149

Sok Central

Till: Wändel-Liminga Ulla; Melander Hans
Ämne: VB: Prozac FUM 2, assessment of responses
Prioritet: Hög
Bifogade filer: Prozac FUM 2, assessment of responses, 1 March 2006.doc

1994-0112, Fontex®, 4 mg/ml, Oral lösning, UK/H/636/03, FUM 02; EMEA/H/A-6(12)/671, 2111:2006/63256

Respons AR FUM 02

IVB -> 0

/rs

Från: MR-DCprocedures, [mailto:MR-DCprocedures@mhra.gsi.gov.uk]
Skickat: den 1 mars 2007 16:40
Till: List-H-MRFG (EUDRA); List-H-MRVE (EUDRA)
Kopia: Dunne, Dr Julia; Riach, Maureen
Ämne: Prozac FUM 2, assessment of responses
Prioritet: Hög

Dear colleagues

Prozac UK/H/0636/001,003 - FUM 2 - Assessment of responses

Please find attached the response Assessment Report for the above mentioned procedure

<<Prozac FUM 2, assessment of responses, 1 March 2006.doc>>
kind regards,

Katherine Haros
MHRA

This email and any files transmitted with it are **confidential**. If you are not the intended recipient, any reading, printing, storage, disclosure, copying or any other action taken in respect of this email is prohibited and may be unlawful.

If you are not the intended recipient, please notify the sender immediately by using the reply function and then permanently delete what you have received.Incoming and outgoing email messages are routinely monitored for compliance with the Department of Healths policy on the use of electronic communications.

For more information on the Department of Healths email policy, click

http://www.dh.gov.uk/DHTermsAndConditions/fs/en?CONTENT_ID=4110945&chk=x1C3Zw

RMS

Response Assessment Report no. 2

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:	1 March 2007
Deadline for comments:	8 March 2007

TABLE OF CONTENTS

1 EXECUTIVE SUMMARY AND RECOMMENDATIONS 3

2 INTRODUCTION 3

3 ASSESSMENT OF RESPONSES 4

3.1 Further information on TADS Jr trial: 4

3.2 Duration of trial 5

3.3 Tanner staging 6

3.4 LH, FSH, testosterone, estradiol, LHRH and prolactin tests 7

3.5 Cognitive and behavioural development 9

3.6 Correlation of height and weight data to sexual maturation 11

3.7 Primary analysis variable 11

3.8 Provision of safety results on an annual basis 12

3.9 Exclusion of patients from further assessment when Tanner stage 5 has been reached for only one of the Tanner developmental indicators 12

3.10 Timing for consent to sexual development study 13

3.11 Definition of clinically relevant delay in sexual maturation during a period of 9 month 14

3.12 Additional measures to increase power 15

4 OTHER NOTES 16

5 CONCLUSION AND RECOMMENDATION 16

1 EXECUTIVE SUMMARY AND RECOMMENDATIONS

This assessment reviews the proposed protocol addendum B1Y-MC-HCLU designed by the MAH to assess the effects of fluoxetine on sexual maturation in children participating in a trial to be sponsored by the NIMH and carried out by the TADS investigators.

Taking into consideration the company's response, the points made by the investigators, the Letter of Undertaking accepted by the European Commission and CPMP guidance CPMP/EWP/462/95, and feasibility, it is considered that the following amendments to would be acceptable:

- Total duration of Follow-Up: 104 weeks after double-blind period.
- Hormone measurements are required.
- Assessment of Tanner staging by nurse practitioners would be acceptable, provided that these nurses have documented and substantial specialized training. Interrater reliability should be tested. Tanner staging should be conducted at 6-monthly intervals for 104 weeks after the end of double-blind treatment.
- Height and weight should be monitored at the same time as Tanner staging is performed.
- The primary analysis variable should be amended to reflect the scientific rationale of the trial.

In addition, the MAH is requested to provide any data they may have obtained or can obtain form the TADS investigators regarding the 18-week and 36-week efficacy and safety data.

2 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 (RSI) 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 first response assessment report was circulated on 12 December 2006. It concluded that except for the question addressing the timing for consent to the sexual development study, none of the questions had been satisfactorily addressed. Comments were received from IT, FR and NL. An second RSI taking into account the CMSs comments was sent to the MAH on 19 December 2006. Responses were received on 2 February 2006.

The report assessed the second set of responses.

In order to facilitate reading, the text includes the previous questions (**bold**), responses and conclusions (*italics*). The assessment of the MAH's second set of responses and the relevant conclusions are provided in boxes.

