DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

WRITTEN REQUEST #2
Amendment #1

NDA 21-015

Solvay Pharmaceuticals, Agent for Unimed Pharmaceuticals, Inc.
Attention: Steven Wojtanowski, R.Ph., MPH
Assistant Director, Regulatory Affairs
901 Sawyer Road
Marietta, GA 30062

Dear Mr. Wojtanowski:

Please refer to your correspondence to IND (b) (4) dated August 29 and September 15, 2006, requesting changes to FDA's April 7, 2005, Written Request for pediatric studies for testosterone.

We have reviewed your proposed changes and are amending the Written Request. This Written Request supersedes the Written Request dated April 7, 2005. Several of your proposed changes in your August 29, 2006, submission have not been incorporated into this Written Request because they either reflect protocol-level information or are implied within.

The full text of the Written Request, as amended, follows. Additions to the April 7, 2005, version of the Written Request are noted in **bold** text and deletions noted by ~~strikethrough~~.

Type of studies:

Study 1 A pharmacokinetic (PK) study of testosterone 1% gel in boys with delayed puberty.

Study 2 A dose titration and safety study of testosterone 1% gel in boys with delayed puberty.

Objectives/Rationale:

Study 1 To assess the pharmacokinetics of three different pediatric doses of testosterone 1% gel.

Study 2 To titrate the testosterone 1% gel dose to a desired serum concentration consistent with what is clinically appropriate for the current stage of puberty and establish a dose regimen that can be safely used for initiating or for progressing puberty.

Indication to be studied:

Treatment of delayed puberty in boys.

Study Design:

Study 1 A multi-center, open-label, sequential dose-escalation, multiple-dose, PK study in boys of adolescent age with delayed puberty. The doses tested should be 0.5 g, 1.5 g, and 2.5 g of testosterone 1% gel (containing 5 mg, 15 mg, and 25 mg of testosterone, respectively). The doses should be administered in escalating order, ~~with a 10- to 14-day washout period~~ **with a washout period of no greater than 14 days** between doses. Each of the 3 doses of testosterone gel should be applied daily for 4 consecutive days. Blood samples will be drawn at steady state (Day 4) for serum testosterone concentration determination.

Study 2 A 6-month, multi-center, open-label, dose-titration study of testosterone 1% gel in boys of adolescent age with delayed puberty. Baseline growth data should be obtained, prospectively or retrospectively, for at least six months prior to initiation of study drug. The starting dose of testosterone 1% gel will be 0.5 g/day. The testosterone 1% gel should be titrated (e.g., weekly) to a daily dose sufficient to produce a clinically appropriate serum testosterone concentration consistent with the treatment of delayed puberty. After establishment of the appropriate dose, as above, serum testosterone concentrations should be measured periodically (e.g., at approximately 8 and 12 weeks after initiation of therapy and at the end of the study [6 months]) to assess the consistency of drug effect on serum testosterone levels.

Although not required to obtain pediatric exclusivity, we request that you make a commitment to monitor study participants annually until Turner Stage V and final height are reached in all patients. To this end, submit the information in your annual reports. The patients should be monitored with respect to the following parameters: **testicular volume,** growth as measured by height, height standard deviation scores (SDS), height velocity, height velocity SDS, bone age advancement, and Tanner Stage progression.

Note: For purposes of clarity, Study 1 and Study 2 are described as separate investigations. However, if you so choose, patients enrolled in Study 1 may be entered into Study 2 once the dose of drug producing pubertal testosterone concentrations has been achieved. This assumes adequate baseline growth data for those enrolled in the PK portion of the protocol.

Age group in which studies will be performed:

Study 1 Boys, ages 13 through 18 years. The study must include enough patients to ensure that ~~18~~ **at least 13** patients complete each dose group. If possible, the study should include enough patients to characterize potential differences in testosterone transdermal absorption as a function of age and race.

Study 2 Boys, ages 13 through 18 years. The study must include enough patients to ensure 50 evaluable patients at the end of the trial. An approximately equal number of permanently hypogonadal (primary and secondary hypogonadism) and constitutional delay of growth and puberty (CDGP) patients must be enrolled.

Study endpoints:

Study 1 Total and unbound testosterone and **total** dihydrotestosterone AUC_{0-24}, C_{max}, C_{min}, C_{avg}, t_{max}, and descriptive statistics. If visual inspection of the concentration curves over time identifies patients who have begun the elimination phase, $t_{1/2}$ should be calculated.

Study 2 The percentage and number of patients treated with each testosterone dose achieving the therapeutic testosterone concentration, Tanner Stage advancement (pubic hair) stage, bone age advancement (measured as the interval change in bone age divided by the interval change in chronological age), and testicular volume.

