*Responses to the pre-review are in italics. R. L. Rosenfield, M.D.*

Dear Dr. Rosenfield,

This letter is a summary of additional concerns and suggested changes that were raised during an initial review of your study. If possible, please respond by Monday, November 1st. We will be sending the study to a reviewer on November 2nd who will present it at the IRB meeting on Tuesday, November 9th.

1. **Age of Children:** In response to the IRB's question regarding the cutoff age of the youngest children to be enrolled into this study, the memo signed by Debbie Walsh, dated 10/12/04 states that "the onset of premature puberty can be as young as 6 months of age (now defined). The critical (diagnostic) samples can be obtained from children as small as 10kg.

   Please clarify if by this statement, you mean that you intend to study children (patients and controls) as young as 6 months of age if they weigh 10kg or more. The reviewer and myself had very strong concerns about enrolling such young children into this study. I anticipate that the Committee is going to feel the same way. If you have additional justification for why children this young should be enrolled, I suggest providing it prior to the meeting. The reviewer has also suggested that you provide evidence that safety with this testing has been confidently shown in children as young as 6 months of age.

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   In addition, please provide references to confirm that the onset of premature puberty can be as young as 6 months of age.

   *Reply. Premature puberty is "defined" as onset of puberty as early as 6 months for the purpose of the study , (since it is premature anytime before 8 years), this particular definition excludes the common normal variants of neonatal and early infantile breast development. Another reference is now provided to my standard textbook chapter, but you can find this in any endocrine textbook.*

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   *In contradistinction, children with premature puberty will not be studied by this protocol unless they weigh at least 10 kg and have bone age advancement 2 S.D. Controls are listed as a separate category and will not be studied under 7 years of age.*

   *Note that a young infant with premature puberty who meets criteria for "complete precocious puberty" (CPP) has a serious condition (typically a brain tumor or hypothalamic hamartoma) that requires prompt diagnosis and treatment. The standard diagnostic tool is a GnRH test. Because of the erratic availability of natural GnRH (Factrel®), we and other pediatric endocrinologists turn to off-label use of leuprolide, sometimes in the form of Lupron®, in young infants. Indeed, we are currently participating in an IRB- and FDA-approved Valera-sponsored multicenter study of a new implant to treat CPP that specifies leuprolide as the key diagnostic test. Consequently, I submit that it is best to do this testing, where necessary, in the context of a monitored GCRC study where possible, i.e., in infants ≥ 10 kg.*

*Furthermore, if the patient has rapidly progressive CPP, the most common form of treatment is currently with long-term depot leuprolide.*

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2. **Supplemental Form C for healthy controls:** I noted that the Supplemental Form C for healthy controls indicates that this study is "no greater than minimal risk to the subject". However, the form C for patients indicates the study is greater than minimal risk with prospect of direct benefit.

   The reviewer felt that the study was greater than minimal risk in all children. I suggest revising Form C for healthy controls by indicating that the study does not meet any of the three criteria outlined on page 2 of the form. You could do this by revising your response to question II.A "Justification" on page 1 of the form. You should elaborate on the risks to the healthy controls in this section as well.

   *Reply. I have revised Form C for both study groups. For both, I point out that leuprolide injection "is the original type of leuprolide preparation that is marketed to this day as a daily injection for the long-term treatment of precocious puberty. In practice, this preparation has been supplanted by the use of a depot preparation (Depo-Lupron®) in a vehicle that slows its absorption to allow monthly injection. Allergic reactions have only been reported to the depot form and are rare (1 case report); they are unheard of in response to a single injection of the short-acting form used for these studies." A PDR page for the pediatric indication is enclosed.*
   *Filling out these forms the way you request presents me with a moral dilemma because I strongly feel that this protocol confers no more than minimal risk, otherwise I would not be proposing these studies. You are demanding that I fill out and sign forms that attest to my agreement with your assessment that this study involves more risk than this. There are no firm national guidelines as to the definitions of the various categories of risk. Since the IRB agrees with you, I have decided to fill out the forms as you request, to avoid further delays to the inevitable submission of this protocol by you for federal review.*

3. **IND Number:** The reviewer did not totally agree that an IND is not needed for use of Leuprolide. Given that your past studies have required an IND for use of Lupron, it's unclear why an IND would not be needed in this case as well. The Committee will have to be convinced that 1) the protocol is not intended to be reported to the FDA in support of a new indication for use or support any other significant change in the drug's labeling; 2) the protocol is not intended to support a significant change in the advertising for the product; and 3) the protocol does not involve a change in route of administration or dosage level, use in a subject population and other change/factor that significantly increases the risks associated with the drug.
   If you have additional information to help support these 3 criteria, I suggest submitting it with your response prior to the meeting.

