DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND 61,238
NDA 20-498

WRITTEN REQUEST
AMENDMENT # 4

AstraZeneca Pharmaceuticals, LP
Attention: Kathleen Gans-Brangs, Ph.D.
Director, Regulatory Affairs
P.O. Box 8355
Wilmington, DE 19803-8355

Dear Dr. Gans-Brangs:

Please refer to your correspondence, dated November 9, 2004, to IND 61,238 requesting changes to FDA's October 1, 2004, Written Request (WR) Amendment # 3 for pediatric studies for Casodex (bicalutamide) in the treatment of gonadotropin-independent precocious puberty in boys with testotoxicosis.

We have reviewed your proposed changes and are amending the WR dated October 1, 2004. For convenience, the full text of the Written Request, as amended, follows. Highlighted **(bold)** text denotes changes. This Written Request, as amended, supersedes the earlier versions of the Written Request.

Type of studies:

Study 1. A relative bioavailability (BA) study between a pediatric bicalutamide oral liquid or dispersible tablet formulation (to be developed) and the marketed 50 mg bicalutamide oral tablet.

Study 2. A relative BA study between a pediatric anastrozole oral liquid or dispersible tablet formulation (to be developed) and the marketed 1 mg anastrozole oral tablet.

Study 3. An efficacy study of bicalutamide and anastrozole.

Objectives/ rationale:

Study 1. To investigate the relative BA of bicalutamide between a pediatric liquid or dispersible tablet formulation and the marketed tablet in adults.

Study 2. To investigate the relative BA of anastrozole between a pediatric liquid or dispersible tablet formulation and the marketed tablet in adults.

Study 3. To assess the efficacy and safety of bicalutamide when used in combination with anastrozole for the treatment of precocious puberty in boys with testotoxicosis.

Indication to be studied:

Treatment of gonadotropin-independent precocious puberty in boys with testotoxicosis.

Study design:

Study 1. This is a randomized, open-label, crossover study in healthy adult volunteers, who will receive orally 50 mg bicalutamide in either liquid/dispersible tablet or tablet form in the first treatment period. After a washout period of at least 63 days, the subjects will receive 50 mg bicalutamide, in either liquid/dispersible tablet or tablet form, whichever they did not receive during the first treatment period. Serial blood samples will be collected at specified times after each treatment to measure plasma bicalutamide concentrations. This study may be conducted at the same time as, but should not be after, the proposed pediatric clinical safety and efficacy study.

Study 2. This is a randomized, open-label, crossover study in healthy adult volunteers, who will receive orally 1 mg anastrozole in either liquid/dispersible tablet or tablet form in the first treatment period. After a washout period of at least 20 days, the subjects will receive 1 mg anastrozole in either liquid/dispersible tablet or tablet form, whichever they did not receive during the first treatment period. Serial blood samples will be collected at specified times after each treatment to measure plasma anastrozole concentrations. This study may be conducted at the same time as, but should not be after, the proposed pediatric clinical safety and efficacy study.

Study 3. A 12-month, open-label, multicenter, observational study of bicalutamide used in combination with anastrozole in boys with testotoxicosis. **The study will have at least 12 protocol-defined completers with a full complement of protocol-defined safety data**. All patients must be naïve to antiandrogen therapy. The occurrence of central precocious puberty (CPP) will be monitored and will include a GnRH stimulation test at regular intervals or at any point where the investigator believes CPP has occurred. If CPP develops, treatment with a GnRH agonist must be initiated. During the study, periodic drug level monitoring for both bicalutamide and anastrozole will be performed. To this end, determine plasma levels for both drugs at the following timepoints: predose, trough drug concentrations before the second dose, between days 8 and 14, and at 1 month, 2 months, and 3 months after the first dose. The determination of plasma drug concentrations should allow quick turnaround time for dose adjustment purposes. Every dose adjustment should be followed by trough plasma drug level measurements between days 8 and 14, and at 21 days, 1 month, 2 months, and 3 months after the dose change. Dose adjustment should be based on trough plasma drug concentrations achieved no sooner than three drug half-lives after the previous dose. An assessment of the dose and dosing schedule for both drugs will be performed after evaluating the pharmacokinetic information for the first four patients on treatment. This process will be repeated for additional panels of four patients until an appropriate dose regimen is established.