3 ASSESSMENT OF RESPONSES

3.1 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 no. 1:

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 no. 1:

The MAH's response regarding both the safety parameters and the planned analysis is too vague. More detail is needed.

Comments NL:

The planned analysis (regression) does not correspond to the conventional analysis used in regulators realm (ITT with LOCF). Therefore the question is if the company could agree with the investigators that they either receive the data in order to carry out the required analysis themselves or alternatively if the investigators would carry out this analysis.

Conclusion:

Issue not resolved.

MAH's Response no. 2:

Lilly has been in contact with the TADS Jr. investigators and no additional information regarding the specifics of the protocol is available at this time.

As stated previously, Lilly will add Addendum B1Y-MC-HCLU for the collection of the additional sexual maturation safety measure to the independently-designed TADS Jr. study. As the TADS Jr. study is an independent investigator study funded by the NIMH, Lilly does not have authority or influence over the design or analysis of this study and only has authority over the study addendum. The TADS Jr. investigators have committed to provide a final protocol by 01 August 2007, at which time Lilly will provide the MHRA with a copy.

Ultimately, the analysis method, the population to be analyzed, and the imputation method for the primary analysis of the TADS Jr. study are choices to be made by the investigators in conjunction with the funding agency, the National Institutes of Mental Health (NIMH). However, during a meeting on 24 January 2007, the TADS Jr. investigators gave preliminary confirmation that it is their current plan (although not finalized and subject to change when the final protocol is complete) to use an ITT population for analysis with missing data handled by a mixed model analysis. Furthermore, the investigators were open to the idea of using a last observation carried forward (LOCF) analysis on change of score with baseline as a covariate and to performing an analysis using a propensity score to account for compliance with therapy.

Assessment of the MAH's response, conclusion

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

3.2 Duration of trial

Question:

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

MAH's response no.1:

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 uninterpretable 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.***

MAH's Response no. 2:

Lilly anticipates considerable attrition in the TADS Jr. study and Addendum B1Y-MC-HCLU if follow-up is extended to 5 years. This expectation is, in part, based on the attrition realised in the original TADS study (TADS Team, 2004). Aside from the age group under investigation and the sexual maturation addendum, the TADS and TADS, Jr. studies are anticipated to be almost identical in design, methods, and analysis (although this will be confirmed in August 2007 when the final protocol is provided by the TADS Jr. investigators). Therefore, the patient retention in TADS provides a reasonable and practical indicator for the patient retention in TADS Jr. Of the 439 patients randomized to treatment in TADS, 56.3% (247) completed the study through week 88 (1.69 years) (personal Communication – C. Kratochvil 09 January 2007).

Lilly agrees that potential bias may be controlled to a limited extent through analysis and interpretation. Because of the expected attrition that is likely to have occurred at 5 years of follow-up, the ability to

control for bias either through analytical methods or through interpretation will be greatly diminished. The results at 5 years of follow-up will be very sensitive to the imputation method chosen (for example, LOCF). Once a patient discontinues there is no further opportunity to observe a change in Tanner stage. If LOCF is used, carrying forward a baseline observation will bias the proportion of patients with a Tanner stage shift downward the longer the observation period, and consequently, the difference between the two treatment will be biased downward. If a "completers" analysis is used, known biases associated with response to treatment will come into play. Regardless of the approach, the design will not allow more than a limited removal of bias by analysis.

Finally, at the 24 January 2007 meeting, the prospect of this extension in follow-up was discussed with the TADS Jr. investigators. It is the opinion of the TADS Jr. investigators that any possible drug effect delay on sexual maturation would be much smaller than a primary acute effect and that at the end of a 5-year follow-up, there is unlikely to be any detectable difference in numbers of patients originally treated with placebo versus fluoxetine as many of the placebo patients might have gone on to be treated with fluoxetine.

However, given all of the above, Lilly is still investigating ways in which a 1-year follow-up (post primary endpoint conclusion) might be successfully implemented in this addendum.

Assessment of the MAH's response, conclusion

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 May 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.***

3.3 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,

The MAH's response is noted. The company should provide evidence for the reliability and validity of Tanner staging through nurse practitioner. 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.

Comments FR:

We are of the opinion that a Tanner stage evaluation by experimented paediatricians every 6 months would be more feasible than every 3 months, and could be made at the same time that biological tests (planned to be performed at 6-monthly intervals).

Conclusion

Issue not resolved.

