OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDA: 22-310	Submission Date(s): 06/25/08
Brand Name	Casodex®
Generic Name	Bicalutamide
Reviewer	Ritesh Jain, Ph.D.
Team Leader	Sally Choe, Ph.D.
OCP Division	Clinical Pharmacology -2
OND division	Metabolic and Endocrine Products
Sponsor	AstraZeneca
Submission Type; Code	Type 6 NDA (Pediatric Exclusivity); Priority
Formulation; Strength(s)	Oral dispersible Tablets, Casodex® in combination with Arimidex®
Indication	Treatment of male pubertal patients with testotoxicosis.

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CASODEX® (bicalutamide) is an anti-androgenic agent commonly used for prostrate cancer. ARIMIDEX® (anastrozole) is a potent and selective nonsteroidal aromatase inhibitor indicated for the treatment of early and advanced breast cancer in postmenopausal women. The purpose of this application is to provide safety, efficacy and pharmacokinetic information on the use of Casodex (bicalutamide) in combination with Arimidex (anastrozole) in male pubertal patients with testotoxicosis. Testotoxicosis is a form of gonadotropin-independent (peripheral) precocious puberty, in which boys experience early onset (2-3 years age) and progression of puberty. Testotoxicosis is caused by luteinizing hormone (LH) receptor mutation leading to increased levels of sex steroids. Affected boys usually begin early pubertal development resulting in rapid growth and bone maturation, progressive virilization and ultimately, premature epiphyseal fusion and short stature in adulthood.

The studies in this submission are conducted in response to FDA's original Pediatric Written Request (WR) dated 04/17/2003 to obtain safety, efficacy and pharmacokinetic information of Casodex in pediatric patients with testotoxicosis. Six amendments have been made on the original WR and pediatric exclusivity was granted on 09/19/2008. No indication is being sought in this application and the clinical efficacy trial failed to meet the primary efficacy endpoint and no indication is being sought in this application by the sponsor. Please see the review by the medical officer, Dr. Dragos Roman for details. The sponsor proposes that appropriate sections of the CASODEX label should be updated to include data from the studies submitted.

1.1 RECOMMENDATIONS

The Office of Clinical Pharmacology/Division of Clinical Pharmacology-2 (OCP/DCP-2) has reviewed NDA 22-310 submitted on 04/17/2003 and finds it acceptable. Recommendation and labeling comments should be conveyed to the sponsor as appropriate.

1.2 PHASE IV commitments

Not applicable.

1.3 SUMMARY of Important Clinical Pharmacology AND BIOPHARMACEUTICS Findings

The studies submitted in this application are based on FDA's Pediatric Written Request (WR) Amendment #6 dated 05/08/2008 to obtain safety, efficacy, and pharmacokinetic information on the use of Casodex in combination with Arimidex in pediatric patients with testotoxicosis. This application contained a total of three studies; two relative oral bioavailability studies investigating the relative bioavailability between the pediatric dispersible tablet formulation and market oral tablets of bicalutamide and anastrozole in healthy adult volunteers and the third clinical study investigating the safety and efficacy of bicalutamide and anastrozole when given together in patients (14 enrolled, 13 completers) with testotoxicosis.

After single dose administration to fasted healthy adult subjects, plasma concentrations of R-bicalutamide (active isomer) after dispersible tablets (2 X 25 mg) administration were comparable to those of the marketed (50 mg) tablet. The relative bioavailability of the dispersible tablet to the marketed tablet was 0.93 (90% CI: 0.89 – 0.96) from comparison of AUC and 0.92 (90% CI: 0.90 – 0.94) from comparison of C_{max}.

Table 1: Statistical comparison of primary pharmacokinetics parameters for R-bicalutamide after oral administration of marketed CASODEX tablet and 2 X 25 mg dispersible tablet

Variable	Dispersible 2 x 25 mg tablets glsmean	Marketed 50 mg tablet (CASODEX) glsmean	Relative bioavailability	90% CI lower limit	90% CI upper limit
AUC (ng.h/mL)	187956.73 (n=29)	202893.04 (n=27)	0.93	0.89	0.96
C_{max} (ng/mL)	792.90 (n=30)	863.18 (n=29)	0.92	0.90	0.94

AUC, area under the plasma concentration-time curve from zero to infinity
CI, confidence interval
Cmax, maximum plasma concentration
glsmean, geometric least squares mean

Also, plasma concentrations of anastrozole were comparable after administration of the marketed and dispersible tablets (1 mg) to fasted volunteers. The relative bioavailability, as assessed by the ratios of the dispersible tablet to the marketed tablet was 0.98 (90% CI: 0.96 – 1.01) from comparison of AUC and 0.98 (90% CI: 0.94 – 1.02) from comparison of C_{max}.