Age group and number of subjects to be studied:

Studies 1 and 2. Adult volunteers, with 24 volunteers completing each study.

Study 3. **Boys – 2 years of age and older, with 12 evaluable patients who have a full complement of protocol-defined efficacy and safety data at the end of one year of treatment.**

Entry criteria:

Studies 1 and 2. **Healthy, adult, non-smoking volunteers who do not receive any prescription or over-the-counter medications (except limited use of acetaminophen as an analgesic) or any dietary supplements.**

Study 3. **Diagnosis of testotoxicosis made by clinical plus biochemical criteria**; no evidence of central precocious puberty as demonstrated by GnRH stimulation test. A minimum of six months of pre-study growth information (height and height velocity, and bone age) will be available prior to enrollment. In addition, bone age radiographs must be available at screening/baseline for calculation of bone age/chronological age ratio in all patients. If, in addition, six months of pre-study bone age information are available, the baseline rate of bone age maturation should be calculated. Collection of pre-study growth data should meet strict endocrinological standards of accuracy and should be well documented.

Endpoints:

Studies 1 and 2. Bicalutamide and anastrozole pharmacokinetic parameters, such as relative BA, $AUC_{0-\infty}$, AUC_{0-t}, CL/ F, V_d/ F, C_{max}, T_{max}, λ_z, $t_{1/2}$, and their descriptive statistics should be evaluated.

Study 3. Primary endpoint: change in growth rate after 12 months of treatment relative to the growth rate during the ≥ 6-month pre-study period.

Additional assessments:

Study 3.

- Change in growth rate (cm. and standard deviation score) after 6 months of treatment relative to the growth rate during the ≥ 6-month pre-study period
- Bone age/chronological age ratio after 6 and 12 months of treatment relative to the bone age/chronological age ratio at baseline
- Change in rate of bone age maturation after 6 and 12 months of treatment relative to the rate of bone age maturation during the ≥ 6-month pre-study period for patients with baseline rate of bone age maturation information available (rate of bone age maturation will be defined as interval change in bone age/interval change in chronological age)
- Comparison of on-study data with historical data from the referenced study (Lescheck et al.) at the end of one year of treatment for growth rate, bone age maturation (if pre-study data are available), and percentage of patients showing improvement in aggressive behavior and acne lesions
- Number and percent of patients who achieve and/or maintain growth rates between the 5th and the 95th percentile
- Change in predicted adult height (PAH) at the end of the study compared to baseline PAH
- Incidence of patients with breast pain and gynecomastia at the beginning and the end of the trial
- Evolution of signs and symptoms of virilization while on study medication (virilization signs and symptoms to be followed are: testicular volume, Tanner staging, number of acne lesions, and aggressive behavior)
- Descriptive statistics of the plasma bicalutamide and anastrozole concentrations

Drug information:

Studies 1 and 2.

Dose:	50 mg bicalutamide or 1 mg anastrozole
Dosage form:	liquid or dispersible tablet (to-be-developed for both test medications), and tablet (for both marketed test medications)
Route of administration:	oral
Regimen:	each subject will receive the liquid or dispersible tablet and tablet for both test medications
Formulation:	pediatric liquid or dispersible tablet (to-be-developed for both test medications), and tablet (for both marketed test medications)

Study 3.

Dosage form:	liquid or dispersible tablet (to-be-developed)
Route of administration:	oral
Regimen:	bicalutamide will be started at a daily dose of 0.5 to 1 mg/kg and will be titrated to a plasma level in a range of 5 to 15 µ g/mL; anastrozole will be started at a daily dose of 0.5 mg and will be titrated with the goal of maintaining normal serum estrogen levels
Formulation:	age appropriate

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:

The safety profile of bicalutamide/anastrozole combination in children is not known. To this end, a 3-month juvenile rat toxicity study (males only) of bicalutamide/ anastrozole combination will be completed and the results will be presented to the agency for review prior to initiating the clinical study.

During the clinical study, bicalutamide-specific adverse events should be monitored, particularly, hepatic adverse events (e. g., elevated transaminases, jaundice, diarrhea, nausea, vomiting, asthenia). Anastrozole-specific adverse events identified in the drug label should also be monitored.

Statistical information:

Change in growth rate after 12 months of treatment relative to growth at baseline will be analyzed using a one-sample T-test. A 95% 2-sided confidence interval also will be calculated for the mean change in growth rate. All other endpoints will be summarized using descriptive statistics. Mean changes and individual changes will be presented.

