DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-498

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

WRITTEN REQUEST
AMENDMENT #1

Dear Dr. Gans-Brangs:

Please refer to your correspondence to IND 61,238, dated October 8, 2003, requesting changes to FDA's April 17, 2003, Written Request for pediatric studies for bicalutamide.

We have reviewed your proposed changes and are amending the Written Request. For convenience, the full text of the Written Request, as amended, follows, with highlighted **(Bold)** text denoting changes. This Written Request supercedes the Written Request dated April 17, 2003.

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 anastrazole.

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 anastrazole 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 anastrazole in boys with testotoxicosis. The study will have at least 12 evaluable patients with complete efficacy and safety data at the end of 1 year of treatment. 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 the anastrazole 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 – 3 years of age and older, with 12 evaluable patients who have complete 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 or any dietary supplements.

Study 3. Diagnosis of testotoxicosis confirmed by DNA analysis of peripheral blood samples; no evidence of central precocious puberty as demonstrated by GnRH stimulation test. A minimum of six months of pre-study growth information (height, height velocity, and bone age) will be available prior to enrollment. 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
- 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 (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, 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 anastrazole 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 μg/mL; anastrazole 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. Any unapproved formulation will need to be supported by a study of relative bioavailability; these studies may be conducted in adults. A formulation you develop for use in children should meet standards for marketing approval. If you cannot develop a potentially marketable formulation, you will need to document the attempt to do so, and the Agency will consider another formulation that is standardized and palatable. Full study reports of any relative bioavailability studies should be submitted to the Agency as part of the response to this Written Request.

Drug-specific safety concerns:

The safety profile of bicalutamide/anastrazole combination in children is not known. To this end, a 3-month juvenile rat toxicity study (males only) of bicalutamide/anastrazole 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 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.

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.

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. Please 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.

Reports of the studies should be submitted as a new drug application (NDA) to the Division of Metabolic and Endocrine Drug Products with the proposed labeling changes you believe would be warranted based on the data derived from these studies. When submitting the reports, please 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. Please also 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.

If you wish to discuss any amendments to this Written Request, submit proposed changes and the reasons for the proposed changes to IND 61,238. 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.

We hope you will fulfill this pediatric study request. We look forward to working with you on this matter in order to develop additional pediatric information that may produce health benefits to the pediatric population.

If you have any questions, call Monika Johnson, Regulatory Project Manager, at (301) 827-9087.

Sincerely,

{See appended electronic signature page}

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

Enclosure:

Agency comments to Questions posed in your October 8, 2003, submission.

FDA responses to October 8, 2003, submitted questions

2.1 Drug specific safety concerns: 3-month juvenile rat study

Question: Will FDA accept and review the unaudited draft report and allow any or all of the studies outlined in the WR to start within 30 days of submission of the unaudited draft report based on FDA's review of this unaudited draft report?

FDA response: The Division is willing to accept an unaudited draft report of the rat juvenile combination toxicity study and agree to delayed submission of the report to 30 days prior to initiation of Study 3. Since Study 1 (Casodex) and Study 2 (Arimidex) are bioequivalence studies in healthy adult volunteers, these studies may proceed prior to submission of the juvenile rat study data. We suggest that Study 3 NOT be initiated until 30 days after submission of the rat study report to allow time for internal review. In addition, we request a desk copy to be sent to the reviewer Dr. Karen Davis-Bruno, to assure timely receipt.

2.2 Study 1: Relative bioavailability of bicalutamide

Question: Does FDA agree to modify wording of Study 1 under Type of studies of the WR from "A relative bioavailability (BA) study between a pediatric bicalutamide oral liquid formulation (to be developed) and the marketed 50-mg bicalutamide oral tablet" to "A relative bioavailability (BA) study between a pediatric bicalutamide oral liquid formulation (to be developed) or a bicalutamide dispersible tablet formulation (to be developed) and the marketed 50-mg bicalutamide oral tablet"?

FDA response: We agree.

2.3 Study 2: Relative bioavailability of anastrozole

Question: Does FDA agree to modify wording of Study 2 under Type of studies of the WR from "A relative bioavailability (BA) study between a pediatric anastrozole oral liquid formulation (to be developed) and the marketed 50-mg anastrozole oral tablet" to "A relative bioavailability (BA) study between a pediatric anastrozole oral liquid formulation (to be developed) or a anastrozole dispersible tablet formulation (to be developed) and the marketed 50-mg anastrozole oral tablet"?

FDA response: We agree.

2.4 Studies 1, 2 and 3: Objectives/rationale, study design and drug information

Question: Does FDA agree to modify wording throughout the WR as indicated from "liquid" to either "liquid or dispersible tablet" or "liquid/dispersible tablet"?

FDA response: We agree.

2.5 Study 3: Dosing issues

2.5.3.1 Study schedule for blood sampling

Question: Does FDA agree to remove this requirement for trial drug plasma concentrations 24 hours after each change in dose from the WR and agree that the proposed study design will meet the terms of the 17 April 2003 WR?