Table 2: Statistical comparison of primary pharmacokinetics parameters for Anastrozole after oral administration of marketed 1 mg ARIMIDEX tablet and 1 mg dispersible tablet

Variable	1 mg dispersible tablet glsmean[a] (N = 28)	1 mg marketed tablet glsmean[a] (N =28)	Relative bioavailability	90% CI lower limit	90% CI upper limit
AUC (ng.h/mL)	638.35	648.87	0.984	0.962	1.006
C_{max} (ng/mL)	12.15	12.46	0.975	0.935	1.017

[a] Geometric least squares mean
CI = confidence interval

The primary efficacy variable in clinical efficacy study is change in growth rate (cm/year) after 12 months of treatment with bicalutamide and anastrozole. The clinical

efficacy trial failed to meet the primary efficacy endpoint and no indication is being sought in this application by the sponsor. Please see the review by the medical officer, Dr. Dragos Roman for details.

2. QBR

2.1 General Attributes

2.1.1. What pertinent regulatory background or history contributes to the current assessment of the clinical pharmacology and Biopharmaceutics of the drug?

The studies in this submission are conducted in response to FDA's original Pediatric Written Request (WR) dated 04/17/2003 to obtain safety, efficacy and pharmacokinetic information of Casodex in pediatric patients with testotoxicosis. Six amendments have been made on the original WR (See Appendix for WR). The written request from the FDA required the sponsor to conduct 3 studies to obtain 6-month pediatric exclusivity for CASODEX (bicalutamide) tablets. The current application provides data from these studies.

Study 1: A relative bioavailability (BA) study between a pediatric bicalutamide orodispersible tablet formulation and the marketed 50 mg bicalutamide oral tablet in adults. (Study # D6873C00003)

Study 2: A relative BA study between a pediatric anastrozole orodispersible tablet formulation and the marketed 1 mg anastrozole oral tablet in adult (Study # D6873C00002).

Study 3: An efficacy and safety study of bicalutamide when used in combination with anastrozole for the treatment of precocious puberty in boys with testotoxicosis (Study # D6873C00047)

2.1.2. What is the mechanism of action and therapeutic indication?

Testotoxicosis is caused by luteinizing hormone (LH) receptor mutation leading to increased levels of sex steroids. The changes seen in testotoxicosis are driven by actions of both androgen and estrogen. Casodex (bicalutamide) is an oral non-steroidal anti-androgenic that competes with intra-cellular testosterone and dihydrotestosterone (DHT) for nuclear androgen receptor binding sites in the target cell. Bicalutamide may assist in the management of testotoxicosis by blocking androgen induced growth and development of secondary sexual characteristics. Casodex is currently indicated for patients with prostrate cancer.

Arimidex (Anastrozole) is a potent and selective nonsteroidal aromatase inhibitor. Aromatase inhibitors are a class of compounds that act systemically to inhibit estrogen synthesis in tissues thereby reducing estrogen production. These compounds prevent synthesis by inhibiting the enzyme aromatase, which catalyzes the conversion of the adrenal androgens, androstenedione and testosterone to the estrogens, estrone and estradiol respectively. Anastrazole may suppress the estrogen level in boys with

testotoxicosis. Anastrozole in indicated for the treatment of early and advanced breast cancer in postmenopausal women.

No indication is being sought in this application.