Change in growth rate and, if pre-study data are available, change in rate of bone maturation after 12 months of treatment will be compared with the data generated in the referenced study (Lescheck et al.)

Conduct two sets of analyses: an all-treated analysis, consisting of patients who are treated and have on-treatment data, and a protocol-valid analysis for all patients who adhere to the protocol.

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.

Although not required at the time of pediatric exclusivity determination, we request that you monitor the study participants until final height is reached in all patients. To this end, submit the information in annual reports. Patients should be monitored with respect to above listed endpoints/assessments every 6 to 12 months.

Timeframe for submitting reports of the studies:

Reports of the above studies must be submitted to the Agency on or before March 31, 2008. 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.

Reports of the studies that meet the terms of the Written Request dated **October 1, 2004**, as amended by this letter must be submitted to the Agency on or before March 31, 2008, in order to possibly qualify for pediatric exclusivity extension under Section 505A of the Act.

Submit protocols for the above studies to **IND 61,238** 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. Please 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) 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. Clearly mark submissions of proposed changes to this request **"PROPOSED CHANGES IN WRITTEN REQUEST FOR PEDIATRIC STUDIES"** in large font, bolded type at the beginning of the cover letter of the submission. We will notify you in writing if we agree to any changes to this Written Request.

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/.

Your November 9, 2004, submission included additional questions regarding the written request and the proposed pediatric studies. Those questions and our responses follow (questions are numbered as in your submission).

3.3 Does the FDA agree with AstraZeneca's interpretation of "all patients must be naïve to anti-androgen therapy"?

A. Enrolling patients with testotoxicosis who were previously treated with ketoconazole and spironolactone is acceptable if they are appropriately "washed out" of the previous medication. For the purpose of this Written Request we agree with your interpretation that neither ketoconazole nor spironolactone is primarily an anti-androgen. An efficacy analysis by background medication should be included in the NDA submission, if feasible. No changes to the Written Request are required.

3.4 Does the FDA agree to AstraZeneca's approach to chronological bone age limit?

A. A bone age of less than or equal to 10 years as opposed to less than or equal to 13 years is acceptable. No changes to the Written Request are required.

3.5 Does the FDA agree to AstraZeneca's approach to assessing aggressive behavior?

A. The planned use of the Children' Aggression Scale-Parent Version (CAS-P) Questionnaire to measure aggressive behavior in children is acceptable.

3.6 Does the FDA agree that an analysis of predicted adult height (PAH) involving less than 12 patients will be acceptable?

A. We agree that the secondary analysis of change in PAH is intended only for patients of age greater than or equal to 6 years. As this is the original and current intent of the Written Request, no changes to the Written Request are required.

3.7 Does the FDA agree with AstraZeneca's interpretation of a +/-2 month window applying to the 6- and 12-month study assessments only and that the greater than or equal to 6 month pre-study assessment will be acceptable if taken 180 days or more before enrollment?

A. Your request is acceptable. Generally speaking, we recommend that an effort be made to collect data across patients in a consistent way to improve the interpretability of the data set.

3.8 Does the FDA agree that within the terms of WR Amendment #3 and the restrictions applied in terms of blood sampling that the 12-month treatment period consists 12 x 28-day months (336 days), and, as such, an evaluable patient is one that completes 12 x 28-day months (336 days) +/- 2 months (56 days) and has received at least 80% of the intended trial therapy over this 336 +/- 56 days period?

A. No. The proposed working definition (one month = 28 days) is acceptable only for blood monitoring. The clinical data at one year should be collected at no less than 300 days, according to a protocol-defined definition of a completer (e.g., a patient with 80% compliance to the study drugs and a minimum of 300 days of treatment). Collecting quality data on linear growth is particularly important since it will be reflected in the primary analysis and, thus, has important labeling implications.

The written request has been modified to state that "*The study will have at least 12 protocol-defined completers with a full complement of protocol-defined safety data.*"

If you have any questions, call Enid Galliers, Chief, Project Management Staff, Division of Metabolic and Endocrine Drug Products, at 301-827-6429.

Sincerely,

{See appended electronic signature page}

Robert J. Meyer, M.D.
Director
Office of Drug Evaluation II
Center for Drug Evaluation Research

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

/s/

Robert Meyer

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