   *Reply. TAP Pharmaceuticals, the makers of Lupron, have ceased all support, including failure to supply free drug for this study. Consequently, we use only generic leuprolide for our studies. We have notified the FDA of this situation in our*

*last annual report, which makes the arguments against providing further reports. This report is enclosed.*

4. **Sending Blood to off-site locations:** During my pre-review, I noted that the protocol and Supplemental Form G (for genetic testing) states blood samples will be sent to several off-site locations, such as University of Michigan and Massachusetts General Hospital for assays. In your response to my pre-review, you removed any reference to these off-site locations (see page 4 of the detailed narrative) and replaced it with "Serum will be stored for assay of inhibin –B, activin, and FAS."

   I also noted a check-box was added to the consent form regarding the use of subjects' blood at other centers for assays of new markers of puberty.

a. The reviewer and I both agreed that if the assays are being done for this study, you must clarify where this is being done. If they are being done at U of M and Mass General (as you initially indicated), this must be explicitly stated in the protocol and in the consent form. You must also have the doctors conducting those assays obtain IRB approval for their activities in this study.

**b.** If, on the other hand, the assays are not being done for this study, but are being run for other research purposes, you must make this very clear in the protocol. In addition, you must revise the consent form to provide more detail regarding the use of samples for future research studies. If you are involved in any other studies using these samples, you will also have to submit new protocols for these other research activities as well.

*Reply. Since no-one else is currently carrying out our protocol, it is possible that collaborative arrangements will change in the future, and these assays may become available here or be done by other laboratories, I have chosen to make general statements about storing samples for special assays. The samples are not being saved for any other research purposes of mine. Hence, the nature of the changes and the check box.*

*The consent forms now state under leuprolide test (p. 2, just above the check box) that blood samples will be obtained for " recently discovered potential regulators and markers of pubertal development when the technology becomes available (such as activin, inhibin and free alpha subunit)." A similar phrase is found in the "Confidentiality" section.*

5. As adults are to be enrolled into this study, the reviewer felt that separate consent forms should be provided strictly for the adults. Currently, the consent form is written only for the parents.

*Reply. An Adult Gonadotropin Deficiency consent form is now provided.*

6. Assent Form Changes: Please clarify what Leuprolide is in the 3rd paragraph. Please do not refer to it as a "medication" in paragraph 4.

*Reply. Done.*

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7. Consent Form Revisions: The reviewer felt that the consent forms were not clear enough. The following changes are suggested to improve its readability.

   I. In the section entitled "What is involved in the study",
      A. Please consider utilizing bullets to outline study procedures rather than a paragraph form.

   "When your child is admitted to the crc, they will undergo the following tests when they first arrive:
   - x-ray
   - urine pregnancy test

      B. Please increase spacing between paragraphs.
      C. Please add that ferrous sulfate will be given to subjects at the end of the study
      D. In regards to the use of blood samples at other centers for assay of new markers of puberty, more information must be provided regarding the use of blood. For example, its unclear if these assays are for this study, or for other studies. It's unclear what identifiers will be sent with samples or what other types of PHI will be sent. Subjects must be told if they can withdraw permission for use of blood.
      E. In the "DNA sample" section, please define "cell lines". Please clarify what other "researchers" will be sent these samples.

*Reply. Done*

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*Note that item D is addressed in the reply to item #4 above.*

*In addition, a minor editorial change was made to better indicate the purpose of the research up front in the "***WHY IS THIS STUDY BEING DONE?"** *section, with a reciprocal change in the initial sentence describing the leuprolide test.*

   II. In the "risks" section, please list any side effects from the iron supplement.

*Reply. Done*

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   III. In the "Options" section, please clarify that Factrel is the normal test used for pubertal disorders and that they could undergo that testing.

*Reply. Done.*

   IV. In the "Confidentiality" section, please add that information is sent to NIH since they help to fund the study.

*Reply. Done.*

V. If samples (i.e., blood and DNA) are being sent outside of U of C you must state who is receiving them, what type of PHI is sent, and why they are being sent.

*Reply. This is addressed in the reply to item #4 above.*

VI. Please specify what "outside laboratories" samples may be sent to "when technology is more advanced". This is not discussed in the protocol. Please add this to the protocol.

*Reply. This is addressed in the reply to item #4 above.*

*Closing remark. I trust that these changes will prove satisfactory. We look forward to prompt approval of our studies in patients with disorders of puberty and prompt forwarding of the IRB's concerns about the proposed studies in healthy control children for 407 review.*

*Sincerely,*

*Robert L Rosenfield, MD*

*ENCLOSURES*

1. *PDR listing for leuprolide injection (pediatric)*
2. *Supplemental Forms C x 2*
3. *FDA annual report 2003 with cover letter, etc for IND #60,003.*
4. *Consent forms 11/1/04 x 2 for child patients and volunteers*
5. *Consent form for Adult GnD*
6. *Assent forms 11/1/04 x 2*

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