2.1.3. What are the proposed dosage and route of administration?

No indication is sought in this study. However, the clinical efficacy and safety study used once-daily oral anastrozole (ARIMIDEX™) orodispersible tablets and bicalutamide (CASODEX™) orodispersible tablets. Study medication was independently titrated in the following ascending doses:

- dispersible bicalutamide 12.5 mg, 25 mg, 50 mg, 100 mg, 150 mg
- dispersible anastrozole 0.5 mg, 1 mg, 2 mg, 4 mg, 8 mg

The dosing of anastrozole and bicalutamide was independently tailored for each patient. Anastrozole and bicalutamide dose revisions were driven by serum estradiol and plasma bicalutamide concentrations, respectively. Doses of each drug were iteratively adjusted until a dose was reached that gave steady-state trough serum estradiol concentrations of <10 pmol/L (2.7 pg/mL) and R-bicalutamide (the active isomer of bicalutamide) trough plasma concentrations within the range 5-15 μg/mL. Anastrozole dose escalation was stopped once a plasma anastrozole concentration of 350 ng/mL or a daily dose of 8 mg was reached.

2.1.4. What is the rationale to select the dosage for Casodex and Arimidex?

Clinical data in adults with prostrate cancer have shown that CASODEX at a dose of 50 mg daily provides effective androgen receptor blockade as demonstrated by significant falls in prostate specific antigen (PSA) and improvement in clinical outcome occurring with Casodex usage at this dose. The plasma mean plasma concentration of bicalutamide after daily 50 mg single dose administration to adult males was observed to be 10 μg/mL, with a typical range of 5- 15 μg/mL. Since the exposure of 5-15 μg/mL is shown to be effective in having anti-androgenic effect in adults, this exposure window was also chosen for pediatric patients with testotoxicosis. The starting dose of Casodex was 12.5 mg, with dose being titrated up to 150 mg based on observed plasma R-bicalutamide concentrations on Day 21 or later.

Boys with testotoxicosis were expected to have elevated serum estradiol concentrations because of the conversion of excess testosterone to estradiol. Dose selection and titration of Arimidex is based on the plasma estradiol concentrations. The plasma estradiol concentrations were kept below10 pmol/L as this represents the plasma estradiol concentration in boys at early puberty. Anastrozole dose escalation was stopped once a plasma anastrozole concentration of 350 ng/mL or a daily dose of 8 mg was reached.

2.1.5. Is any DSI (Division of Scientific Investigation) inspection requested for any of the clinical studies?

No DSI inspection was requested for any of the studies.

2.2 General Clinical Pharmacology

2.2.1. What is known about the general pharmacology of Casodex and Arimidex?

Refer to original NDA 20-541 approved by FDA on December 27, 1995 for Arimidex and NDA 20-498 approved by FDA on October 4, 1995 for Casodex.

2.2.2. What is the primary measurement of efficacy?

The primary efficacy variable in the clinical efficacy study is change in growth rate (cm/year) after 12 months of treatment with bicalutamide and anastrozole. Efficacy analysis was done by measuring the height of the patients at ≥ 6 months pre-study period, at baseline and after 12 months of treatment. Growth rate at baseline is derived from retrospective data as follows:
GR_B (cm/year) = [height (cm) at baseline – height (cm) at ≥ 6 months pre-study period]/ [time interval in years between baseline and pre-study assessment].

Change in growth rate after 12 months of the treatment can be obtained by difference in the growth after 12 months (GR_{12} cm/year) and growth rate at baseline (GR_B cm/year).

2.2.3. What is the pharmacodynamic response to bicalutamide and anastrozole?

The primary efficacy variable in clinical efficacy study is change in growth rate (cm/year) after 12 months of treatment with bicalutamide and anastrozole. The clinical efficacy trial failed to meet the primary efficacy endpoint. Please see the review by the medical officer, Dr. Dragos Roman for details.

2.2.4. Are the active moieties in the plasma appropriately identified and measured?

Yes.

