedures
36. Pituitary Analyses Anterior
37. Pituitary Analyses Posterior
38. Postpartum Breast Disorders
39. Prostatic Neoplasms and Hypertrophy
40. Reproductive Hormone Analyses
41. Reproductive Organ and Breast Histopathology
42. Reproductive Organ and Breast Imaging Procedures
43. Reproductive Tract Disorders Congenital NEC
44. Reproductive Tract Disorders NEC (Excl Neoplasms)

45. Reproductive Tract Signs and Symptoms NEC
46. Scrotal Disorders NEC
47. Sexual Function and Fertility Disorders NEC
48. Spermatogenesis and Semen Disorders
49. Testicular and Epididymal Disorders NEC
50. Testicular and Epididymal Neoplasms
51. Testicular and Scrotal Therapeutic Procedures
52. Uterine Disorders NEC
53. Uterine Neoplasms
54. Uterine Structure and Position Disorders
55. Uterine Tone Disorders
56. Vaginal Therapeutic Procedures
57. Vulvovaginal Cysts and Neoplasms
58. Vulvovaginal Disorders NEC
59. Vulvovaginal Signs and Symptoms

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Appendix 1.
Analysis of Male Reproductive, Skeletal Muscle, Sexual
Maturation, and Growth Effects of Fluoxetine and
Norfluoxetine
