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Ämne: UK/H/0636/001,003; Post-licensing commitment to assess sexual maturation in children; UK Assessment Report

Dear Colleagues,
Please find attached the Assessment Report for the above mentioned procedure.
Please note that your comments are awaited by **30/04/2007**

kind regards,

Katherine Haros
MHRA

<<AR 23 April 2007.doc>>

RMS

Assessment Report

Post-licensing commitment to assess sexual maturation in children

CLINICAL

Prozac

(fluoxetine)

UK/H/0636/001,003

Applicant: Eli Lilly

Start of the procedure:	12 October 2006
Date of this report:	23 April 2007
Deadline for comments:	30 April 2007

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1 RECOMMENDATIONS

Based on the review of the MAH's response the RMS considers that the following issues need to be addressed before this procedure can be concluded:

1. Serial measurements of the gonadotrophins LH and FSH should be provided at 6 monthly intervals. Samples should be taken at 20 minute intervals for 120 minutes between 7.00 and 9.00 a.m.
2. Height, weight and BMI should be expressed in standard deviation scores (z-scores) using normative data relevant to the study sites. Change from baseline in height, weight and BMI z-scores should be calculated for the fluoxetine +CBT and placebo + CBT at 12 weeks and be compared using a parametric test. Comparisons between treatment groups for the same parameters should also be undertaken for each visit during the 104 weeks follow-up phase.
3. An amended draft protocol should be submitted taking into consideration all amendments agreed in this procedure. The amended draft protocol should also address procedures for measuring height and weight and and for specialized training and assessment of interrater reliability for Tanner rating.

2 EXECUTIVE SUMMARY

As a post-licensing commitment the MAH agreed to assess sexual maturation in children by collaborating with clinical investigators who are developing a prospective placebo-controlled trial to compare fluoxetine and CBT in children with major depressive disorder.

This assessment reviews the MAH's responses to the questions raised in the third round of assessment of the proposed draft protocol dated 29 September 2006 for a *Study of Sexual Maturation in Children Enrolled in the Treatment of Children with Depression (TADS Jr.)*, trial number B1Y-MC-HCLU(1).

The TADS Jr. trial will be performed by independent investigators at 12 US sites. It will assess the efficacy of fluoxetine in 360 children aged 8 to ≤12 years with MDD. Children not or only partially responding to 6-weeks of once weekly CBT sessions will be randomised to 12 weeks of either CBT alone, CBT + placebo or CBT + fluoxetine. The primary endpoints will be CDRS-R change (magnitude) and CDRS-R ≤28 (remission) after 12 weeks of treatment. After 12 weeks treatment will be unblinded. Patients will receive booster CBT or pharmacotherapy as clinically appropriate for another 24 weeks.

The submission for funding of this trial to the NIMH has been delayed repeatedly. The latest anticipated date has been specified as 1 October 2007.

The MAH will act as the sponsor of a protocol addendum to assess sexual maturation in children enrolled in TADS who are randomized to either fluoxetine +CBT or placebo + CBT and have a baseline Tanner stage < 5.

Children will be followed up for 104 weeks after the double-blind treatment period. The table below provides an overview of assessments to be performed.

Assessment	To be assessed by	Timing
Tanner staging	Nurse practitioners Physician assistants	• Last baseline visit • End of 12-week double-blind treatment period • End of 6-month open-label post-treatment period • then 6-monthly intervals
LH, FSH, testosterone (boys) and estradiol (girls)	To be defined	6-monthly intervals
LHRH and prolactin tests	To be defined	annually
Height and weight	To be defined	At each visit

The primary outcome is a safety outcome. The primary analysis variable will be whether a patient has an increase in Tanner stage during the double-blind portion of the study. Only patients with both a baseline and a post-baseline double-blind observation will be included in this analysis. A Mantel-Haenszel test of difference in proportions stratified by site be be performed.

This same assessment will be conducted for the 104 weeks follow-up period, comparing baseline to the last observed post-baseline Tanner stage.

The RMS notes that it would have been desirable to include a longer follow-up period and children of a greater age range.