2.3 Intrinsic Factors

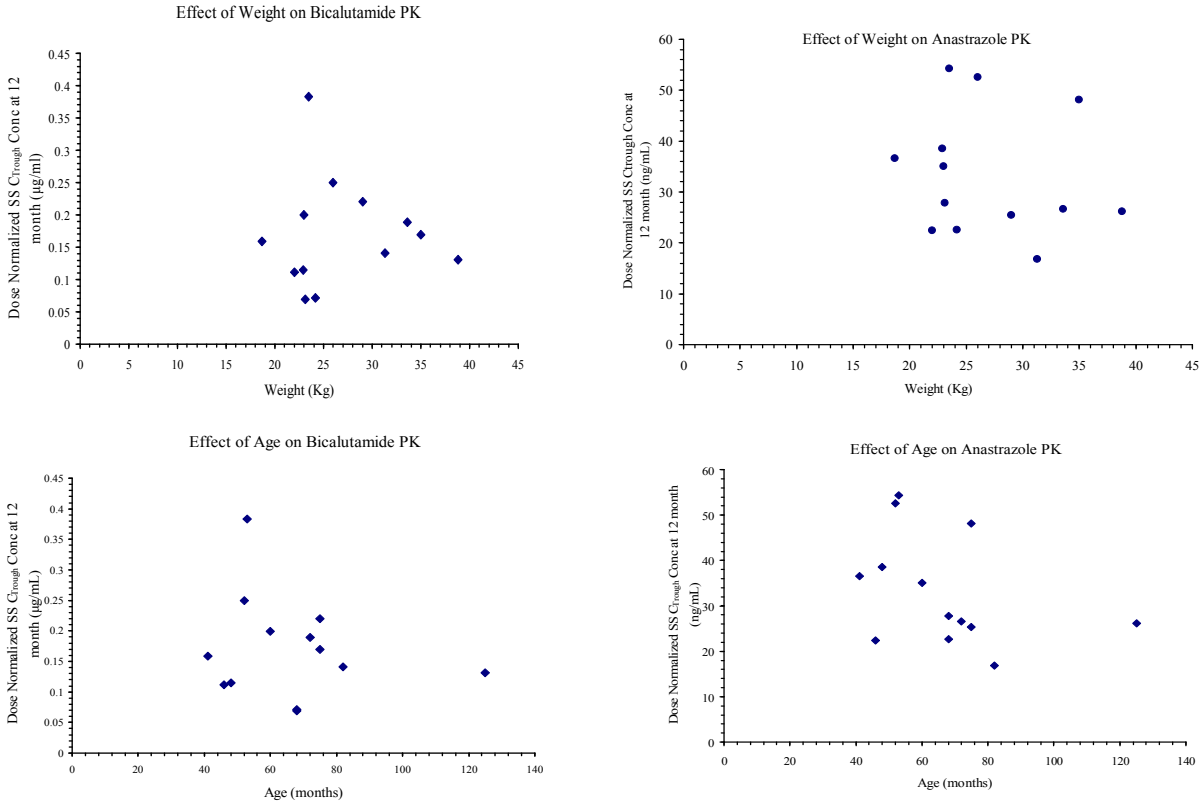
2.3.1. What are the pharmacokinetics characteristics of bicalutamide and anastrozole in pediatric patients?

The mean plasma trough concentrations for R-bicalutamide remained in the pre-specified concentration range of 5-15 μg/mL. For the 13 patients who were stabilized for bicalutamide, (i.e. attained their potential therapeutic dose), 8 patients were on 50 mg, 4 patients on 100 mg, and 1 patient on 12.5 mg bicalutamide. The final stabilized dose for anastrozole was 0.5 mg for 10 patients and 1 mg for 3 patients. The steady-state R-bicalutamide and anastrozole concentrations appeared to be attained in the majority of

patients by Day 21 and Day 8, respectively, following once a day dosing. Please see 4.2.3. Clinical Study Report D6873C000047 for details.

2.3.2. What is the influence of age and weight on PK of bicalutamide and anastrozole in pediatric patients?

No definitive conclusion on the effect of age and body weight on steady state C_{trough} concentrations of bicalutamide and anastrozole can be drawn due to the limited number of sample size. However, in one of the previous reviews of NDA 22-214 by Dr. Manoj Khurana it was found that body weight is an important covariate for the determination of clearance and volume of distribution of anastrozole in pediatric patients.



2.3.3. Is dose proportionality evaluated?

The sponsor claims in their proposed package insert that (b) (4) Please see 4.2.3. Clinical Study Report D6873C000047 for details.

2.4 Extrinsic factors

Not applicable.