Entry Criteria:

Studies 1 and 2 Enrolled patients will have a diagnosis of primary hypogonadism, secondary hyogonadism, or CDGP. Testosterone naïve patients will have a serum total testosterone concentration at or below 50 ng/dL. Testosterone naïve patients will be prepubertal as defined by a testicular volume ≤ 3 mL ~~and absence of pubic hair~~. Both androgen-naïve and previously androgen-treated patients may be included. An approximately equal number of permanently hypogonadal (primary and secondary hypogonadism) and CDGP patients must be included. Patients with untreated endocrinopathies (growth hormone deficiency, hypothyroidism) will be excluded. Patients must assent to the treatment in addition to the parent/guardian's consent. Bone age must be at least 10.5 years.

Drug information

- *Dose:*

  Study 1 0.5 g, 1.5 g, and 2.5 g of testosterone 1% gel
  Study 2 0.5 g, 1.0 g, 1.5 g, and 2.5 g of testosterone 1% gel

- *Dosage form:* gel

- *Route of administration:* transdermal

- *Regimen:*

Study 1 0.5 g daily dose for four days, ~~no drug administration for 10 to 14 days~~, 1.5 g daily dose for four days, ~~no drug administration for 10 to 14 days,~~ and then 2.5 g daily dose for four days **with a washout period of no longer than 14 days between doses**. ~~Once the desired serum testosterone concentrations are reached, dosing of the patients should be stopped.~~

Study 2 ~~0.5 g/1.0 g/1.5 g/2.5 g daily according to a specific titration regimen (e.g., weekly)~~ **The starting dose of testosterone 1% gel will be 0.5 g/day. The testosterone 1% gel should be titrated (e.g., weekly) to a daily dose sufficient to produce a clinically appropriate serum testosterone concentration consistent with the treatment of delayed puberty.**

- *Formulation:* multi-dose bottle to be used with the (b) (4) pump (b) (4) and marketed single-dose packet (2.5 g single-dose packets)

Use an age-appropriate formulation in the studies described above. If the studies you conduct in response to this Written Request demonstrate this drug will benefit children, then an age-appropriate dosage form must be made available for children. This requirement can be fulfilled by developing and testing a new dosage form for which you will seek approval for commercial marketing. If you demonstrate that reasonable attempts to develop a commercially marketable formulation have failed, you must develop and test an age-appropriate formulation that can be compounded by a licensed pharmacist, in a licensed pharmacy, from commercially available ingredients.

Development of a commercially marketable formulation is preferable. Any new commercially marketable formulation you develop for use in children must meet agency standards for marketing approval.

If you cannot develop a commercially marketable age-appropriate formulation, you must provide the Agency with documentation of your attempts to develop such a formulation and the reasons such attempts failed. If we agree that you have valid reasons for not developing a commercially marketable, age-appropriate formulation, then you must submit instructions for compounding an age-appropriate formulation from commercially available ingredients that are acceptable to the Agency. If you conduct the requested studies using a compounded formulation, the following information must be provided and will appear in the product label upon approval: active ingredients, diluents, suspending and sweetening agents; detailed step-by-step compounding instructions; packaging and storage requirements; and formulation stability information.

Bioavailability of any formulation used in the studies should be characterized, and as needed, a relative bioavailability study comparing the approved drug to the age-appropriate formulation may be conducted in adults.

- *Drug-specific safety concerns*:

  Safety concerns are liver enzyme elevation, occurrence of gynecomastia, application site reaction, rapid advancement of puberty and bone maturity/skeletal growth, and lipid profile and hematological abnormalities. All these safety parameters should be monitored during the study.

- *Statistical information, including power of study and statistical assessments:*

  Study 1 Patient disposition, demographics, and baseline disease characteristics will be summarized. Serum concentrations and PK parameters for total and unbound testosterone and **total** dihydrotestosterone will be summarized at baseline and by dose. Changes from baseline C_{avg} for total and unbound testosterone and **total** dihydrotestosterone will be summarized by dose. Pre-dose (trough) concentrations for estradiol, follicle-stimulating hormone, and sex hormone-binding globulin will be summarized at baseline by dose. The data summarizations will include total patients (hypogonadal and CDGP patients) and separate summaries for the hypogonadal and CDGP subpopulations.

  Study 2 Present descriptive statistics (including mean and standard deviation values) of on-study data for the following parameters: growth velocity, bone age, bone age advancement, testicular volume. Growth velocity during the trial should be compared with growth velocity at baseline. Summary data should be presented for the number and percent of patients achieving and maintaining pubertal testosterone concentrations at each testosterone dose. Tanner stage (pubic hair) transitions from baseline to end-of-study should also be summarized by final dose of study drug. The data summarizations will include total patients (hypogonadal and CDGP patients) and separate summaries for the hypogonadal and CDGP populations.

