Sok Central

Till: Wändel-Liminga Ulla; Melander Hans
Ämne: VB: Eudralink - Prozac 20mg Capsules (PL 0006/0195) and Oral Liquid (PL 0006/0272) - FUM no. 2 (UK/H/0636/001,003) sexual maturation in children. REVISED Response to RFI no. 5

Bifogade filer: HCLU REVISED DRAFT Addendum_6_JULY_2007.doc; 016 Cover letter TADs Jr FUM RFI 5 Response 6July.doc


HCLU REVISED RAFT Addendum_6_


016 Cover letter TADs Jr FUM R...

Sätts in i part IVB 1994-0112

Dear Dr Riegl,

Please see the attached cover letter and revised draft addendum, HCLU.

ind regards,

Carly Anderson
Eli Lilly and Company
Eva-Britt

-----Ursprungligt meddelande-----
Från: anderson_carly@lilly.com [mailto:anderson_carly@lilly.com]
Skickat: den 6 juli 2007 17:14
Till: Sok Central
Ämne: Eudralink - Prozac 20mg Capsules (PL 0006/0195) and Oral Liquid (PL 0006/0272) - FUM no. 2 (UK/H/0636/001,003) sexual maturation in children. REVISED Response to RFI no. 5

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Dr. Martina Riegl
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6 July 2007

RE: RESPONSE TO REQUEST FOR FURTHER INFORMATION

Prozac 20mg Capsules (PL 0006/0195) and Oral Liquid (PL 0006/0272) - FUM no. 2 (UK/H/0636/001,003), Post-licensing commitment to assess sexual maturation in children

Dear Dr. Riegl,

With reference to your fifth request for further information regarding the above mentioned follow-up measure for fluoxetine and addendum HCLU, dated 7 June 2007, and following our telephone conversation of 27 June, please find attached a revised version of the draft protocol addendum (HCLU) to the TADS Jr study. This revised addendum includes the additional safety measures that Lilly has agreed to conduct (Tanner Staging, Hormone Assessment and Height and Weight Measurements).

If you require anything further, please do not hesitate to contact me.

Yours sincerely,

Dr Carly Anderson
Acting on behalf of Dr Diane Mackleston for Eli Lilly and Company fluoxetine MAHs.

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cc. Concerned Member State representatives

Protocol Addendum B1Y-MC-HCLU(1)
A Study of Sexual Maturation in Children Enrolled in the Treatment of Children with Depression (TADS Jr.) Protocol

Fluoxetine Hydrochloride (LY110140)

Eli Lilly and Company
DRAFT

This addendum is to be performed in addition to all procedures required by the TADS Jr. protocol or any subsequent amendments to that protocol.

Protocol Addendum B1Y-MC-HCLU(1)
A Study of Sexual Maturation in Children Enrolled in the Treatment of Children with Depression (TADS Jr.) Protocol

Table of Contents

1. Rationale for Addendum/Regulatory History

Delayed sexual maturation has been observed in toxicology studies conducted in juvenile rats administered fluoxetine. Lilly believes that the findings of testicular toxicity observed in the juvenile toxicology study with fluoxetine cannot easily be extrapolated to human exposure; however, the Committee for Medicinal Products for Human Use (CHMP) have requested additional safety information regarding sexual maturation in children and adolescents. On 31 May 2006, Lilly made a commitment to the CHMP to further investigate sexual maturation as a secondary endpoint in an independent study of children aged 8 to 12 years who have been diagnosed with major depressive disorder (MDD). This additional safety measure investigating sexual maturation is sponsored by Lilly and patients will be required to sign a second, separate consent form to be included in this addendum.

Further negotiations with MHRA (May 2007) have led to the inclusion of an additional safety measure to assess hormone levels. This additional safety measure is sponsored by Lilly and patients will be required to sign a third and separate consent form to be included in this aspect of the addendum.

Participation in either and/or both safety measures included in this addendum is not required for patients enrolled in the TADS Jr. study.

Enrollment into the addendum will end when enrollment in the protocol ends.

2. Protocol Additions

2.1. Additional Safety Measures

Table 1. Summary of assessments

Assessment	Timing
*Tanner staging	• Last baseline visit • End of 12-week double-blind treatment period • End of 12-week double-blind treatment period + 6 months , + 12 months, + 18 months, + 24 months
LH and FSH	Serial measurement at approximately 20-minute intervals for 120 minutes, between 7:00 a.m. and 9:00 a.m. (+/- 2 hrs) • Last baseline visit • End of 12-week double-blind treatment period • End of 12-week double-blind treatment period + 6 months , + 12 months, + 18 months, + 24 months
Testosterone (boys) and Estradiol (girls)	Single measurement using the blood draw nearest the final draw at 9:00 am • Last baseline visit • End of 12-week double-blind treatment period • End of 12-week double-blind treatment period + 6 months , + 12 months, + 18 months, + 24 months
LHRH	LHRH infusion test occurs at end of 120 minute LH/FSH serial measurements. Stimulated LH/FSH measumrements occur approximately 30 minutes after infusion • Last baseline visit • End of 12-week double-blind treatment period + 12 months, + 24 months
Prolactin	Single measurement at approximately 30-minutes into LH/FSH serial measurements • Last baseline visit • End of 12-week double-blind treatment period + 12 months, + 24 months
Height, weight, BMI	Each visit

* To be assessed by a nurse practitioner, physician assistant, or physician.
Abbreviations: FSH = follicle-stimulating hormone; LH = luteinizing hormone; LHRH = luteinizing-hormone releasing hormone; BMI = body mass index.