2.5 GENERAL Biopharmaceutics

After single dose administration to fasted healthy adult subjects, plasma concentrations of R-bicalutamide were comparable after administration of the marketed (50 mg) and dispersible tablets (2 X 25 mg). The relative bioavailability of the dispersible tablet to the marketed tablet was 0.93 (90% CI: 0.89 – 0.96) from comparison of AUC and 0.92 (90% CI: 0.90 – 0.94) from comparison of C_{max}. Also, the relative bioavailability for anastrozole, as assessed by the ratios of the dispersible tablet to the marketed tablet was 0.98 (90% CI: 0.96 – 1.01) from comparison of AUC and 0.98 (90% CI: 0.94 – 1.02) from comparison of C_{max}. Thus, the exposure of the two formulations can be considered to be similar.

2.6 Analytical Section

Study D6873C00002: Quantitative assessment of anastrozole concentration in human plasma was conducted employing a validated HPLC-MS/MS method. Samples were extracted using a liquid-liquid extraction procedure. Extracted samples were (b) (4) (b) (4) analyzed by HPLC with an (b) (4) mass spectrometer. The calibration curves were analyzed at anastrozole concentrations of 0.1, 0.250, 1.0, 2.5, 10.0, 25, 50, and 60 ng/mL. The lower limit of quantification (LOQ) for anastrozole was 0.1 ng/mL. Between-batch precision (%CV) results for QC samples prepared at low, medium, and high QC concentrations of anastrozole was less than or equal to 11.0 % and accuracy (%Bias) ranged from -1.0 to -0.4 %. Between-batch precision (%CV) results of the calibration standards of anastrozole were less than 4 % and accuracy (%Bias) ranged from -0.8 to 1.0 %.

Study D6873C00003: Quantitative assessment of R- and S- bicalutamide concentration in human plasma was conducted employing a validated HPLC-MS/MS method. Samples were extracted using a liquid-liquid extraction procedure. Extracted samples were (b) (4) analyzed by chiral HPLC with an (b) (4) (b) (4) mass spectrometer. The calibration curves were analyzed at R- and S-bicalutamide concentrations of 10, 20, 100, 500, 2500, 4500, and 5000 ng/mL. The lower limit of quantification (LOQ) for bicalutamide was 10 ng/mL. Between-batch precision (%CV) results for QC samples prepared at low, medium, and high QC concentrations of R-bicalutamide was less than or equal to 6.8 % and accuracy (%Bias) ranged from -0.8 to -0.3 %. For S-bicalutamide precision (%CV) was less than or equal to 5.4 % and bias ranged from -1.5 to -0.5 %. Between-batch precision (%CV) results of the calibration standards of R-bicalutamide was less than or equal to 3 % and accuracy (%Bias) ranged from -0.8 to 1.6 %. For S-bicalutamide precision (%CV) was less than 3 % and bias ranged from -1.0 to 1.6 %.

Study D6873C000047: Quantitative assessment of anastrozole and R-bicalutamide concentration in human plasma was conducted employing a validated HPLC-MS/MS method (b) (4). R-bicalutamide plasma samples were extracted using a liquid-liquid extraction procedure. Extracted samples were analyzed by chiral HPLC with an (b) (4) mass spectrometer. The calibration curves were

analyzed at R- bicalutamide concentrations of 40, 80, 200, 1000, 5000, 9000, and 10000 ng/mL. The lower limit of quantification (LOQ) for bicalutamide was 40 ng/mL. Between-batch precision (%CV) results for QC samples prepared at low, medium, and high QC concentrations of R-bicalutamide was between 5.9 to 9.8 % and accuracy ranged from 99.5 % to 101.9 %. A between-batch precision (% CV) result of the calibration standards of R-bicalutamide was between 4.5 to 10.7 % and accuracy ranged from 98.7 to 102%.

Anastrozole plasma samples were extracted using a (b) (4) . Extracted samples were analyzed by HPLC with an (b) (4) mass spectrometer. The calibration curves were analyzed at anastrozole concentrations of 1, 2, 5, 10, 50, 100, 250 and 500 ng/mL. The lower limit of quantification (LOQ) for bicalutamide was 1 ng/mL. Between-batch precision (%CV) results for QC samples prepared at low, medium, and high QC concentrations of anastrozole was between 6.1to 8.6 % and accuracy ranged from 99.1 % to 103.2 %. A between-batch precision (% CV) result of the calibration standards of anastrozole was between 2.7 to 9.4 % and accuracy ranged from 98.1 to 101.5%.