- *Labeling that may result from the studies*: Appropriate sections of the label may be changed to incorporate the findings of the studies.

- *Format of reports to be submitted*: Full study reports not previously submitted to the Agency addressing the issues outlined in this request with full analysis, assessment, and interpretation. In addition, the reports are to include information on the representation of pediatric patients of ethnic and racial minorities. All pediatric patients enrolled in the studies should be categorized using one of the following designations for race: American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or other Pacific Islander or White. For ethnicity one of the following designations should be used: Hispanic/Latino or Not Hispanic/Latino.

- *Timeframe for submitting reports of the studies:* Reports of the above studies must be submitted to the Agency on or before December 30, 2007. Please keep in mind that pediatric exclusivity attaches only to existing patent protection or exclusivity that has not expired at the time you submit your reports of the studies in response to this Written Request.

- *Response to Written Request:* As per the Best Pharmaceuticals for Children Act, section 4(A), within 180 days of receipt of this Written Request you must notify the Agency as to your intention to act on the Written Request. If you agree to the request then you must indicate when the pediatric studies will be initiated.

  Please submit protocols for the above studies to an investigational new drug application (IND) and clearly mark your submission "**PEDIATRIC PROTOCOL SUBMITTED FOR PEDIATRIC EXCLUSIVITY STUDY**" in large font, bolded type at the beginning of the cover letter of the submission. Notify us as soon as possible if you wish to enter into a written agreement by submitting a proposed written agreement. Clearly mark your submission "**PROPOSED WRITTEN AGREEMENT FOR PEDIATRIC STUDIES**" in large font, bolded type at the beginning of the cover letter of the submission.

  Submit reports of the studies as a **new drug application (NDA) to the Division of Metabolism and Endocrinology Products** with the proposed labeling changes you believe are warranted based on the data derived from these studies. When submitting the reports, clearly mark your submission **"SUBMISSION OF PEDIATRIC STUDY REPORTS – PEDIATRIC EXCLUSIVITY DETERMINATION REQUESTED"** in large font, bolded type at the beginning of the cover letter of the submission and include a copy of this letter.
  In addition, send a copy of the cover letter of your submission, via fax (301-594-0183) or messenger, to the Director, Office of Generic Drugs, HFD-600, Metro Park North II, 7500 Standish Place, Rockville, MD 20855-2773.

  In accordance with section 9 of the Best Pharmaceuticals for Children Act, *Dissemination of Pediatric Information*, if a pediatric supplement is submitted in response to a Written Request and filed by FDA, FDA will make public a summary of the medical and clinical pharmacology reviews of pediatric studies conducted. This disclosure, which will occur within 180 days of supplement submission, will apply to all supplements submitted in response to a Written Request and filed by FDA, regardless of the following circumstances:

  1. the type of response to the Written Request (complete or partial);
  2. the status of the supplement (withdrawn after the supplement has been filed or pending);
  3. the action taken (i.e. approval, approvable, not approvable); or
  4. the exclusivity determination (i.e. granted or denied).

FDA will post the medical and clinical pharmacology review summaries on the FDA website at http://www.fda.gov/cder/pediatric/Summaryreview.htm and publish in the *Federal Register* a notification of availability.

If you wish to discuss any amendments to this Written Request, submit proposed changes and the reasons for the proposed changes to your application. Submissions of proposed changes to this request should be clearly marked **"PROPOSED CHANGES IN WRITTEN REQUEST FOR PEDIATRIC STUDIES"** in large font, bolded type at the beginning of the cover letter of the submission. You will be notified in writing if any changes to this Written Request are agreed upon by the Agency.

As required by the Food and Drug Modernization Act and the Best Pharmaceuticals for Children Act, you are also responsible for registering certain clinical trials involving your drug product in the Clinical Trials Data Bank (http://clinicaltrials.gov & http://prsinfo.clinicaltrials.gov/). If your drug is intended for the treatment of a serious or life-threatening disease or condition and you are conducting clinical trials to test its effectiveness, then you must register these trials in the Data Bank. Although not required, we encourage you to register effectiveness trials for non-serious diseases or conditions as well as non-effectiveness trials for all diseases or conditions, whether or not they are serious or life-threatening. Additional information on registering your clinical trials, including the required and optional data elements and the FDA Draft Guidance for Industry, "Information Program on Clinical Trials for Serious or Life-Threatening Diseases and Conditions," is available at the Protocol Registration System (PRS) Information Site http://prsinfo.clinicaltrials.gov/.

If you have any questions, call Jennifer Johnson, Project Manager, at (301) 796-2194.

Sincerely,

{See appended electronic signature page}

Curtis J. Rosebraugh, M.D., MPH
Deputy Director
Office of Drug Evaluation II
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Curtis Rosebraugh

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