2.1.1. Tanner Staging

Patients' stage of sexual maturation will be assessed by utilizing the Tanner staging measure for determining pubertal development in male and female patients (Tanner and Davies 1985; Tanner 1987). Tanner staging will include a clinical assessment of pubic

hair development (both males and females), genital development (males), and breast development (females).

The Tanner stage evaluation for this addendum will be performed by a trained medical professional, defined as an adequately trained nurse practitioner, physician, and/or physician assistant. This medical professional will receive thorough training prior to participation in this addendum through the use of pictures that represent all 5 stages of pubertal development separately. Similarly, pictures will be used to assess the medical professional in their rating of Tanner stage. The medical professional will be required to demonstrate 100% accuracy in their assessment capabilities before they are allowed to assess patients in this addendum. This stringent training and assessment of the medical professionals will ensure interrater reliability for the Tanner stage ratings.

For female patients, the trained medical professional will also ask the status and date of menarche. For male patients, the trained medical professional will measure testicular volume using an orchidometer.

This additional evaluation using Tanner staging will occur at six time points during the TADS Jr. study:

- Visit Gate C (last baseline)
- End of the 12-week double-blind treatment period
- End of the 6-, 12-, 18-, and 24-months post-treatment period.

Participation in this aspect of the addendum requires signature of a separate informed consent document (Informed Consent #2).

2.1.2. Hormone Assessment

Serial measurements of luteinizing hormones (LH) and follicle-stimulating hormones (FSH) will require blood draws to be taken at approximately 20-minute intervals for 120 minutes between the hours of 7:00 a.m. and 9:00 a.m (+/- 2 hrs). In addition, testosterone (boys) and estradiol (girls) will be measured using the blood draw nearest the final draw at 9:00 a.m.. These measurements will occur at six time points during the TADS Jr. study:

- Visit Gate C (last baseline)
- End of the 12-week double-blind treatment period
- End of the 6-, 12-, 18-, and 24-months post-treatment period.

Prolactin will be assessed using an additional blood draw 30-minutes into the LH/FSH measurement at the last baseline visit, at the 12-month post-treatment period, and at the 24-month post-treatment period.

Luteinising-hormone releasing hormone (LHRH) infusion will occur at the end of the LH/FSH 120 minute measurement period. Approximately 30 minutes after the LHRH infusion, stimulated LH/FSH will be assessed using an additional blood draw at the last baseline visit, at the 12-month post-treatment period, and at the 24-month post-treatment period.

Participation in this aspect of the addendum requires signature of a separate informed consent document (Informed Consent #3). Patients will be offered the opportunity to use EMLA to reduce the pain of needle insertion.

2.1.3. Height and Weight Measurements

As outlined in the TADs Jr protocol, height and weight measurements will be taken at each visit throughout the 12-week treatment period and the 104-week follow-up period. Stadiometers will be provided to all research sites to promote accuracy in height measurement. Height and weight measurements will be used to calculate body mass index (BMI) as a means of correlating height/weight growth with sexual maturation (Burrows et al. 2004; Bini et al. 2000).

2.2. Study Population

Patients must meet all inclusion and exclusion criteria for the TADS Jr. protocol in order to be evaluated as part of this addendum. For this addendum specifically, the following inclusion and exclusion criteria must also be met in order to participate.

2.2.1. Inclusion Criteria

Patients are eligible to be included in the study only if they meet **all** of the following criteria:

[1] Are enrolled in the TADS Jr. study.

[2] Are randomized to either the fluoxetine in combination with cognitive behavioural therapy (CBT) or the placebo in combination with CBT treatment groups within the TADS Jr. study.

[3] Have a baseline Tanner stage less than 5 in the genitalia development domain for boys or the breast development domain for girls.

2.2.2. Exclusion Criteria

Patients will be excluded from the study if they meet **any** of the following criteria:

[4] Have a medical history of a condition known to influence sexual maturation (for example, Klinefelter's syndrome or Turner's syndrome).

[5] Are investigator site personnel directly affiliated with this study and/or their immediate families. Immediate family is defined as a spouse, parent, child, or sibling, whether biological or legally adopted.

[6] Are Lilly employees.

2.3. Sample Size and Statistical Methods

2.3.1. General Considerations

Statistical analysis of this addendum will be the responsibility of Lilly.

