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Dear colleagues,

Prozac FUM 2 - Post licensing commitment to assess sexual maturation in children - Day 22

Enclosed please find the assessment of responses. Please send your comments by 18 December 2006.
<<Prozac FUM 2 Assessment of responses 12 Dec 2006.doc>>
Please do not hesitate to contact me should you require any further information.

Kind regards

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RMS

Response 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:	12 December 2006
Deadline for comments:	18 December 2006

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1 Introduction

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.

The preliminary assessment report was circulated on 27 October 2007. Comments were received from FR, NL and IT. A Request for Supplementary Information taking into account the CMS's comments was sent to the Marketing Authorisation Holder (MAH) on 2 November 2006. A response document lacking the cited references were received on 16 November 2006. The cited references were made available on 29 and 30 November 2006.

This report assesses the responses.

2 Assessment of responses

2.1 Further information on TADS Jr trial:

Question:

The draft protocol of the TADS Jr trial is lacking in detail. Please provide further information on safety parameters to be measured and on the design and treatments of phase III of the trial. Consideration should be given to assessing alkaline phosphatase levels.

Conventional ANCOVA analyses of the change in CDRS-R, with terms for baseline, site and treatment, using imputation for missing data, and analysis of the responder rates at the end of each stage, also using imputation, should be included.

MAH's response:

On 09 November 2006, Lilly discussed these suggestions with the TADS Jr. investigators. They are planning to submit their final protocol on 01 June 2007. This later date is due to a recent change in the NIMH grant submission process.

The final safety parameters have not been finalized, but they are considering including the Columbia Suicide Severity Rating Scale, the Scale for Prodromal Symptoms, and standard measures of safety.

The proposed study is likely to consist of 12 weeks of blinded fluoxetine or placebo treatment followed by 24 weeks of unblinded follow-up (phase III). If the patient is doing well, the investigator is encouraged to continue the randomized treatment during phase III. However, the treating investigator may prescribe other clinically appropriate medications as needed.

Regarding alkaline phosphatase the investigators emphasized that this is a marker for bone formation such as bone growth, mineralization, and bone turnover, but not a specific marker for sexual maturation or puberty. However, as a specific measure for growth, there is wide variability in the values and as a single parameter it would be difficult to make a clear clinical interpretation of the results.

The TADS Jr. investigators stated the analysis would be based upon a regression model similar to what was done in the TADS study. Imputation would be used, although the method has not been finalized. A responder analysis is planned. The TADS Jr. investigators have agreed to provide the final protocol when available through Lilly.

Assessment of the MAH's response, conclusion

The MAH's response regarding both the safety parameters and the planned analysis is too vague. More detail is needed. ***Issue not resolved.***

2.2 Duration of trial

Question:

The protocol should be amended as follows: The duration of follow-up should be 5 years.

MAH's response:

This study will consist of 12 weeks of blinded fluoxetine or placebo treatment followed by 24 weeks of follow-up, during which time treatment will be unblinded and patients may change therapy. Tanner staging will be conducted at randomization, at 12 weeks (the primary evaluation at the end of double-blind therapy) and at the end of the study (secondary evaluation 24 weeks following the double-blind phase). The longer the follow-up time beyond the double-blind phase, the more likely that patients may receive other drugs (including fluoxetine) introducing confounding factors which will lead to clinically interpretable results.

Assessment of the MAH's response, conclusion

The MAH's response is not accepted. Whilst the MAH's point regarding the possibility of introduction of bias by treatment with other drugs during the follow-up period is valid, this can be taken into consideration when analysing/interpreting the results and should not be taken as a rationale for designing a trial that is unlikely to provide any meaningful results. ***Issue not resolved.***

2.3 Tanner staging

Question:

The protocol should be amended as follows: Tanner staging including assessment of menarche and testicular volumes should be conducted by experienced paediatricians at 3-monthly intervals.

MAH's response:

o In the United States, a nurse practitioner is a registered nurse with advanced academic and clinical training who is able to diagnose and manage most common illnesses either independently or as part of a health care team. A nurse practitioner provides some care previously offered only by physicians and in most states has the ability to prescribe medications. The nurse practitioners who will be assessing Tanner staging in this study will be highly medically trained for this purpose.

o Having a nurse practitioner perform Tanner staging in the investigator's office will prevent the patients from having to visit an additional office to participate in the study, thereby reducing the burden on the patients and potentially increasing recruitment and protocol compliance.

o As per subsequent responses, Lilly does not plan on conducting Tanner staging at 3-monthly intervals, but rather at Week 12 and then Week 36 to minimize the burden on patients, particularly as the data from Week 24 (post-randomization) is not likely to provide additional clinical value.

Assessment of the MAH's response, conclusion

The MAH's response is noted. The MAH should clarify how nurse practitioners would be trained for this study, and how much experience nurse practitioners working in psychiatric outpatient clinics would have in assessment of Tanner stages. ***Issue not resolved.***

2.4 LH, FSH, testosterone, estradiol, LHRH and prolactin tests

Question:

The protocol should be amended as follows: Serial measurements on 9.00 a.m. blood samples of LH, FSH, testosterone (boys) and estradiol (girls) should be performed at 6-monthly intervals. LHRH and prolactin tests should be performed yearly.