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4.2 INDIVIDUAL STUDY REVIEW

4.2.1 Clinical Study D6873C00003

Title: An open-label, randomised, single-centre, cross-over Phase I study to determine the relative bioavailability of bicalutamide 50 mg when administered orally as dispersible tablet and marketed tablet (CASODEX™) in healthy male volunteers.

Investigator and Study Center(s):

Thierry Duvauchelle MD
ASTER, 3 et 5, rue Eugene Millon
75015 Paris
France

Study Sponsor:

AstraZeneca
Alderley Park
Macclesfield
Cheshire, SK10 4TG, UK

Bioanalytical Analysis:
(b) (4)

STUDY PERIOD: 04 October 2004 (First volunteer enrolled) – 09 March 2005 (Last volunteer completed)

Objective:
The primary objective of this study was to determine the relative bioavailability of bicalutamide when administered as dispersible oral 2 x 25 mg tablets compared with the marketed oral 50 mg tablet (CASODEX) in healthy adult male volunteers.

The secondary objectives of the study were:

- To characterize and compare the pharmacokinetics of bicalutamide 50 mg when administered as dispersible oral tablet and marketed oral tablet (CASODEX) in healthy adult male volunteers

- To ensure the safety of volunteers, and their tolerability to bicalutamide.

Study Design:
This study was a single centre, randomized, open-label, two-period cross-over study in thirty adult male volunteers. The study consisted of two treatment periods (Periods I and II). Each volunteer received two single oral doses of bicalutamide (one in each Period). In Period I volunteers were randomized to receive a single oral dose of either

- 50 mg marketed bicalutamide tablet (CASODEX), or
- 2 x 25 mg dispersible bicalutamide tablets

In Period II volunteers crossed over to receive the formulation not received in Period I. Volunteers were kept in the Clinical Pharmacology Unit (CPU) from the evening before each dose of bicalutamide until at least 48 hours following dosing. The dose was taken at the same approximate time in both periods. In each Period, samples for PK analysis were collected over a 5-week interval. There was a minimum 63-day washout period between doses. Each volunteer returned for a post-study medical examination within the 14 days following the last PK sample in Period II. For each subject, 19 blood samples were withdrawn for the assessment of R- and S-bicalutamide concentrations in plasma over a 5-week period.

Study Population:
Thirty healthy adult male volunteers were enrolled in this study. The mean age of the study population was 48 years (range 36 to 60 years), mean height was 175.7 cm (range 157 to 187 cm) and mean weight was 76.78 kg (range 52.2 to 90.5 kg). The BMI for the study population was 24.82 (range 20.91 to 28.93). All 30 volunteers were nonsmokers at entry to the study.

Bioanalytical Analysis:
Quantitative assessment of R- and S- bicalutamide concentration in human plasma was done employing a validated HPLC-MS/MS method. Samples were extracted using a liquid-liquid extraction procedure. Extracted samples were (b) (4) (b) (4) analyzed by chiral HPLC with an (b) (4) mass spectrometer. The calibration curves were analysed at R- and S-bicalutamide concentrations of 10, 20, 100, 500, 2500, 4500, 5000 ng/mL. The lower limit of quantification (LOQ) for bicalutamide was 10 ng/mL. Between-batch precision (%CV)

results for QC samples prepared at low, medium, and high QC concentrations of R-bicalutamide was less than or equal to 6.8 % and accuracy (%Bias) ranged from -0.8 to -0.3 %. For S-bicalutamide precision (%CV) was less than or equal to 5.4 % and bias ranged from -1.5 to -0.5 %. Between-batch precision (%CV) results of the calibration standards of R-bicalutamide was less than or equal to 3 % and accuracy (%Bias) ranged from -0.8 to 1.6 %. For S-bicalutamide precision (%CV) was less than 3 % and bias ranged from -1.0 to 1.6 %.

