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Subject:	Prozac 20mg Capsules (PL 0006/0195) and Oral Liquid (PL 0006/0272) - FUM no. 2 (UK/H/0636/001,003) sexual maturation in children. Response to RFI no. 2
From:	anderson_carly@lilly.com
To:	central.sok@mpa.se
Sent:	Wed, 31 Jan 2007 17:44:59 +0000
Expiration:	Thu, 15 Feb 2007 17:44:59 +0000

94-0112 → IV B 7 0

Dear Dr Riegl,

Please see the attached cover letter and response document. Outstanding electronic references will be provided shortly.

Many thanks,
Carly Anderson
Eli Lilly and Company

Filename	Type	Size
003 Cover letter TADs Jr FUM RFI 2 Response 31Jan.doc	MS Word Document	51kb
am-j-psych-2005-autism.pdf	Portable Document Format File	1828kb
rynn-m-2006.pdf	Portable Document Format File	1231kb
vitiello-b-2006.pdf	Portable Document Format File	1379kb
Response to RFI 2 TADS Jr and HCLU_31Jan07_FINAL.doc	MS Word Document	900kb

To save the file, click on the file name.

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31 January 2007

Dear Dr. Riegl,

RESPONSE TO REQUEST FOR FURTHER INFORMATION

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

With reference to your second request for further information of 19 December 2006 regarding the fluoxetine TADS Jr. study and addendum, please find attached the responses to these questions and comments.

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

Yours sincerely,

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

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cc. Concerned Member State representatives

Fluoxetine Regulatory Response: Revised Reponse Assessment Report Following CMS Comments on Post-licensing Commitment to Assess Sexual Maturation in Children

Prozac®
(Fluoxetine hydrochloride)

UK/H/0636/001,003, FUM no. 2: Approved: 31 January 2007

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.

Table of Contents

1. Background

As a post-licensing commitment, Lilly agreed to work with clinical investigators who are developing a prospective placebo-controlled trial to compare fluoxetine and cognitive behavioral therapy (CBT) in children with major depressive disorder to include the assessment of sexual maturation. Questions and comments regarding this proposed study were sent to Lilly on 2 November 2006 and responses were provided as requested on 16 November 2006.

On 19 December 2006, the MHRA submitted a second Request for Supplementary Information that assesses the response sent by Lilly on 16 November 2006, including additional comments from representatives from the Netherlands, France and Italy. The MHRA concluded that "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 satisfactorily address these questions."

Lilly provides responses to these further questions and comments in Section 2 below. The responses provided are based primarily on the 31 May 2006 Letter of Undertaking submitted by Lilly to the CHMP who subsequently accepted and agreed with the conditions outlined in this letter prior to reaching a positive CHMP opinion on a paediatric indication for fluoxetine. A copy of this letter is provided as Attachment 5.1 to this document. This Letter of Undertaking includes an outline of the design and scope of the agreed study.

2. Questions/Answers

In order to retain the flow of correspondence between Lilly and the MHRA and Concerned Member States (CMSs), Lilly has utilized the same format as the MHRA and provided complete summaries of each original question in italics with our latest response at the end of each issue.

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:

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.

Response from Lilly:

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.

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 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.***

Response from Lilly:

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.

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,

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.

Response from Lilly:

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.

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:

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.

Response from Lilly:

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.

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.***

Response from Lilly:

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.

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.

Response from Lilly:

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).

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.***

Response from Lilly:

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.

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.

Response from Lilly:

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.

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.***

Response from Lilly:

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.

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.***

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.

Response from Lilly:

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.

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,

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.

Response from Lilly:

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.

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).

Response from Lilly:

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

3. Conclusion

Lilly is commited to fulfilling the follow-up measures committed to in the Letter of Undertaking, dated 31 May 2006. Lilly aims to work with the MHRA and CMSs to reach agreement on the specifics regarding the assessement of sexual maturation in pediatric patients treated with fluoxetine.