MAH's Response no. 2:

Attachment 5.2 to this response document includes Tanner staging assessment information and guidance utilized by Lilly in Study B4Z-MC-LYAI (atomoxetine hydrochloride). These documents will be provided to the qualified nurse practitioners who will be participating in the TADS Jr. and Addendum B1Y-MC-HCLU studies. Furthermore, it should be noted that these nurse practitioners are highly qualified individuals with existing knowledge of Tanner staging evidenced from their medical examination that qualifies them as a nurse practitioner.

Assessment of the MAH's response, conclusion

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 specialised training will be required and interrater reliability should be tested.

3.4 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 no. 1:

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:

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.

Comments FR:

Measurements of Inhibin B test should be added, as this is an additional parameter to measure the exocrine testicular function.

Conclusion

Issue not resolved.

MAH's Response no. 2:

The use of Tanner staging is repeatedly referenced in the literature as the standard means by which to assess sexual maturation (Herman-Giddens et al. 1997; Parent et al. 2003; Kaplowitz and Oberfield 1999; Karpati et al. 2002; Wu et al. 2002). While several studies have utilized hormone level assessment in addition to Tanner staging, these studies were already collecting blood and there was a putative drug mechanism known to possibly effect the hormones (deJongh et al. 2002; Stein et al. 1999; Wiegman et al. 2004). Additionally, the American Academy of Pediatrics (AAP) Pediatric Research in Office Settings (PROS), who are leaders in paediatric assessments have investigated the prevalence and mean ages of onset of pubertal characteristics in young girls treated in paediatric practices in the United States using Tanner staging. A parallel assessment in males is ongoing by the PROS group to address the timing of the emergence of puberty in young boys and is also utilizing Tanner staging. Neither study has utilized blood draws to assess hormone levels.

During the 24 January 2007 meeting with the TADS Jr. investigators, the topic of hormone assessment was discussed. The TADS Jr. investigators made the following main points:

- Although the blood draws are for the purposes of the sexual maturation addendum only (HCLU), they are predicted to interfere with compliance in the main TADS Jr. study,
- given that the chance of finding any detectible differences in hormone levels is so small, it would not be ethical to draw blood for this purpose,
- given that the patient population is children with depression, it is believed that the majority will refuse the blood draws. This will then lead to a lot of missing data and will make any possible analysis difficult, if not impossible, to interpret, and
- hormones function as a mediator value and the TADS Jr. study and the Lilly sexual maturation addendum (HCLU) are not powered to detect a hormone level difference in treatment groups.

Given all of the above, Lilly does not believe that assessing hormone levels through blood draws is an ethical and/or viable addition to this proposed addendum.

Assessment of the MAH's response, conclusion

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.

3.5 Cognitive and behavioural development

Question:

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

MAH's response no. 1:

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.

MAH's response no. 2:

As stated in Article 2 of the Commission Decision of 21 August 2006 concerning Prozac and associated medicinal products for human use containing fluoxetine, the national marketing authorisations held by Lilly, in accordance with Article 32(4) of Directive 2001/83/EC, are subject to the conditions set out in Annex IV to this Decision. These conditions are as follows:

'1. Toxicological Studies:

The MAH should perform the following studies and report the results to the RMS:

- Juvenile rat study to evaluate neurohormonal status of hypothalamic-pituitary-gonadal (HPG) axis during sexual maturation of juvenile CD male and female rats administered fluoxetine.

- Juvenile rat study to characterize the development and potential reversibility of testicular toxicity (ie, neurohormonal and histopathologic evaluations) in male juvenile CD rats administered fluoxetine.

- Juvenile rat study to characterize the effects on specified emotional behaviours. In this study, fluoxetine would be administered to CD rats from postnatal day 33 to postnatal day 62 with evaluations in the elevated zero maze, forced swimming test and prepulse inhibition test, once during treatment and 2 months post-treatment.

2. Clinical evaluation of the effect of fluoxetine on sexual maturation

- NIMH Prospective placebo-controlled study: The MAHs committed to assess the possibilities to include the evaluation of the effect of fluoxetine on sexual maturation in children aged 8 – 12 years old within the protocol being developed under the auspices of National Institute of Mental Health (NIMH) in United States as well as to discuss with the study investigators the improvement of the trial design by extending the duration of the follow-up and increasing of the upper age range of patients in this study during. The MAHs committed to provide this protocol to the RMS as soon as it is made available to them.

- The MAH committed to further investigate whether or not the existing in Member States can be used to provide evaluable data on the effects of fluoxetine on sexual maturation.'

