DEPARTMENT OF HEALTH & HUMAN SERVICES

Office of the Secretary
Office of Public Health and Science

Office for Human Research Protections
Rockville, Maryland 20852

[April 12, 2006]

TO: Assistant Secretary for Health

FROM: Director, Office for Human Research Protections

SUBJECT: Recommendation for Approval of HHS Support for Research Involving Children-ACTION

ISSUE

This document provides a recommendation by the Office for Human Research Protections (OHRP) that the Department of Health and Human Services (HHS) approve with required modifications/stipulations the proposed research protocol entitled "Gonadotropin Releasing Hormone (GnRH) Agonist Test in Disorders of Puberty." In making this recommendation, OHRP has reviewed the proposed research, considered the opinions of experts in pertinent disciplines, and reviewed all public comments received. In addition, OHRP has considered the position of the Food and Drug Administration (FDA) as detailed in the memorandum signed by the Acting Commissioner on February 2, 2006 (Tab A). This protocol was referred to OHRP on June 22, 2005, for HHS 45 CFR 46.407 consideration, by the University of Chicago Institutional Review Board, Biological Sciences Division (UC-IRB-BSD) through Dr. Mary Ellen Sheridan, Associate Vice President for Research and Director of Research for Administration, University of Chicago.

DISCUSSION

Regulatory Background

All human subjects research studies conducted or supported by HHS that are not otherwise exempt under 45 CFR 46.101(b) and that propose to involve children as subjects require institutional review board (IRB) review and approval in accordance with the provisions of HHS regulations at 45 CFR part 46, subpart D (Additional Protections for Children Involved as Subjects in Research) as well as basic protections required under subpart A (Federal Policy for the Protection of Human Subjects). Pursuant to HHS regulations at 45 CFR 46.407, if an IRB reviewing a protocol to be conducted or supported by HHS does not believe that the proposed research involving children as subjects meets the requirements of HHS regulations at 45 CFR 46.404 (research not involving greater than minimal risk), 46.405 (research involving greater than minimal risk but presenting the prospect of direct benefit to the individual), or 46.406 (research involving a minor increase over minimal risk and no prospect of direct benefit to the

individual subjects, but likely to yield generalizable knowledge about the subject's disorder or condition), and was suitable for review under the procedure provided in 45 CFR 46.407 (research not otherwise approvable which presents an opportunity to understand, prevent or alleviate a serious problem affecting the health or welfare of children), the research may proceed only if the following conditions are met:

> (a) The IRB finds and documents that the research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children; and
>
> (b) The Secretary, after consultation with a panel of experts in pertinent disciplines (for example: science, medicine, education, ethics, law) and following opportunity for public review and comment, determine either:
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> (1) that the research in fact satisfies the condition of 45 CFR 46.404, 46.405, or 46.406, or
>
> (2) that the following conditions are met:
>
> (i) the research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children;
>
> (ii) the research will be conducted in accordance with sound ethical principles; and
>
> (iii) adequate provisions are made for soliciting the assent of children and the permission of their parents or guardian, as set forth in 45 CFR 46.408.

Under FDA's Interim Final Rule, effective April 30, 2001 (21 CFR Part 50, subpart D), the FDA adopted similar regulations (21 CFR 50.51, 50.52, 50.53, and 50.54) requiring IRB review to provide additional safeguards for children enrolled in research regulated by the FDA.

After reviewing the protocol, the UC-IRB-BSD determined that the full study could not be approved under 45 CFR 46.404, 46.405, or 46.406, but that, as required under 45 CFR 46.407, the IRB asserts the study presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children. Accordingly, the University of Chicago referred the proposed investigation to OHRP on June 22, 2005 for a determination under 45 CFR 46.407. OHRP in turn referred the protocol to the FDA to assess whether the study was subject to FDA regulations. On July 28, 2005, the FDA informed the University of Chicago IRB by letter that the proposed study was also subject to 21 CFR part 50, subpart D.