4. References

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5. Attachments

5.1. 31 May 2006 Letter of Undertaking

Eli Lilly European Regulatory Team

Tel: +44 1276 483381

Date: 31 May 2006

Dr. D. Brasseur

European Medicines Agency
7 Westferry Circus
Canary Wharf
London
E14 4HB
United Kingdom

Dear Dr Brasseur,

Re: EMEA/H/A-6(12)/671 (Fluoxetine capsules and oral solution, Eli Lilly and Company)

Eli Lilly and Company agree to undertake the following Post-Authorisation Commitments requested by the CHMP and commit to submit the data listed below within the specified timeframes.

We also agree to submit any variation application resulting from the assessment of the below mentioned data.

PIL User Testing

Additionally, as requested, we commit to review the need for and timing of user testing for the PL and labelling with the UK as Reference Member State.

Yours sincerely,

John C Saunders

(Acting on behalf of Dr. D Mackleston, for Eli Lilly and Company Fluoxetine MA Holders)

Specific Obligations:

Description:	Due Date
Module 4 – Pharmaco –Toxicological[1]	
Juvenile rat study – neurohormonal investigation of sexual maturation (see also Attachment 1)	Draft Protocol: 30/06/06 Protocol: 31/08/06 Study Report: 31/10/07
Juvenile rat study – characterization of testicular pathogenesis (see also Attachment 2)	Draft Protocol: 30/06/06 Protocol: 31/08/06 Study Report: 31/10/07
Juvenile rat study – characterization of 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.	Draft Protocol: 30/06/06 Protocol: 31/08/06 Study Report: 31/10/07
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	Lilly / NIMH meeting minutes: 30 June 2006 Draft Protocol: 01/10/06 NIMH Approval & funding: 01/07/07

[1] The timeline for the final reports for these three preclinical studies varies by study. The characterization of testicular pathogenesis has a six-month live-phase. Hence, with the protocol being finalise 31 August and a study start in October 2006, the live phase will be complete by April 2007. Taking into account the time needed for pathological examinations and report writing, we estimate that the final report will be available by 31 October 2007. We propose that we provide the three preclinical reports together to CHMP at this one time.

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.	Final Protocol: 01/08/07 FPV: 4Q/07 LPV: 4Q/12[2] Final Study Report: 2013

Follow-up Measures:

Description:	Due Date
Module 4 – Pharmaco –Toxicological	
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.	24/12/07
Module 5 – Clinical	
We undertake to investigate further whether or not existing registries in Member States can be used to provide evaluable data on the effects of fluoxetine on sexual maturation.	30/11/06 & 30/11/07
We undertake to evaluate mania and hypomania in the paediatric population as specific topics in future PSURs.	Ongoing

[2] We apologise for this long duration, but we only heard 25 May that the timeline for conducting this study is much longer than we previously anticipated, but this does illustrate the problems associated with such studies. We undertake to investigate the possibility of interim data analysis being made available for a subset of patients.

Attachment 1. Proposed Rat Neurohormonal Study

Purpose: evaluate neurohormonal status of hypothalamic-pituitary-gonadal (HPG) axis during sexual maturation of juvenile CD male and female rats administered fluoxetine

Doses: 0, 10, and 30 mg/kg

Dosing Schedule: daily from Postnatal Day (PND) 21 to 61

Neuroendocrine Assessment

- Females: LH, FSH, prolactin, inhibin, estradiol, progesterone on PNDs 28, 30, 33, 35, 44 and 50
- Males: LH, FSH, prolactin, inhibin, testosterone on PNDs 28, 40, 50, and 61

Results from this study would demonstrate whether fluoxetine is associated with an effect on the HPG axis in juvenile rats.