FDA response: Trough plasma drug concentration after the very first dose will provide important safety data since neither bicalutamide nor anastrozole pharmacokinetics in children is known. However, eliminating the trough plasma drug concentration sample 24 hours after each subsequent dose change is acceptable.

You should state in the blood sampling schedule whether the blood samples were for predose (baseline) or trough plasma drug concentrations after dosing.

2.6 Study 3: Drug-specific safety concerns
Question: Does FDA agree that inclusion of the listed evaluations will meet the provision of the WR?

FDA response: Close monitoring of patients for possible adverse events, including liver function monitoring and standard biochemistry and hematology tests are acceptable.

Adverse events labeled for bicalutimade and anastrozole must be assessed in the clinical trial even if they were identified in adult populations. They will be captured in the report of treatment-emergent adverse events.

2.7 Study 3: Issues regarding endpoints(s)

2.7.1 Pre-treatment bone growth measurements

Question: Does FDA agree that the measurement of bone growth before treatment in the testotoxicosis study starts will need to be from patient records and hence will be outside the study, and that this approach is acceptable according to the 17 April 2003 WR?

FDA response: A minimum of 12 evaluable patients are required for the testotoxicosis clinical trial. Due to the small number of patients, good quality data are necessary. To this end, retrospective data on bone age should be obtained from original X-rays and should be read within the trial, in a centralized fashion, by an experienced radiologist. Retrospective X-ray reports are not acceptable.

For height and height velocity data, since patients with testotoxicosis are followed by endocrinologists, retrospective height measurements collected in an endocrinology office/center are acceptable.

2.7.2 Breast pain and 2.7.3 Gynecomastia

Question: Does the FDA agree that this approach is acceptable and would meet the provisions outlined in the 17 April 2003 WR?

FDA response: Your described approach for collection of the treatment-emergent adverse event data related to gynecomastia and breast pain during the clinical trial is acceptable to the Division.

2.8 Study 3: Estradiol range

Question: Does FDA agree that this approach is acceptable according to 17 April 2003 WR?

FDA response: Use of the normal range for estradiol provided by the referenced laboratory is acceptable, in particular if the measured levels fall within the normal range. However, if levels higher than normal are recorded, as this information needs to be reviewed and potentially labeled, they should be presented in a way that allows a comparison between patients (e.g., using standard deviation, "times over upper limit of normal," etc.).

2.9 Study 3: Statistical requirements

2.9.1 Definition of evaluable patients

Question: Does FDA agree to this definition of evaluable patients and that this approach meets the provisions of the WR as defined in the 17 April 2003 WR?

FDA response: A minimum of 12 evaluable patients are required for the testotoxicosis clinical trial. Due to the small number of patients, good quality data are necessary. To this end, all 12 patients must have efficacy and safety data for one year (within 2-month window for assessments specified in the protocol). Additional patients may be enrolled to assure that 12 patients will complete 12 months of treatment. Adding the "80% compliance with the study drug' criterion to the definition of an evaluable patient is acceptable.

2.9.2 Definition of all-treated analysis population

Question: Does FDA agree to the definitions of all-treated analysis population as outlined, and agree that this approach meets the provisions of the 17 April 2003 WR?

FDA response: No, we do not agree that all-treated population or primary analysis of the all-treated population as you describe them meet the provisions of the WR. The all-treated population for primary endpoint should include all patients who receive at least one dose of study treatment and have at least one on-treatment measurement. The all-treated analysis should include <u>all</u> patients in the all-treated population. The secondary (robustness) analysis you describe reflects the intent of the all-treated analysis in the WR. Though not specifically mentioned in the WR, LOCF is the preferred imputation procedure for missing 12-month data although other procedures that minimize bias in favor of treatment may be used in addition.

The WR also specifies a protocol-valid analysis in patients that adhere to the protocol. Since protocol adherence was not defined explicitly in the WR, there is a certain degree of flexibility in defining this population and performing an analysis in this population that examines the drug in patients who are likely to fully benefit from the effect of treatment.

2.10. Other

2.10.1 Special Protocol Assessment

Question: Would FDA consider allowing the full protocol to be subject to a special protocol assessment procedure?

FDA response: The Division has answered all the clinical questions raised by the sponsor in full, thus making the need for a protocol assessment redundant.

ADDITIONAL COMMENTS FROM THE DIVISION CONCERNING THE SELECTION OF PEDIATRIC DOSES FOR BICALUTAMIDE AND ANASTROZOLE IN THE CLINICAL STUDY

We note in your discussion of "dosing issues" in section 2.5 that you intend to escalate the bicalutamide dose above the approved adult dose of 50 mg (i.e., 100 mg and 150 mg). Similarly, we note that you intend to escalate the anastrozole dose above the approved adult dose of 1 mg (i.e., 2 mg, 4 mg, and 8 mg). Although bicalutamide and anastrozole are titrated to pharmacodynamic endpoints and/or serum drug levels, any doses that exceed the approved doses should be clearly justified by animal toxicology data.

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/s/

Robert Meyer

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