In cases where FDA regulations apply, OHRP has delegated its authority to the FDA to convene the required panel of experts to both review the proposed research and to advise the Secretary. In order to conduct the expert panel review, the FDA utilizes the Pediatric Ethics Subcommittee (PES) of the established Pediatric Advisory Committee (PAC) to develop recommendations to be forwarded to the PAC, which then makes its final recommendations to the FDA Commissioner. The recommendations of the PAC and the decision by the FDA Commissioner are then used to advise the Secretary. Although the authority to convene the panel of experts has been delegated to the FDA, OHRP works in close collaboration with the FDA in all aspects of the review including the selection of experts to participate on the PES.

Overview of Study Design, Goals and Rationale

The primary purpose of the protocol is to develop and validate a gonadotropin releasing hormone agonist (GnRHag) test, using leuprolide acetate, to facilitate in the differentiation between the various disorders of puberty. To do this, the principal investigator proposes to administer a single subcutaneous injection of leuprolide acetate (10 mcg/kg) and measure serial blood samples of luteinizing hormone (LH), follicle stimulating hormone (FSH), testosterone (males) and estradiol (females) in children and young adults with and without a disorder of puberty, over the course of 24 hours. The results of the serial measurement from the leuprolide challenge test will be compared to similar measurements done during a validated sleep test conducted in the same subjects the night prior to the leuprolide challenge test. The proposed study would include two groups of children: 1) children with disorders of puberty, referred to the investigator for evaluation, and, 2) healthy children, ages 7-18 years, recruited as normal controls in order to obtain information that would facilitate the interpretation of results in children with disorders of puberty (i.e., normative data). Due to the rare nature of gonadotropin deficiency (GnD), adult subjects with and without GnD will also be enrolled for comparison. Additional details about the study design can be found in the attached protocol summary developed by the OHRP medical officer (Tab B).

According to the protocol, the main goal of the study is to establish the diagnostic effectiveness of a GnRHag test (leuprolide challenge test) and norms for it in order to improve the differential diagnosis of the most common disorders of puberty. This, the principal investigator asserts, may provide for a more accurate diagnosis and earlier treatment for these disorders. The specific hypothesis stated in the protocol is as follows:

> *"The hormonal responses to the injection of a challenge dose of GnRh agonist (GnRHag) will distinguish among disorders of puberty as well as a sleep test. Specifically, we will test the hypotheses that the responses to injection of GnRH agonist leuprolide acetate will:*
>
> *a. Distinguish among the causes of precocious puberty*
>
> *b. Distinguish among the causes of delayed puberty*"

The proposed research involves the following interventions and activities: a 36-hour admission to the General Clinical Research Unit at the University of Chicago; insertion of an indwelling venous catheter for obtaining blood samples; total blood sampling of 150-240 cc (5-8 oz); subcutaneous injection of a single dose of leuprolide (10 mcg/kg); x-rays for bone age; banking of DNA obtained from blood samples, and; discharge on ferrous sulfate (oral iron, 300 mg daily for one month) to facilitate reconstitution of phlebotomized blood.

The principal investigator states that the above-described research is necessary because of the two currently available means of diagnosing these pubertal disorders, a sleep test, which measures the natural sleep-associated change in LH levels at 20 minutes intervals overnight, and a diagnostic test using natural GnRH (marketed as Factrel) which stimulates the release of preformed LH and FSH are unsatisfactory. The investigator asserts the sleep test is impractical as a routine diagnostic tool, mainly because of the expense and lack of insurance coverage, and that manufacturing cutbacks have made the Factrel increasingly difficult to obtain. Since Factrel has frequently been unavailable, pediatric endocrinologists have turned to leuprolide acetate, which is FDA approved for other indications, for diagnostic testing even though norms have not been established.

Review of FDA Panel of Experts

On November 15, 2005, the Pediatric Ethics Subcommittee (PES) of the FDA's PAC held a public meeting to discuss the protocol referral from the UC-IRB-BSD. The PES consisted of twelve members who brought multiple specialities and perspectives to the expert panel. There were five individuals with ethics background, two general pediatricians, two patient-family representatives, a consumer representative, and two pediatric expert consultants in the areas of adolescent medicine and endocrinology. Additionally, there was an opportunity for public comment both prior to the public meeting via the FDA docket, and at the meeting itself.