Attachment 2. Proposed Rat Testicular Study

Purpose: to characterize the development and potential reversibility of testicular toxicity (ie, neurohormonal and histopathologic evaluations) in male juvenile CD rats administered fluoxetine

Dose Levels: 0, 10, and 30 mg/kg

Dosing Schedule: daily

- 2 groups/dose level dosed from PND 21 to PND 55
- 2 groups/dose level dosed from PND 21 to PND 70
- 2 groups/dose level dosed from PND 21 to PND 91

Neuroendocrine assessment on PND 55, 70, 91 and 181

- LH, FSH, testosterone, inhibin b

Pathology at each scheduled necropsy (PND 55, 70, 91 and 181)

- Organ weights (absolute): testes, prostate
- Histopathologic evaluation of testes, prostate, seminal vesicles, and epididymis

Results from this study will characterize the development of testicular lesions, and the reversibility of these findings at multiple time points; and potentially identify specific cellular targets and/or neurohormonal mechanisms involved in the development of these lesions.

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.

5.2. Tanner Staging

Investigator Worksheet: Female Tanner Staging

Patient Number ___ ___ ___ ___

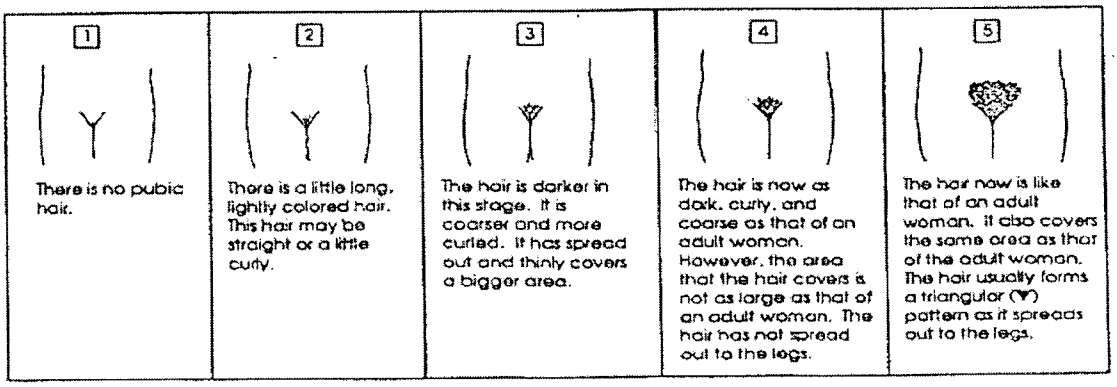
Visit Number ___ ___

Investigator Worksheet

Tanner Stage Pubic Hair Development

The pictures on this page show **different amounts of pubic hair.** A girl goes through each of the five stages shown. Please look at each picture. Read the sentences. Put an **X** in the box above the picture that is *closest* to the amount of pubic hair you have.