MAH's response:

o The objective of the proposed addendum study design is to clinically evaluate the potential for delayed sexual maturation between treatment groups. The biochemical measures, as mentioned above, do not have validated standards to delineate the progression of puberty and therefore may not yield useful clinical information in addition to Tanner staging, which is currently considered the gold standard for assessment of sexual maturation (Ankarberg-Lindgren and Norjavaara 2004; Janfaza et al. 2006).

o The study agreed as part of the post-licensing commitment did not include blood sampling throughout the study period. It is our view that the requested assessment are not within the protocol agreed to as part of the post-licensing commitment which referred to the monitoring of change in Tanner staging as the study objective. In addition, inclusion of blood sampling has the potential to deter individuals from participating in the optional sexual maturation assessment. This has to be measured against the useful information likely to be obtained from such limited assessment.

Assessment of the MAH's response, conclusion

The MAH's response is not accepted. Eli Lilly undertook to evaluate the effect of fluoxetine on sexual maturation in children. Measurements of LH, FSH, testosterone, estradiol, LHRH and prolactin are considered necessary to establish the effect of fluoxetine on sexual maturation in children. ***Issue not resolved.***

2.5 Cognitive and behavioural development

Question:

The protocol should be amended as follows: Cognitive and behavioural development should be assessed.

MAH's response:

The MAH believes these requested assessments to not be in the scope of assessment of sexual maturation as agreed to as part of the post-licensing commitments.

Assessment of the MAH's response, conclusion

The MAH's response is not accepted. Effects of fluoxetine on cognitive and behavioural development have not been established. There is evidence from preclinical studies that administration of fluoxetine may have an impact on behavioural development. The MAH's refusal to take the opportunity to assess effects of fluoxetine on cognitive and behavioural development in children is not considered ethical. ***Issue not resolved.***

2.6 Correlation of height and weight data to sexual maturation

Question:

The protocol should be amended as follows: Height and weight data should be correlated to sexual maturation data.

MAH's response:

The collection of height and weight data is part of the main TADS Jr. study protocol. Lilly will discuss any possible correlation with the TADS Jr. investigators and provide further information as soon as possible.

Assessment of the MAH's response, conclusion

The MAH's response is not accepted. The MAH should commit to correlate height and weight data to sexual maturation data in a meaningful way. ***Issue not resolved.***

2.7 Primary analysis variable

Question:

The protocol should be amended as follows: The primary analysis variable should be amended to reflect the scientific rationale of the trial.

MAH's response:

The primary analysis variable was reflected in Attachment 3 to the letter of commitment for this study. This analysis variable has been used in statin studies evaluating sexual maturation (de Jongh and colleagues 2002).

Assessment of the MAH's response, conclusion

The MAH's response is not accepted as the planned primary analysis variable (whether a patient has an increase in Tanner stage during the 12 week double-blind portion of the study) cannot be expected to provide any meaningful data. The primary analysis variable should be amended to reflect the scientific rationale of the trial. ***Issue not resolved.***

2.8 Provision of safety results on an annual basis

Question:

The protocol should be amended as follows: Results should be provided on an annual basis.

MAH's response:

Results will be evaluated after 12 weeks of double-blind therapy (primary evaluation) and at the completion of the study, 24 weeks following the double-blind phase.

Assessment of the MAH's response, conclusion

The MAH's response is not accepted. With the proposed patient population, design and reporting frequency, the trial is unlikely to yield any useful results. ***Issue not resolved.***

2.9 Exclusion of patients from further assessment when Tanner stage 5 has been reached for only one of the Tanner developmental indicators

Question:

Please provide a justification for excluding patients from further assessment when Tanner stage 5 has been reached for only one of the Tanner developmental indicators.

MAH's response:

In this study, Tanner staging will be applied such that a patient will be determined to be in a particular stage when s/he meets one or more criteria for that stage (ie, breast development, genitalia development, and pubic hair growth). When a patient is determined to be in Tanner stage 5, observation for sexual development will be discontinued. That is, s/he will not receive further

Tanner staging assessments because no further stage can be attained after stage 5. Therefore, additional assessments would provide no additional information and would place undue additional burden on the patient. If a patient is determined to be in Tanner stage 5 at the baseline visit, they would be excluded from the addendum as they would not be "at risk" for having the outcome of interest, which is advancing one or more Tanner stages.

Assessment of the MAH's response, conclusion

The answer does not address the question. The MAH should provide a scientific rationale and justification for excluding patients from further assessment when Tanner stage 5 has been reached for *only one* of the Tanner developmental indicators. ***Issue not resolved.***

2.10 Timing for consent to sexual development study

Question:

Please clarify at which point of the patient recruitment process patients/parents will be informed about the option to participate in this protocol amendment and asked for consent.

