Sok Central

Till: Wändel-Liminga Ulla; Melander Hans; Ahlström Lena
Ämne: VB: Eudralink - Prozac - FUM no. 2 following EMEA/H/A-6(12)/671, response to Request for Further Information

Bifogade filer: 008 Response to Qs on TADS Jr and Ad 6 Nov 06.doc; brev.htm; Response to Qs on TADS Jr[1]. and Addendum _16_nov_06_FINAL.doc


008 Response to Qs on TADS Jr ...


brev.htm (3 KB)


Response to Qs on TADS Jr[1]. ...

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

svar på frågor FUM 02 -> IVB -> 0
/Anna

-----Ursprungligt meddelande-----
Från: anderson_carly@lilly.com [mailto:anderson_carly@lilly.com]
Skickat: den 22 november 2006 14:44
Till: Sok Central
Ämne: Eudralink - Prozac - FUM no. 2 following EMEA/H/A-6(12)/671, response to Request for Further Information

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Subject:	Prozac - FUM no. 2 following EMEA/H/A-6 (12)/671, response to Request for Further Information
From:	anderson_carly@lilly.com
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Sent:	Wed, 22 Nov 2006 13:44:15 +0000
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Please see the attached letter and response document. References are to follow.

Many thanks,

Carly Anderson
Eli Lilly and Company

Filename	Type	Size
008 Response to Qs on TADS Jr and Ad 6 Nov 06.doc	MS Word Document	51kb
Response to Qs on TADS Jr. and Addendum _16_nov_06_FINAL.doc	MS Word Document	81kb

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16 November 2006

Dr. Martina Riegl
Medicines and Healthcare products Regulatory Agency
Market Towers
1 Nine Elms Lane
Vauxhall
London SW8 5NQ

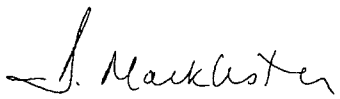
Dear Dr. Riegl,

REQUEST FOR FURTHER INFORMATION

Prozac Capsules and Oral Solution (UK/H/0636/001,003) - FUM no. 2, Post-licensing commitment to assess sexual maturation in children

With reference to your request for further information of 2 November 2006 regarding the fluoxetine TADS Jr. study and addendum, please the find the responses to these questions/comments. Please do not hesitate to contact me if you need anything further.

Yours sincerely



Diane Mackleston
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Fluoxetine Regulatory Response: Request for Further Information on Post-licensing Commitment to Assess Sexual Maturation in Children

Prozac®
(Fluoxetine hydrochloride)

UK/H/0636/001,003, FUM no. 2: 16 November 2006

Eli Lilly and Company

The information contained in this document will undergo revisions, during the lifecycle of this plan, as new information about risks, exposures, and other important safety information about fluoxetine becomes available to the Global Product Safety division within Eli Lilly and Company.

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1. Background

Following an Article 6(12) referral, a Commission Decision to include the treatment of children and adolescents (ages 8 to 18 years) with major depressive disorder (MDD) in the Prozac SPC for capsules and oral liquid was granted (21 August 2006). As part of this approval Lilly agreed by letter submitted to the Chairman of the CHMP on 31 May 2006 to the following post-licensing commitment concerning the assessment of sexual maturation following exposure to fluoxetine in this population:

Module 5 – Clinical	
We undertake to work with clinical investigators who are developing a protocol under the auspices of National Institute of Mental Health in United States to include the evaluation of the effect of fluoxetine on sexual maturation in children aged 8 – 12 years old. The protocol for this study is still being developed, but outline information is provided in Attachment 3. No more detail is available currently, but we agree to provide the protocol from this study to EMEA and CHMP as soon as it is provided to Eli Lilly and Company by the investigators. This study is colloquially termed "TADS Jr" With regard to extending the duration of follow-up, increasing the upper age range of patients in this study and accelerating the enrolment rate, we undertake to pursue these matters with the study investigators at our scheduled meeting with them in June. We agree to provide the minutes of this meeting between Lilly and the investigators.	Lilly / NIMH meeting minutes: 30 June 2006 Draft Protocol: 01/10/06 NIMH Approval & funding: 01/07/07 Final Protocol: 01/08/07 FPV: 4Q/07 LPV: 4Q/12 Final Study Report: 2013

A copy of the outline of the commitment study, referred to above as Attachment 3, is provided in the Appendix.

Lilly submitted a draft protocol (TADS Jr.) and a draft protocol addendum (B1Y-MC-HCLU) to the MHRA, as reference member state, on 29 September 2006. The draft protocol addendum submitted at that time is consistent with the outline information of the study proposed in our commitment letter.

Section 2 provides the questions from concerned member states on these protocols and the responses from Lilly.

2. Questions/Answers

2.1. TADS Jr. Study

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.