3 ASSESSMENT OF RESPONSES

3.1 Duration of Follow-Up

Question

The company's concern regarding attrition rates are noted. A one-year follow-up period is considered inadequate given the age range of the trial population (8-12 years), the few assessments and the lack of sizable progression of puberty over 24 weeks. The MAH is reminded of their commitment letter to the CHMP of 31 Mary 2006 which stated that they are further investigating the possibility to have longer term evaluations at 52 and/or 104 weeks. A follow-up of five years would be desirable, a duration of 104 weeks after the 12-week double-blind treatment period is the absolute minimum that would be acceptable. Issue resolved provided the follow-up will be 104 weeks after the 12-week double-blind treatment period.

MAH's response

Lilly has discussed this addition for addendum B1Y-MC-HCLU with the investigators of the TADS Jr. protocol and they have agreed to the extended follow-up period of 104 weeks following the 12-week double-blind treatment period, provided Lilly funds this additional 2 years, which has been committed by Lilly. However, the TADS Jr. investigators did voice concern over the value of the data gathered during

the 2-year open-label follow-up period. It is important to note that during this follow-up period, treatment will be the decision of the treating physician. This treatment may include fluoxetine, other antidepressants, or discontinuation of fluoxetine and all other antidepressants for time periods specified by the physician. Concomitant medication will be tracked, but the therapy during the follow-up period will be confounded with treatment response during the double-blind portion of the study and with any response made during the follow-up period itself.

Assessment of the MAH's response, conclusion

The MAH have agreed to a follow-up duration of 104 weeks after the 12-week double-blind treatment period which is the absolute minimum that would be acceptable. **Issue resolved.**

3.2 Hormone Measurements

Question

The investigators point out that the blood draws would likely interfere with compliance in the trial, and children would likely refuse blood draws. To alleviate this concern, offering use of EMLA to reduce pain from needle insertion might be considered.

The MAH's comment that collecting blood in other studies was justified as there was a putative drug mechanism known to possibly effect the hormones is noted. Preclinical studies have raised a concern with respect to fluoxetine and its effect on sexual maturation; the measurement of hormones in children is considered mandatory. It is noted that no final study protocol was agreed as part of the post-licensing commitment. Issue not resolved.

MAH's response

While Lilly maintains the same reservations previously presented regarding the potential to add value of the hormone assessments, Lilly agrees to perform these assessments requested by the MHRA:

- blood draws at 9:00 a.m. (as recommended by the MHRA) at 6-monthly intervals to assess LH, FSH, testosterone (boys) and estradiol (girls)
- annual LHRH and prolactin assessments.

Given the ethical concerns previously stated and the likelihood that the time-specific nature of these blood draws might effect participation, Lilly proposes to utilize an additional informed consent document specifically for the collection and timing of blood samples which will allow patients to participate in other areas of the protocol and addendum even if parents have reservations about allowing their child to undergo blood tests. In an effort to possibly increase participation in the blood draws, Lilly will offer the possibility to use EMLA to reduce pain from needle insertion.

This proposal will provide the possibility and opportunity to collect the hormone data for assessment without deterring participation in the TADS Jr. protocol and/or sexual maturation addendum for those patients that refuse for whatever reason to participate in the blood draw.

Assessment of the MAH's response, conclusion

The MAH have agreed to a perform the hormone measurements. It would appear that the MHRA's request for serial measurements of LH and FSH has been misinterpreted as a request for single measurements. **Issue resolved provided 6 monthly serial measurements of the gonadotrophins LH and FSH are provided.** Samples should be taken at 20 minute intervals for 120 minutes between 7.00 and 9.00 a.m.

3.3 Tanner staging

Question

The company has not supplied any evidence for the reliability and validity of Tanner staging through US qualified nurse practitioners. The MAH's proposal to assess Tanner stages at baseline, week 12 and week 36 can be accepted. Further assessments should be carried out at 6-monthly intervals. It would appear that the National Institute of Child Health and Human Development (NICHD) Study of Early Child Care and Youth Development allowed for assessment of Tanner staging by nurse practitioners. However, central training was provided to ensure across-site consistency in Tanner staging and all clinicians had to be specifically certified for Tanner staging. (see http://secc.rti.org/display.cfm?t=m&i=Chapter_58_1). If nurse practitioners are used in this trial, substantial specialized training will be required and interrater reliability should be tested.