PH1	PH2	PH3	PH4	PH5

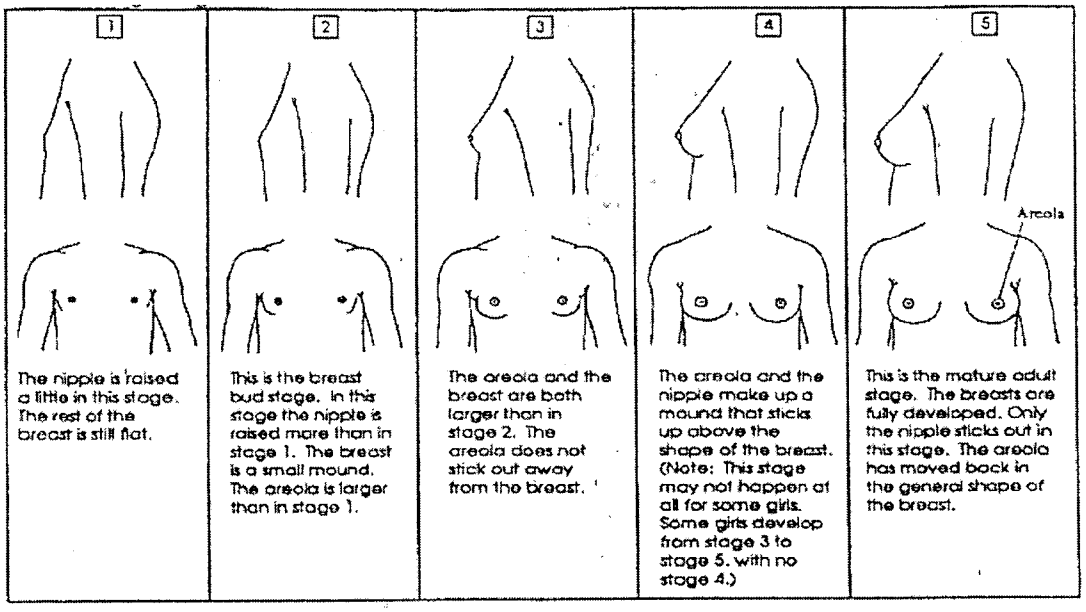


Note: Your stage of pubic hair growth *may* or *may not* be the same as your stage of breast growth.

Tanner Stage Breast Development Worksheet

The pictures on this page show **different stages of how the breasts grow**. A girl can go through each of the five stages shown. Please look at each of the pictures. Read the sentences. Put an **X** in the box above the picture that is *closest* to your stage of growth.

B1	B2	B3	B4	B5



Morris, Naomi M. and J. Richard Udry. 1980. "Validation of a Self-Administered Instrument to Assess Stage of Adolescent Development," Journal of Youth and Adolescence 9(3):271-180

Investigator Worksheet: Male Tanner Staging

Patient Number ___ ___ ___ ___

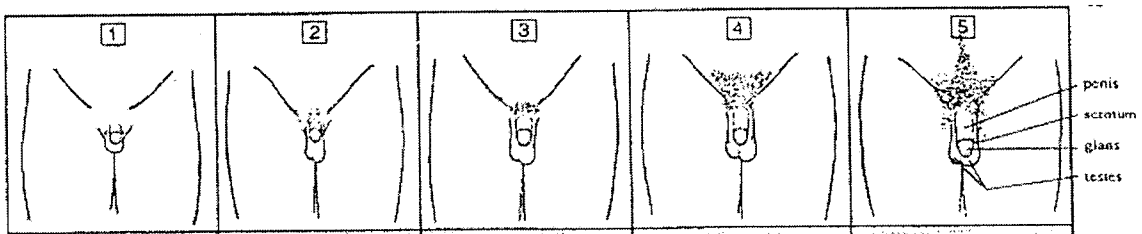
Visit Number ___ ___

Investigator Worksheet

Tanner Stage Pubic Hair Development

The pictures below show **different amounts of male pubic hair.** A boy goes through each of the five stages as shown. Please look at each picture. Read the sentences. Put an **X** in the box above the picture that is *closest* to your stage of pubic hair growth. Do *not* look at penis size.

PH1	PH2	PH3	PH4	PH5



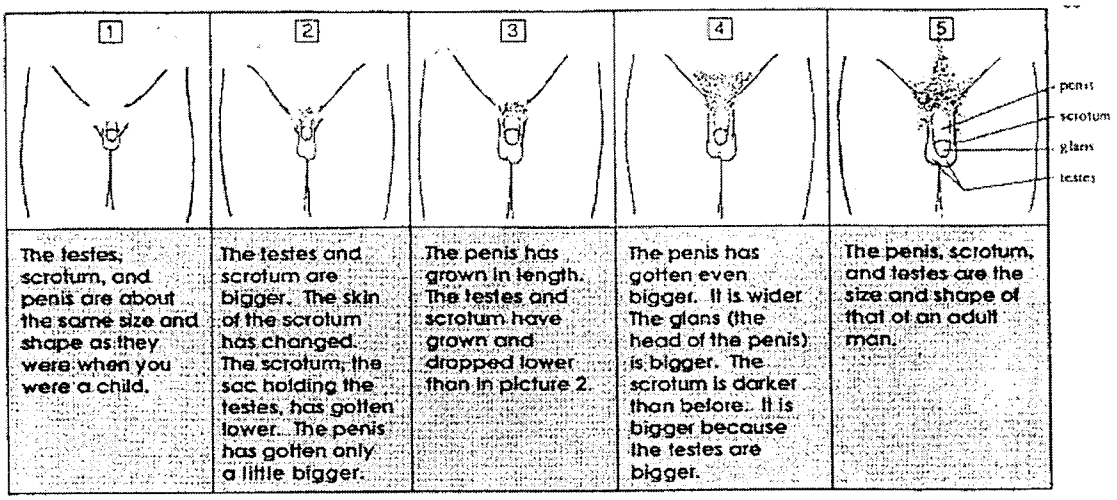
There is no pubic hair at all.	There is a little soft, long, lightly colored hair. Most of the hair is at the base of the penis. This hair may be straight or a little curly.	The hair is darker in this stage. It is more curled. It has spread out and thinly covers a bigger area.	The hair is now as dark and curly as that of an adult man. The area that the hair covers is not as big as that of an adult man. The hair has not spread out to the legs.	The hair has spread out to the legs. The hair is now like that of an adult man. It covers the same area as that of an adult man.