No agreement was made in the form of follow-up measures between Lilly and the CHMP to assess cognitive and behavioural development. Discussions during the paediatric Article 6(12) referral procedure, as captured in the revised CHMP Joint Assessment Report dated 31 May 2006, regarding cognitive and behavioural development resulted in the addition of the following agreed text in the SPC section **4.4. Special warnings and precautions for use, *Use in children and adolescents under 18 years of age***: '...In addition, only limited evidence is available concerning long-term effect on safety in children and adolescents, including effects on growth, sexual maturation and cognitive, emotional and behavioural developments (see section 5.3).'

Furthermore, while an assessment of emotional behaviour was not specified as a condition to the Article 6(12) referral procedure it was raised during discussions between Lilly and the CHMP during this procedure and was agreed, as outlined in the recommendations of the revised CHMP Joint Assessment Report dated 31 May 2006, that '...A commitment should be made to the effect that depending on the results of the preclinical study addressing long-term effect on emotional behaviours, additional studies in humans will be carried out if required.'

Indeed, Lilly's Letter of Undertaking, dated 31 May 2006 (Attachment 5.1), specified that 'If the RMS considers that the results of the preclinical studies warrant label changes or further study, we agree to discussions with RMS to assess what further measures would be valid, useful and achievable', by 24 December 2007, where the preclinical studies referenced refer to those mentioned above. Furthermore, comments from France in the CHMP Joint Assessment Report included 'all post authorization commitments should be fully defined and agreed upon before – rather than after – the granting of the indication, if applicable.' Cognitive and behavioural development was therefore not included in the clinical study proposed at that time and was not part of the agreed commitment.

Lilly would like to note that adhering to the terms in the Letter of Undertaking (Attachment 5.1) which were agreed by the CHMP and Lilly does not make for unethical behaviour.

Assessment of the MAH's response, conclusion

The MAH's response is noted. Although the requirement for long-term studies to determine effects on cognitive and behavioural development is set out in CHMP Guideline CPMP/EWP/462/95.and therefore is not a requirement that would have needed to be specifically addressed in the Letter of Undertaking, the MAH's response is accepted.

Issue resolved provided that additional studies in humans will be carried out if required, depending on the results of the preclinical study addressing long-term effect on emotional behaviours.

3.6 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 no. 1:

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.

MAH's response no. 2:

The study is designed to evaluate if there is a potential signal for delayed sexual maturation. Given the size of the study and the likely variability in height and weights of the subjects in the study, the ability to assess correlation with sexual maturation will be limited. For the sexual maturation addendum, HCLU, height and weight data will only be collected for each patient at the baseline Tanner stage assessment. Since this is not a study of growth there are no plans for additional measures of height and weight nor will a stadiometer or other specialized instruments be used for this one-time height and weight data collection. This protocol is in accordance with the protocols from other studies investigating sexual maturation through the use of Tanner staging (Herman-Giddens et al. 1997; Parent et al. 2003; Kaplowitz and Oberfield 1999; Karpati et al. 2002; Wu et al. 2002).

Assessment of the MAH's response, conclusion

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 measurements of height and weight at each visit. ***Issue not resolved.***

3.7 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 no. 1:

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.

MAH's response no. 2:

Attachment 3 of Lilly's Letter of Undertaking (Attachment 5.1) submitted to the CHMP and MHRA provided the primary analysis variable for the assessment of sexual maturation. It is Lilly's understanding that the conditions of this letter were accepted by all CMSs at the time of the CHMP opinion and were later endorsed by the EU Commission Decision of 21 August 2006. Thus Lilly does not accept that these conditions should be changed post-hoc.

Assessment of the MAH's response, conclusion

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.***

3.8 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 no. 1:

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.

MAH's response no. 2:

Attachment 3 of Lilly's Letter of Undertaking (Attachment 5.1) submitted to the MHRA provided the primary analysis variable for the assessment of sexual maturation. It is Lilly's understanding that the conditions of this letter were accepted by all CMSs at the time of the CHMP opinion and were later endorsed by the EU Commission Decision of 21 August 2006.

Assessment of the MAH's response, conclusion

The MAH's response is noted. ***Issue resolved***, *i.e. the requirement for annual reporting of trial results, can lapse,* ***provided that the total duration of follow-up is no less than 104 weeks.***

3.9 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 no.1:

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.