MAH's response

Lilly agrees to:

- adequately train the nurse practitioners, physicians, and/or physician assistants who will assess Tanner staging according to this addendum.
- ensure interrater reliability.
- conduct Tanner stage assessments at 6-montly intervals throughout the 104-week follow-up period in addition to those already defined during the 12-week double-blind treatment period.

During the 26 March 2007 meeting with the TADS Jr. investigators they discussed that physicians assistants will also be performing the Tanner staging. Lilly is not aware if the EU has a similar profession and therefore is providing the following links to better describe the role of physicians assistants: http://en.wikipedia.org/wiki/Physician_assistant,
http://www.aapa.org/spec/AAPAOM/OMPAInformation2.html,
http://www.paworld.net/whatpadoes.htm.

Assessment of the MAH's response, conclusion

In the US, physician assistants (Pas) practice medicine under the supervision of physicians and surgeons. They are formally trained to provide diagnostic, therapeutic, and preventive health care services, as delegated by a physician.

The MAH has agreed to assess Tanner stages at baseline, week 12 and week 36 and thereafter in 6-monthly intervals. The assessment of Tanner stages by accredited physician assistants is considered acceptable given that the MAH has committed adequately train them and ensure interrater reliability. **Issue resolved provided the ensures interrater reliability by testing for interrater reliability.**

3.4 Height and Weight

Question

The MAH does not plan to monitor height and weight, nor to correlate these parameters to sexual maturation. It is considered essential that height and weight are reported to evaluate how any delay in sexual maturation might impact upon the magnitude of the pubertal growth spurt and also the effects of fluoxetine on weight gain. The MAH's response is therefore not accepted, and the Protocol Addendum should be amended to include measurement of height and weight at each visit.

MAH's response:

Lilly agrees to collect height and weight data at each visit throughout the protocol and the 104-week follow-up period in order to assess the effect of treatment on the relationship of sexual maturity to growth.

However, Lilly remains concerned about the possibility to assess a correlation of height and weight with sexual maturation, specifically given the size of the study and the likely variability of the patients included in this study. Additionally, as would be the case for any treatment beyond the double-blind treatment period, it is unlikely that any meaningful conclusions can be made regarding this growth data and sexual maturation, given the possible effects of concomitant medications, diet, illness, and a multitude of possible confounding factors during the 104-week follow-up period.

Lilly has continued to evaluate possible correlations between height and/or weight and sexual maturation and proposes to calculate body mass index (BMI) as a means to correlate height/weight growth with sexual maturation. Burrows and colleagues (2004) and Bini and colleagues (2000) suggest that biological development is associated with BMI. While Lilly is agreeable to providing BMI measurements, reservations remain in the value of this information following the 104-week open-label follow-up period during which time any treatment may be administered.

Assessment of the MAH's response, conclusion

The MAH has agreed to collect height and weight data at each visit. The provision of BMI data is acceptable. **Issue resolved provided data are analysed as follows**:

Height, weight and BMI should be expressed in standard deviation scores (z-scores) using normative data relevant to the study sites.

Change from baseline in height, weight and BMI z-scores should be calculated for the fluoxetine +CBT and placebo + CBT at 12 weeks and be compared using a parametric test. This will allow a direct assessment of the short term influence of fluoxetine on length and body composition / BMI growth.

Comparisons between treatment groups for the same parameters should also be undertaken for each visit during the 104 weeks follow-up phase. Although it is acknowledged that height and weight may be influenced by other factors, such as treatments taken beyond the 12-week treatment period,the comparison between treatment groups is still a randomised comparison and can provide useful information.