Note: Your stage of pubic hair growth *may* or *may not* be the same as your stage of growth of the testes, scrotum, and penis.

Tanner Stage Genital Development Worksheet

The pictures below show **stages of growth of the testes, scrotum, and penis.** A boy goes through each of the five stages as shown. Please look at each picture. Read the sentences. Put an **X** in the box above the picture that is *closest* to your stage of growth. Do not look at pubic hair growth.

G1	G2	G3	G4	G5

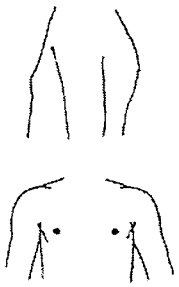
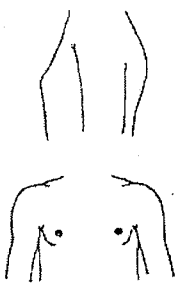
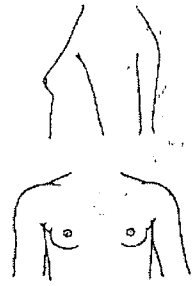
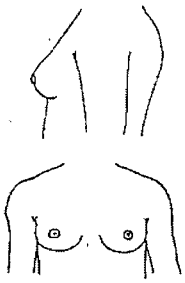
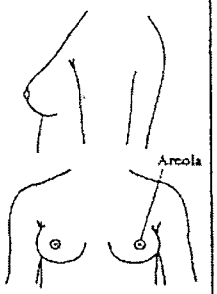


Morris, Naomi M. and J. Richard Udry. 1980. "Validation of a Self-Administered Instrument to Assess Stage of Adolescent Development," Journal of Youth and Adolescence 9(3):271-180

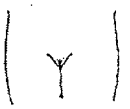
Tanner Staging Diagram: Female

Card 02

26 The pictures on this page show **different stages of how the breasts grow.** A girl can go through each of the five stages shown. Please look at each of the pictures. Read the sentences. Put an **X** in the box above the picture that is *closest* to your ~~stage of growth~~.

1	2	3	4	5
				
The nipple is raised a little in this stage. The rest of the breast is still flat.	This is the breast bud stage. In this stage the nipple is raised more than in stage 1. The breast is a small mound. The areola is larger than in stage 1.	The areola and the breast are both larger than in stage 2. The areola does not stick out away from the breast.	The areola and the nipple make up a mound that sticks up above the shape of the breast. (Note: This stage may not happen at all for some girls. Some girls develop from stage 3 to stage 5, with no stage 4.)	This is the mature adult stage. The breasts are fully developed. Only the nipple sticks out in this stage. The areola has moved back in the general shape of the breast.

27 The pictures below show **different amounts of female pubic hair.** A girl goes through each of the five stages shown. Please look at each picture. Read the sentences. Put an **X** in the box above the picture that is *closest* to the amount of pubic hair you have.