MAH's response no. 2:

Lilly agrees to assess patients in both domains for Tanner staging (pubic hair and genitalia for boys and pubic hair and breast for girls) and to only exclude patients from study participation if they have reached Tanner stage 5 for both domains.

Assessment of the MAH's response, conclusion

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

3.10 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 no. 1:

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.

Comments NL and Additional Question:

The company should clarify whether consenters will be randomized separately. If not then there is a risk that the groups to be compared with respect to Tanner will not be, strictly speaking, equivalent.

MAH's response no. 2:

The randomization process of the TADS Jr. study is both clinically and statistically independent of whether or not a child participates in the sexual maturation addendum (B1Y-MC-HCLU). The investigator, the child, and the child's family will all be blinded to the therapy assigned. This blinding removes the possibility of the actual therapy assigned from biasing whether the child will participate in the addendum. Hence, the groups to be compared should remain equivalent.

Assessment of the MAH's response, conclusion

Issue resolved provided that *the MAH considers stratification of treatment allocation for consenters/non-consenters.*

3.11 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 no.1:

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

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.

Comments NL:

The company estimated that 10-15% of the sample of children aged 8 to 12 will experience a Tanner stage change within the follow-up period of 24 weeks. Given that in the sample of Jongh et al (2002) with an older sample (10-17) 14% experienced a change, it is reasonable to take the lower limit of 10% as reasonable expectation for proportion of children with changed Tanner stage.

A power calculation based on this figure of 10% change in placebo and 5% in Prozac (that could be considered a clinically relevant difference due to Prozac) and a type I error of 0.05 (two-sided) an N of 435 per group would be needed in order to achieve a power of 80% to detect this difference. Instead the planned study will recruit a total of 240 patients, hence a maximum of 120 per group from which a yet unknown number will refuse participation in this part of the study. Hence it is clear that the power of the study to detect a clinically relevant difference is by far too small.

***Conclusion:* Issue not resolved.**

MAH's response no. 2:

This study is designed to identify if there is a potential signal of delayed sexual maturation in children receiving fluoxetine and was never powered to statistically detect a difference. As stated in Attachment 3 of Lilly's Letter of Undertaking (Attachment 5.1), the primary analysis for sexual maturation was a clinical, not statistical, interpretation of the one-sided 97.5% confidence intervals of each treatment group. The fluoxetine estimate will be interpreted within the context of the placebo estimate. Although a specific clinically relevant difference is difficult to identify, if the point estimate for fluoxetine is lower than the one-sided confidence interval for placebo, this may suggest the possibility of a signal for delayed sexual maturation in humans receiving fluoxetine. Any additional information collected during the TADS Jr. study will be considered when addressing sexual maturation.

Assessment of the MAH's response, conclusion

The MAH's response is noted.

3.12 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 no.1:

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).

MAH's response no. 2:

Lilly acknowledges the conclusion from the MHRA and continues to abide by the Letter of Undertaking (Attachment 5.1).

Assessment of the MAH's response, conclusion

The MAH's response is noted.

4 OTHER NOTES

B M Kuehn reported in JAMA 2007;297:453-455 that further results from TADS were presented at the annual meeting of the American Academy of Child and Adolescent Psychiatry in Toronto in October 2005. It would appear that after 18 weeks of treatment, children receiving cognitive-behavioral therapy alone had a response rate comparable with children receiving fluoxetine; after 36 weeks of treatment, those receiving cognitive-behavioral therapy alone had a response rate comparable with those who received both treatments. There is no mention of safety data in this article.

Assessor's comment

The MAH is requested to provide any data they may have obtained or can obtain form the TADS investigators regarding the 18-week and 36-week efficacy and safety data.

5 CONCLUSION AND RECOMMENDATION

Taking into consideration the company's response, the points made by the investigators, the Letter of Undertaking accepted by the European Commission and CPMP guidance CPMP/EWP/462/95, and feasibility, it is considered that the following amendments to would be acceptable:

- Total duration of Follow-Up: 104 weeks after double-blind period.
- Hormone measurements are required.
- Assessment of Tanner staging by nurse practitioners would be acceptable, provided that these nurses have documented and substantial specialized training. Interrater reliability should be tested. Tanner staging should be conducted at 6-monthly intervals for 104 weeks after the end of double-blind treatment.
- Height and weight should be monitored at the same time as Tanner staging is performed.
- The primary analysis variable should be amended to reflect the scientific rationale of the trial.

In addition, the MAH is requested to provide any data they may have obtained or can obtain from the TADS investigators regarding the 18-week and 36-week efficacy and safety data.