3.5 Primary Analysis Variable

Question

The MAH states that their letter of undertaking provided the primary analysis variable. It is noted that no 'primary analysis parameter' was specified in the document the MAH refers to. The document does state that the MAH will propose to evaluate the percentage of patients that progress at least one Tanner stage in 12 weeks and after 24 weeks, with possibly also weeks 52 and/or 104. The MAH's response is therefore not accepted. Issue not resolved.

Response from Lilly:

Lilly proposes the following text to be included in the protocol:

> "The primary outcome is considered a safety outcome. The primary analysis variable will be whether a patient has an increase in Tanner stage during the double-blind portion of the study. This same assessment will be conducted for the 104 weeks follow-up period to provide information requested by European regulators but will not be considered the primary analysis variable. The proportion of patients treated with fluoxetine in combination with CBT who have an increase in Tanner stage from baseline to either the end of the double-blind portion or the end of the 104 week follow-up will be compared with the proportion of patients treated with placebo in combination with CBT using a

Mantel-Haenszel test of difference in proportions stratified by site. For the analysis of the double-blind portion, only patients with both a baseline and a post-baseline double-blind observation will be included. For the 104-week follow-up, only patients with both a baseline and at least one long-term follow-up measurement will be included in the analysis comparing baseline to the last observed post-baseline Tanner stage."

There are several scientific reasons why Lilly does not consider the result at the end of 116 weeks (12 + 104) as primary. Firstly, the 104 weeks of post-therapy follow-up are open-label with no assigned therapy and as a result other therapy effects may confound and bias the assessment. Also, since the total time post-baseline is 116 weeks, a large proportion of children are likely to have a shift upward in Tanner stage. This would leave only a few, perhaps 5 to 15% who have not shifted, so that statistically, the magnitude of effect is similar as after 12 weeks but with the roles of "success" and "failure" reversed. Statistically there would be no difference in power except that at the end there will be fewer children available to observe lowering the ability to distinguish drug effect. Despite these reservations, Lilly agrees to provide the MHRA with an analysis of the 116-week data as requested. The statistical analysis plan will document further summaries of the Tanner stage data by visit.

Assessment of the MAH's response, conclusion

The applicant has agreed to evaluate the percentage of patients that progress at least one Tanner stage at both weeks 12 (observed cases) and 104 (LOCF), with the week 12 assessment considered to be primary. It is agreed that week 12 provides the cleanest comparison of the treatments as this is the end of the double-blind treatment period. However given the lack of sizable progression of puberty over 12 weeks it cannot be expected that 12-week data in children aged 8-12 years provide relevant information. The commitment to provide the 104 week follow-up data is valuable. **Issue resolved.**

3.6 TADS Safety Data

Question

In addition, please provide any data that you may have obtained or can obtain from the TADS investigators regarding the 18-week and 36-week efficacy and safety data from the TADS trial.

MAH's response:

Lilly discussed this request with the TADS investigators and were informed that a publication containing 18-week and 36-week data has been accepted for publication and is expected to be published in a few months. Lilly will provide this manuscript to the MHRA once published. Additionally, the full data set is tentatively scheduled to be made available in the public domain in May 2008.

Assessment of the MAH's response, conclusion

The MAH's response is noted. **Issue resolved.**

4 CONCLUSION

Based on the review of the MAH's response the RMS considers that the following issues need to be addressed before this procedure can be concluded:

4. Serial measurements of the gonadotrophins LH and FSH should be provided at 6 monthly intervals. Samples should be taken at 20 minute intervals for 120 minutes between 7.00 and 9.00 a.m.
5. Height, weight and BMI should be expressed in standard deviation scores (z-scores) using normative data relevant to the study sites. Change from baseline in height, weight and BMI

z-scores should be calculated for the fluoxetine +CBT and placebo + CBT at 12 weeks and be compared using a parametric test. Comparisons between treatment groups for the same parameters should also be undertaken for each visit during the 104 weeks follow-up phase.

6. An amended draft protocol should be submitted taking into consideration all amendments agreed in this procedure. The amended draft protocol should also address procedures for measuring height and weight and and for specialized training and assessment of interrater reliability for Tanner rating.