7. E-mail correspondence dated September 24, 2004 from Tasha Osafo, Administrator of Regulatory Compliance, to Dr. Rosenfield.

To: Debbie Walsh
From: Tasha Osafo
Subject: Protocol 13472A-Pre-Review
Cc: Robert Rosenfield

Dear Dr. Rosenfield,

We have received the new protocol submission for Dr. Rosenfield entitled "Gonadotropin Releasing Hormone (GnRH) Agonist Test in Disorders of Puberty". This study is scheduled for full review on Tuesday, October 5. I have conducted a pre-review of the study and my suggested changes are outlined below. Please provide your response by Tuesday, September 27th if it all possible.

1. **Supplemental Form C:** supplemental form c indicates that the study is greater than minimal risk but there is the prospect of a direct benefit to subjects. this may be the case for the children who have disorders of puberty. However, this is not the case for healthy children. Please submit another form c specifically filled out for the healthy children.

2. **Outside IRB Approvals:**

a. The protocol indicates that serum will be stored for assay of inhibin-B in subgroups via a collaborative arrangement with Dr. Carol Foster at the University of Michigan. Please provide notice of IRB approval from U of M for this activity.

b. The protocol indicates that FAS will be assayed by RIA in a collaboration with Dr. William F. Crowley, Jr. at Massachusetts General Hospital. Please provide notice of IRB approval from Mass. General's IRB for this activity.

c. The protocol states "molecular genetic studies of the basis of GnD are in collaboration with Dr. Lawrence Layman". It is unclear to me if Dr. Layman is a doctor at U of C. If not, IRB approval from his institution also needs to be provided.

3. **Protocol Submission Form:** Please revise the protocol submission form to address my comments outlined below. Please provide a copy of the revised form, signed by the PI, for my review.

a. Page 2, "Additional Performance Sites": Assuming U of C is the lead site for this study, please add U of M and Mass. General as other sites where research activity is being performed.

b. On page 3, "Purpose of the Study", the statement provided is not in lay language.

Please explain the purpose of the study using non-technical language.

c. On page 4, question #1 asks for the number of evaluable subjects to be enrolled. The response provided is "360". However, if I read it correctly, the detailed narrative indicates that only 290 subjects are to be enrolled (on pages 5 and 6) The following is how I came to 290 from the figures provided in the narrative. Please double -check the number of subjects expected to be enrolled.

Controls: Prepubertal boys-**20** (9-13 years)
Prepubertal girls-**20** (8-12 years)
Early pubertal boys-**20** (9-15 years)
Early pubertal girls- **20** (9-15 years)

Patients: Premature thelarche, idiopathic girls- **20** (less than 8 years)
Complete (gonadotropin dependent) sexual prococity, girls- **20** (less than 8 years)
Complete (gonadotropin dependent) sexual prococity, boys- **20** (less than 9 years)
Gonadotropin-independent precocity, either sex -**20** (girls < 8, boys < 9)
Constitutional delay of puberty, prepubertal, boys- **20**
Constitutional delay of puberty, prepubertal, girls- **10**
Constitutional delay of puberty, early pubertal, boys- **20**
Constitutional delay of puberty, early pubertal, girls- **10**
Gonadotropin deficiency (GnD), prepubertal, boys-**20**
Gonadotropin deficiency (GnD), prerpubertal, girls- **10**
Gonadotropin deficiency (GnD), pubertal with partial GnD, boys-**20**
Gonadotropin deficiency (GnD), pubertal with partial GnD, girls- **10**

d. Page 5, question 7: the response to question 6 indicated that "economically disadvantaged" are to be included in the research. Question 7 asks for a rationale for the special populations to be included in the research. Please revise your response to indicate why "economically disadvantaged" are included in this study as they are considered a vulnerable population by the U of c.

e. Page 7, Question 1: question 1 asks if **adult** subjects will have the capacity to give informed consent. Your response is "yes". However, as this study includes individuals 17 and younger, this question is not applicable. I suggest unchecking "yes" and stating "not applicable" in the text box.

f. Page 7, Question 2: Please provide a description of the assent process. Clarify if you will ask children if they want to participate and how you will assess if they understand. Please clarify what actions you will take if the children do not want to participate, but the parent wants the child to be in the study.

g. Page 11, "Risks of the Research": In your response, item #6 states that "anxiety symptoms may occur. These include numbness or tingling of the hands or feet, and

constipation". Please clarify what is causing these symptoms, i.e., the leuprolide?

h. Page 12, Question 3 "Why are the risks reasonable"-please revise this section to address why the risks are reasonable to healthy controls. Currently it only addresses the risks in relation to the patients.

4. **Detailed Narrative:** Please revise the detailed narrative to address my comments outlined below. Please provide a copy of the revised narrative for my review.

a. Page 5, Section G and H: The protocol submission form indicates that 360 subjects are to be enrolled. However, after I add up the breakdown of subjects described in sections g and H of the narrative, I arrive at a total of 290 subjects to be enrolled. Please clarify why there is a difference in subject number between these two documents.

b. Page 6, Section H, "Specific Aim 2", item 2: You state that you will recruit 10 prepubertal and 10 pubertal females with partial GnD. However, your grant states that you are enrolling 20 prepubertal and 20 pubertal females.
Please check your figures and clarify how many you plan to enroll.

c. Page 8, Section J: Item d indicates that "anxiety symptoms" may occur. Please revise this item to indicate what is causing the anxiety, i.e., lupron?

d. Page 9, section J.3: Please revise this section to indicate that there is no benefit to the healthy volunteers.

e. Page 9, Section M: Please revise this section to include a description of how assent will be obtained from children. Clarify if you will ask children if they want to participate and how you will assess if they understand. Please clarify what actions you will take if the children do not want to participate, but the parent wants the child to be in the study.

5. **Supplemental Form D:** I am confused regarding the status of Leuprolide. You state that the IND for lupron (#60,003) is functionally inactive and its mention in the consent form has been dropped as Tap pharmaceuticals has passed on funding aspects of this study. I'm not sure what you mean by "functionally inactive". If the IND is no longer valid because of Tap pharmaceutical not funding the study, then why aren't you reapplying for a new IND?

Also, if the IND is "inactive", why is it included on Supplemental Form D and in the consent form still?

6. **Package Insert:** Please provide the package insert for Leuprolide.

7. **Consent Form:** Please see the consent forms which I will fax to you with my suggested changes.

8. **Ad:** Please see the ad which I will fax to you with my suggested changes.

9. **Age of Subjects:** Some of the subject population is defined as girls younger than 8 or boys younger than 9. It is unclear to me what is the lowest age you will agree to accept into this study. Please clarify in your protocol and protocol submission form.

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