1	2	3	4	5
				
There is no pubic hair.	There is a little long, lightly colored hair. This hair may be straight or a little curly.	The hair is darker in this stage. It is coarser and more curled. It has spread out and thinly covers a bigger area.	The hair is now as dark, curly, and coarse as that of an adult woman. However, the area that the hair covers is not as large as that of an adult woman. The hair has not spread out to the legs.	The hair now is like that of an adult woman. It also covers the same area as that of the adult woman. The hair usually forms a triangular (▼) pattern as it spreads out to the legs.

Note: Your stage of pubic hair growth *may* or *may not* be the same as your stage of breast growth.

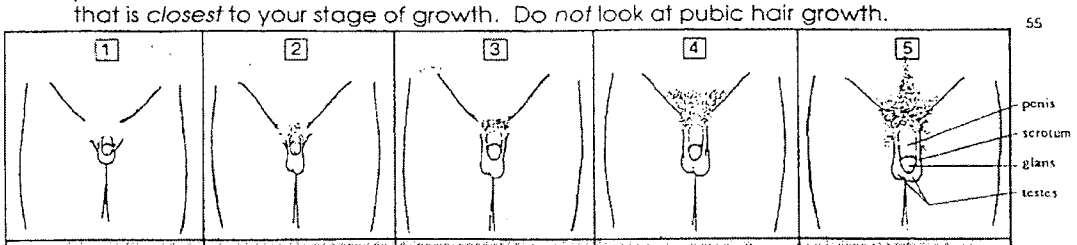
Tanner Staging Diagram: Male

ADOLESCENT DEVELOPMENT
& BEHAVIOR PROJECT

75 The pictures below show **stages of growth of the testes, scrotum, and penis.** A boy goes through each of the 5 stages as shown. Please look at each picture. Read the sentences. Mark an **X** in the box above the picture that is *closest* to your stage of growth. Do *not* look at pubic hair growth.

Card 06

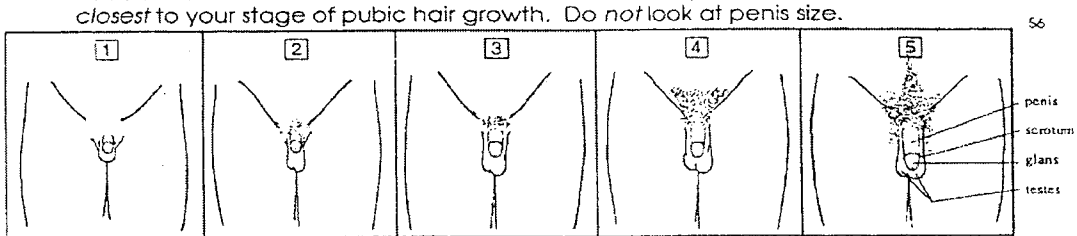
55



1	2	3	4	5
The testes, scrotum, and penis are about the same size and shape as they were when you were a child.	The testes and scrotum are bigger. The skin of the scrotum has changed. The scrotum, the sac holding the testes, has gotten lower. The penis has gotten only a little bigger.	The penis has grown in length. The testes and scrotum have grown and dropped lower than in picture 2.	The penis has gotten even bigger. It is wider. The glans (the head of the penis) is bigger. The scrotum is darker than before. It is bigger because the testes are bigger.	The penis, scrotum, and testes are the size and shape of that of an adult man.

76 The pictures below show **different amounts of male pubic hair.** A boy goes through each of the 5 stages as shown. Please look at each picture. Read the sentences. Mark an **X** in the box above the picture that is *closest* to your stage of pubic hair growth. Do *not* look at penis size.

56



1	2	3	4	5
There is no pubic hair at all.	There is a little soft, long, lightly colored hair. Most of the hair is at the base of the penis. This hair may be straight or a little curly.	The hair is darker in this stage. It is more curled. It has spread out and thinly covers a bigger area.	The hair is now as dark and curly as that of an adult man. The area that the hair covers is not as big as that of an adult man. The hair has not spread out to the legs.	The hair has spread out to the legs. The hair is now like that of an adult man. It covers the same area as that of an adult man.

Note: Your stage of pubic hair growth may or may not be the same as your stage of growth of the testes, scrotum, and penis.