Response from Lilly:

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.

2.2. Protocol Addendum B1Y-MC-HCLU(1)

2.2.1. Question and Lilly Responses:

The protocol should be amended as follows:

- *The duration of follow-up should be 5 years.*
    - 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 uniterpretable results.
- *Tanner staging including assessment of menarche and testicular volumes should be conducted by experienced paediatricians at 3-monthly intervals.*
    - 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.
    - 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.
    - 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.
- *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.*

- 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).
- 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 assessement 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.

- *Cognitive and behavioural development should be assessed.*
  - 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.
- *Height and weight data should be correlated to sexual maturation data.*
  - The collection of height and weight data is part of the main TADS Jr. study proptocol. Lilly will discuss any possible correlation with the TADS Jr. investigators and provide further information as soon as possible.
- *The primary analysis variable should be amended to reflect the scientific rationale of the trial.*
  - 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).
- *Results should be provided on an annual basis.*
  - 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.

- *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.*
    - 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.
- *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.*
    - 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.

2.2.2. Comments from Netherlands

- *Tanner stage II (beginning of puberty is experienced on average at age 11/12, stage III at age 12/14, stage IV at age 13/14, and V 15/16. Hence, only a small proportion of the children included in TADS JR. will be available to provide relevant data for the outcome of this study. Assuming the estimated 240 children randomised to fluoxetine and CBT or Placebo and CBT are equally divided on the 8-12 age range, only one fourth (i.e. 60 children) will be at the relevant age (11-12) at the time of treatment and follow-up, of which an unknown fraction will refuse participation in this portion of the study.*

- *Including children of all ages in the analysis will lead to a dilution of the potential difference between the treatment groups since no difference will be found (nor can it be expected) in the younger age groups.*
- *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.*

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 basline to 24-week follow-up. They concluded that there was no evidence of an adverse effect on pubertal development.

- *Since power is expected to be low, additional measures to increase power should be entertained. –*
- *For example:*
    - *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.*

- *Extend efforts to encourage participation of children from the TADS JR in the sexual maturation part of the study. – Pts will be asked twice, not doing blood draw, limit # of assessments done, etc...*

Lilly 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

2.3. References

Ankargerg-Lindgren C, Norjavaara E. 2004. Changes of diurnal rhythm and levels of total and free testosterone secretion from pre to late puberty in boys: testis size of 3 ml is a transition stage to puberty. Eur J Endocrinol 151:747-757.

de Jongh S, Ose L, Szamosi T, Gagne C, Lamber M, Scott R, Perron R, Dobbelaere D, Saborio M, Tuohy M, Stepanavage M, Sapre A, Gumbiner B, Mercuri M, van Trotsenburg A.S., Bakker H, Kastelein. 2002. Efficacy and safety of statin therapy in children with familial hypercholesterolemia: a randomized, double-blind, placebo-controlled trial with simvastatin. Circulation 106:2231-2237.

Janfaza M, Sherman TI, Larmore KA, Brown-Dawson J, Klein KO. 2006. Estradiol levels and secretory dynamics in normal girls and boys as determined by an ultasensitive bioassay: a 10 year experience. J Ped Endo Metab 19:901-909.

Sun SS, Schubert CM, Chumlea WC, Roche AF, Kulin HE, Lee PA, Himes JH, Ryan AS. 2002. National estimates of the timing of sexual maturation and racial differences among US children. Pediatrics 110(5):911-9.

Appendix - Post-licencing Commitment Study Outline

Attachment 3. Clinical Evaluation of the Effects of Fluoxetine on Sexual Maturation in Children

Lilly has the opportunity for participation in a prospective placebo-controlled study that is planned by an external investigative group and is being funded by the National Institute of Mental Health (NIMH) in the U.S. This study is the best option to explore possible effects of paediatric fluoxetine treatment on sexual maturation. It is Lilly's understanding at this time that it contains the following design criteria:

- Initiate study with approximately 500 children, ages 8 to 12 years of age, with diagnoses of major depression
- 6 weeks of cognitive behavioural therapy (CBT) is first phase of study
- Patients with inadequate response after the 6 weeks of CBT (estimated to be N=360) will be randomized to 12 weeks of one of the following treatment groups:
    - Continued CBT alone (N=120)
    - CBT plus placebo treatment (N=120)
    - CBT plus fluoxetine treatment (N=120)
- Possibility for a longer-term follow-up (up to 24 weeks*)
- Includes Tanner Staging evaluation at 0, 12, 24 weeks*

Lilly's proposal to this external investigative group will be to evaluate the percentage of patients that progress at least one Tanner Stage in 12 weeks and after 24 weeks*, recognising that this will probably be a secondary endpoint in the study. 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.

* Lilly is further investigating the possibility to have longer term evaluations at 52 and / or 104 weeks.