After substantial discussion and the opportunity for public comment the PES forwarded to the PAC a recommendation that the protocol be approved providing multiple stipulations were met. On November 16, 2005, the PAC met and endorsed all required stipulations and recommended modifications provided by the PES and in addition added two required stipulations and a single recommended modification. The PAC, in turn, provided the endorsed stipulations and recommended modifications to the FDA for consideration. On February 2, 2006, the FDA accepted all required stipulations and recommended modifications forwarded by the PAC and added a single required stipulation of its own. Specific details about the approval categories, required modifications/stipulations and recommended modifications approved by the Acting FDA Commissioner can be found in the attached FDA memorandum (Tab A).

Public Review and Comment

On October 7, 2005, a *Federal Register* Notice was published soliciting public review and comment, pursuant to the requirements of 45 CFR 46.407, for a period of 26 days. Documents related to the protocol were made available on the OHRP website, including the proposed protocol, parental permission documents, subject assent documents, and IRB deliberations on the proposed protocol. These documents were also made available on the FDA website, and a docket was established on the FDA website for the submission of public comments. Eight comments were received in response to the *Federal Register* notice and no public comments were received in the open PES meeting. An abstracted verbatim listing of all comments received can be found in Tab C of this letter. In general, four of the comments received in response to the *Federal Register* notice were unsupportive of the study and four were supportive. The public comments which were unsupportive of approving this research proposal included a concern about the risk of serious adverse effects from the administration of leuprolide, including during short term and long term use; concerns related to hazards for patients and medical personnel from direct contact with leuprolide; charges of misconduct against the TAP Pharmaceutical Inc., a manufacturer of leuprolide; secrecy surrounding settlements of lawsuits against TAP Pharmaceutical Inc.; the alleged mysterious disappearance of a website devoted to victims of leuprolide; and the inadequacy of the consent process in the proposed protocol. Comments of support included a statement from a parent of a child who had cancer and abnormal pubertal development, and who had participated in a clinical trial involving leuprolide, expressing the view that the drug was safe and effective, and stressed the need for better tests to evaluate precocious puberty. The other supportive comments came from various medical societies that are directly involved with supporting research in endocrine related disorders. All comments and concerns were addressed by the PES with recommendations forwarded to and endorsed by the PAC.

OHRP FINDINGS AND RECOMMENDATIONS

OHRP has reviewed the research protocol and other related documents, considered the recommendations provided by the PAC, reviewed the eight comments received from the public, and considered the position of the FDA as outlined in the memorandum from the Acting FDA Commissioner. Additionally, OHRP has considered the relevant requirements set forth in 45 CFR 46, subpart A and have concluded that the investigator and the UC-IRB-BSD have taken the appropriate steps to ensure that the study population will be adequately protected. OHRP concurs with the approval position taken by the FDA and agrees with all findings relative to the "Approval Categories" for each of the cohorts proposed for study, all required stipulations and all recommended modifications outlined in the FDA memorandum. Further, OHRP believes that the proposed research addresses a fundamentally important and serious topic, namely the early detection and differentiation of disorders of puberty affecting adolescents and that the development of a validated GnRHag test, using leuprolide acetate, may result in improved treatments. Accordingly, OHRP finds that the research protocol can be approved under 45 CFR

46.407, with stipulated revisions to the protocol design and parental permission/child assent documents and process. OHRP recommends the Assistant Secretary for Health approve the "Approval Category" findings, required stipulations and recommended modifications as outlined below. Providing that approval is given, the findings, required stipulations and recommended modifications will be forwarded to the investigator and the reviewing IRB for action. The IRB or other appropriate institutional official must then submit the approved revised protocol to HHS for final concurrence before the research can proceed. Once OHRP reviews the revised protocol, it will communicate the outcome to the IRB, PI, institution, and funding agency.