Safety analyses will be conducted on the data from patients randomized to either fluoxetine in combination with CBT or placebo in combination with CBT. Analyses will be on an intent-to-treat basis with modifications suggested by Gillings and Koch (1991). The analyses will include all data from all randomized patients having both a baseline and post-baseline Tanner stage evaluation according to the treatment the patients were assigned, regardless of compliance to therapy. However, patients receiving neither active study drug nor placebo will not be evaluated. Also, if a subject is known to have taken only one treatment although randomized to the other, the subject will be analyzed in the intent-to-treat analysis according to the actual treatment taken (Instances of this possibility will be carefully recorded and should be limited in number.). Any patient inadvertently enrolled with a baseline Tanner stage of 5 in the genitalia development domain for boys or the breast development domain for girls will not be included in the analyses since this patient will have already achieved maximum sexual maturity according to the primary measurement of the addendum.

Investigators with few randomized patients per treatment group may be pooled for statistical analysis purposes. The number of patients and pooling of sites will be consistent with the policy of the TADS Jr. primary researchers.

All tests of treatment effects will be conducted at a two-sided alpha level of 0.05, unless otherwise stated.

2.3.2. Patient Characteristics

Patient age, gender, and baseline Tanner stage will be compared between treatment groups using numerical summaries. For age (and any other continuous baseline variable made available by the TADS Jr. investigators), the mean response by therapy will be compared using a t-test. For gender, the count and percentage of patients will be compared using Fishers exact test. For the baseline Tanner stage, both a summary by count of each stage and comparison of means using a t-test will be made for the treatment groups.

2.3.3. Height and Weight Measurements

Height, weight, and BMI will be expressed in standard deviation scores (z-scores) using US CDC growth charts (2000 CDC Growth Charts) that are appropriate for all study sites.

The change from baseline to 12-weeks in height, weight and BMI z-scores will be calculated for patients receiving fluoxetine in combination with CBT and those receiving placebo in combination with CBT. These data will then be compared using a parametric test to allow a direct assessment of the short term effect of fluoxetine on the BMI.

A comparison between treatment groups for the same parameters will also be undertaken at each visit during the 104 weeks follow-up period.

2.3.4. Primary Outcome and Methodology

The primary analysis variable will be whether a patient has a Tanner stage increase in the genitalia/breast development domain during the 12 week double-blind portion of the study. The percentage of patients that progress at least one Tanner Stage in the genitalia/breast development domain in the 12 week double-blind phase will be computed. One-sided 97.5% confidence intervals will be created for each treatment group to allow a clinical evaluation of the potential association of fluoxetine and delayed puberty. A similar assessment of Tanner stage increase in the pubic hair domain will be performed for the 12 week double-blind portion of the study as a sensitivity analysis. This analysis will show how sensitive the conclusion is to which domain is chosen (i.e. does the result support the primary finding). Finally, a Mantel-Haenszel test of difference in proportions stratified by site will also be provided as supportive information. Only patients with both a baseline and at least one post-baseline double-blind observation will be included

A secondary analysis variable will be whether a patient has a Tanner stage increase in the genitalia/breast development domain from baseline through the open-label, 104-week follow-up portion of the study. The percentage of patients that progress at least one

Tanner Stage in the genitalia/breast development domain from baseline through the 104 week follow-up portion of the study will be computed. One-sided 97.5% confidence intervals will be created for each treatment group to allow a clinical evaluation of the potential association of fluoxetine and delayed puberty. A similar assessment of Tanner stage increase in the pubic hair domain will be performed from baseline through the 104 week follow-up portion of the study as a sensitivity analysis. This analysis will show how sensitive the conclusion is to which domain is chosen (i.e. does the result support the primary finding). Only patients with both a baseline and at least one post-baseline open-label observation will be included.

The maximum of the LH and the FSH values over the 2-hour blood draw periods will be analyzed. For all hormone measurements, the last observation carried forward (LOCF) will be analyzed for all randomized patients with both a baseline and post-baseline value. The hormone measurements will be compared between treatments using a t-test (or equivalent one-way analysis of variance) on the change from baseline. These comparisons will be made on the intent-to-treat basis of all randomized patients described previously. Summary statistics will be provided for each visit post-baseline using data available at that visit without carrying forward any previous values (an observed case analysis).

3. References

2000 CDC Growth Charts: United States. National Center for Health Statistics. website: http://www.cdc.gov/growthcharts

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Burrows R, Diaz N, Muzzo S. 2004. Variations of body mass index (BMI) according to degree of pubertal development. Rev Med Chil 132:1363-1368.

Gillings D, Koch G. 1991. The application of the principle of intention-to-treat to the analysis of clinical trials. Drug Information Journal 25:411-424.

Tanner JM. 1987. Issues and advances in adolescent growth and development. J Adolesc Health Care 8:470-478.

Tanner JM and Davies PSW. 1985 Clinical longitudinal standards for height and height velocity for North American children. J Pediatr 107:317-329.