MAH's response:

During the original consent process for the TADS Jr. protocol, all patients will be invited to participate in the addendum. Those who agree will be consented using the separate addendum informed consent document (ICD) at that time. At the point of randomization, all patients who originally refused to participate in the addendum will be invited again and those who agree will be consented using the addendum ICD at that time.

Assessment of the MAH's response, conclusion

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

2.11 Definition of clinically relevant delay in sexual maturation during a period of 9 month

Question:

The study protocol should define what a clinically relevant delay in sexual maturation is during a period of 9 month. A power calculation should be performed taking into account, the number of children that are expected to be available for analysis, the definition of a clinically relevant delay, as well as normal variation in development.

Summary of MAH's response:

Although children ages 8 to 10 years are at the early phases of sexual maturation, Lilly would still expect approximately 10 to 15% of our sample of children ages 8 to 12 years to change at least one Tanner stage from baseline to 24-week follow-up. Sun and colleagues (2002) described the timing of sexual maturation among 4,263 US children ages 8 to 16 years surveyed in the National Health and Nutrition Examination Survey (NHANES) III from 1988 to 1994. They reported that among non-Hispanic whites, 25% of girls enter stage 2 by approximately age 9.5 years and 50% by approximately 10.5 years. Among non-Hispanic white boys, 25% enter stage 2 by approximately age 11 years and 50% by approximately 12 years. Furthermore, among boys and girls of all races the interval between attainment of each stage from 2 to 5 is approximately 1 to 2 years with a slightly longer interval from stage 4 to 5.

Assuming that there is no differential by age between the treatment groups, a similar number of patients would be expected to change at least one Tanner stage within each treatment group. Because the interval between the earlier Tanner stages and the later Tanner stages is approximately the same, having younger patients enrolled in the trial would not lead to dilution of a potential effect. Although the power is expected to be low for the Mantel-Haenszel test of difference in

proportions stratified by site, a clinical interpretation will be made by evaluating the one-sided 97.5% confidence interval for each group to determine if there is a potential signal. A similar endpoint was used in a report by de Jongh and colleagues (2002) which found that 17% of treated and 14% of placebo patients changed at least one Tanner stage from baseline to 24-week follow-up. They concluded that there was no evidence of an adverse effect on pubertal development.

Assessment of the MAH's response, conclusion

It is noted that patients included in the study cited by the MAH (de Jongh et al, Circulation 2002;106:2231-2237) were 10 to 17 years old. The study included assays for gonadal and pituitary hormones. At study entry, boys were in Tanner stage II or above, and girls were postmenarchal for at least a year before the initiation of the study. Follow up in these patients was for 48-weeks.

The MAH's response does not directly address the question. The company is requested to provide

a) A definition of what a clinically relevant delay in sexual maturation is during a period of 9 month.

b) A power calculation should be performed taking into account, the number of children that are expected to be available for analysis, the definition of a clinically relevant delay, as well as normal variation in development.

c) The size of difference considered to be of clinical importance should be considered in advance and pre-specified, not justified after the data have been seen.

Issue not resolved.

2.12 Additional measures to increase power

Question:

Since power is expected to be low, additional measures to increase power should be entertained. For example: A) Extending efforts to include adolescents in the TADS Jr. as well as to increase proportion of children at the higher age ranges (11-12) compared to younger children. B) Extend efforts to encourage participation of children from the TADS Jr. in the sexual maturation part of the study.

MAH's response:

The TADS Jr. trial is the responsibility of a group of independent US investigators; however, Lilly has discussed with them the possibility of including children beyond the age of 12. The TADS Jr. investigators expressed a concern that including children beyond the age of 12 will affect the independent funding by NIMH as it will overlap with the previously-completed TADS study. One of the primary TADS Jr. investigators, Dr. Graham Emslie, also expressed his opinion that "adding older children would not add scientific value and further would bias the pre-puberty study towards older children which would be unacceptable to their stated objective" (minutes dated 09 June 2006). The investigators do believe that a significant proportion of higher age children (11- and 12-year-olds) will enter the study due to the age of presentation with this disease.

Lilly believes that the following actions will maximize participation and minimize the burden on the patients in the sexual maturation addendum:

- Patients will be asked twice (once at consent and if necessary at randomization) if they would agree to participate in the protocol addendum.
- The use of nurse practitioners to evaluate Tanner stage will allow the patients to complete the protocol at one location.

- Minimizing the number of Tanner staging evaluations
- Not undertaking blood sampling.

Assessment of the MAH's response, conclusion

The MAH's response is noted.

It is noted that the proposed trial design is unlikely to yield results that will either confirm or refute effects of fluoxetine on sexual development unless Tanner staging is carried out by experienced and well trained paediatricians and LH, FSH, testosterone, estradiol, LHRH and prolactin are measured at regular intervals over an adequate period of time (5 years).

3 Conclusion and Recommendation

Except for the question addressing the timing for consent to the sexual development study, none of the questions has been satisfactorily addressed. The MAH should be asked to satisfactorily address these questions.