OHRP Approval Category, Risk Assessment and other Findings

1. The portion of the study involving children with the pubertal abnormalities could be approved under 21 CFR 50.52 and 45 CFR 46.405 as a clinical investigation involving greater than minimal risk but presenting the prospect of direct benefit to individual subjects.

2. The portion of the study involving healthy children could be approved under 21 CFR 50.54 and 45 CFR 46.407 as a clinical investigation not otherwise approvable but that presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children, after all required stipulations have been met.

3. The risks of the research procedures present only a minor increase over minimal risk considering the risks associated with a single injection of leuprolide acetate, the use of an indwelling venous catheter, the risks of blood loss from the proposed serial sampling, and the psychological risks of hospitalization for 36 hours in children.

4. The proposed clinical investigation presents a "reasonable opportunity" to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children.

5. The research will be conducted in accordance with sound ethical principles.

6. Adequate provisions are made for soliciting the assent of children and the permission of their parents or guardian, as set forth in 45 CFR 46.408, providing all required stipulations to the parental permission and child assent documents and process have been met.

OHRP Required Stipulations/Modifications:

A. Relative to the Protocol

    1. Results from the diagnostic testing of the sleep study and the leuprolide challenge test must not be disclosed to the normal children or their parents since the clinical

significance of these results, particularly abnormal results, would be uncertain and could result in psychological harm to the children (e.g., by conveying the false impression that the child was or might be abnormal).

2. All children participating in the proposed study must be given the opportunity to have their samples collected during the study destroyed when they reach the age of majority.

3. There must be a midpoint assessment of the variability of the data collected from the healthy controls and a reaffirmation of the appropriateness of the sample size and reassessment of the utility of that data against the data obtained from the children with a disorder of puberty already collected.

4. The principal investigator must clarify in the protocol any plans he has relative to the longitudinal follow-up of subjects participating in the proposed study.

B. Relative to the Parental Permission/Child Assent Documents and Process

1. The parental permission and assent documents must state more clearly, at the beginning of the documents, that the study is not expected to provide direct medical benefit to the children in the control group, and suggestions of direct medical benefit later in the documents must be removed or revised.

2. Although the study only involves a single dose of leuprolide acetate, the consent process and parental permission/child assent documents must briefly address adverse effects from the long-term use of leuprolide.

3. There must be a robust assent monitoring process designed within the framework of the Clinical Research Center.

4. The principal investigator must clarify in the parental permission and child assent documents any plans he has relative to the longitudinal follow-up of subjects participating in the proposed study.

OHRP Recommended Modifications:

1. The assent monitoring of a sample of the healthy control children should be done to assure that they understand that they could refuse to participate.

2. The principal investigator may want to exclude the siblings of enrolled children with abnormalities from the study, as they may experience undue influence in the assent process.

RECOMMENDATIONS

1. HHS should support the proposed research protocol entitled "Gonadotropin Releasing Hormone (GnRH) Agonist Test in Disorders of Puberty," with stipulated revisions to the protocol and parental permission/child assent process and documents as outlined above.

2. This decision should be made available to the public via appropriate methods, such as placement on the OHRP website.

DECISION

1. HHS should support the proposed research protocol entitled "Gonadotropin Releasing Hormone (GnRH) Agonist Test in Disorders of Puberty," with stipulated revisions to the protocol and parental permission/child assent process and documents as outlined above.

Approved _[/s/ John O. Agwunobi]_____ Disapproved _____ Date_____

2. This decision should be made available to the public via appropriate methods, such as placement on the OHRP website.

Approved _[/s/ John O. Agwunobi]_____ Disapproved _____ Date _____

[/s/ Bernard A. Schwetz]

Bernard A. Schwetz, D.V.M., Ph.D.

3 Attachments:
Tab A - Letter Signed by FDA Acting Commissioner
Tab B - OHRP Medical Officer's Summary of Proposed Protocol
Tab C - Public Comments on Proposed Protocol