Data Analysis:
PK analysis of both R- and S- bicalutamide plasma concentration data was performed by non-compartmental analysis. The relative bioavailability of the dispersible tablet in each individual volunteer was determined from the ratios of the AUC and C_{max} of R-bicalutamide obtained following dosing of the dispersible tablet to the AUC and C_{max} of R-bicalutamide obtained following dosing of the marketed tablet. ANOVA was used to compare the log transformed AUC and C_{max} between the dispersible tablet and marketed tablet. The results were presented in terms of the geometric least square means (glsmeans) for each formulation, the relative bioavailability (i.e. the ratios of glsmeans of dispersible 2 x 25 mg tablets versus marketed 50 mg tablet), and the associated 90% confidence intervals.

There were two protocol deviations, volunteer0017 (took prohibited medication and did not take part in period II) and volunteer0028 (took prohibited medication in period II). So out of 30 volunteers, 28 completed the study and two were withdrawn because of the reasons as described above. Secondary PK parameter were calculated wherever the data allowed. The following pharmacokinetic (PK) variables for both R-bicalutamide and S-bicalutamide were determined: Time to reach the maximum plasma concentration (t_{max}), area under plasma concentration-time curve from zero to time t (AUC_{0-t}), terminal rate constant (λ_z), terminal half-life ($t_{1/2}$), total apparent drug clearance (CL/F), and volume of distribution at steady state (V_{ss}/F).

Pharmacokinetics Results:
The plasma pharmacokinetics of R-bicalutamide following a single oral dose of either a 50 mg marketed tablet (CASODEX) or 2 x 25 mg dispersible tablets was assessed in healthy adult male volunteers. Majority of individuals who completed the study, the R-bicalutamide AUC was well estimated with the extrapolated portion being less than 10%. There were two exceptions, Volunteer 22 on both formulations and Volunteer 28 for the marketed formulation for whom the terminal phase could not be well estimated and thus AUC was not calculable. On these three occasions the percentage AUC extrapolated was considerably higher than other occasions and the terminal phase could not be followed for three times the calculated $t_{1/2}$. For these occasions PK parameters were not reported.

Thus statistical analysis of AUC was completed for 27 on the marketed formulation and for 29 on the dispersible formulation. As C_{max} was estimated for each profile the statistical analysis of C_{max} was completed for 29 on the marketed and 30 on the dispersible formulations respectively.

Plasma concentrations of R-bicalutamide were comparable after administration of the marketed and dispersible tablets to fasted volunteers. The relative bioavailability of the dispersible tablet to the marketed tablet was 0.93 (90% CI: 0.89 – 0.96) from comparison of AUC and 0.92 (90% CI: 0.90 – 0.94) from comparison of C_{max}.

Sponsor's PK analyses for secondary parameters of R-bicalutamide were similar with T_{max} ranging from 9-72 hours, $t_{1/2}$ ranging from 80-124 hours.

Table 1: Primary PK parameters of R-bicalutamide

Variable	Marketed 50 mg tablet (CASODEX)	Dispersible 2 x 25 mg tablets
AUC (ng.h/mL)		
N	27	29
Geometric mean	203900	188100
CV (%)	24.60	20.39
C_{max} (ng/mL)		
N	29	30
Geometric mean	867.8	792.9
CV (%)	16.10	12.58

AUC, area under the plasma concentration-time curve from zero to infinity. AUC could not be estimated for 3 profiles
C_{max}, maximum plasma concentration
CV, coefficient of variation
N, number of volunteers

Table 2: Statistical comparison of primary pharmacokinetics parameters for R-bicalutamide after oral administration of marketed CASODEX tablet and 2 X 25 mg dispersible tablet

Variable	Dispersible 2 x 25 mg tablets glsmean	Marketed 50 mg tablet (CASODEX) glsmean	Relative bioavailability	90% CI lower limit	90% CI upper limit
AUC (ng.h/mL)	187956.73 (n=29)	202893.04 (n=27)	0.93	0.89	0.96
C_{max} (ng/mL)	792.90 (n=30)	863.18 (n=29)	0.92	0.90	0.94

AUC, area under the plasma concentration-time curve from zero to infinity
CI, confidence interval
Cmax, maximum plasma concentration
glsmean, geometric least squares mean

Table 3: Secondary PK parameters for R-bicalutamide

Variable	Marketed 50 mg tablet (CASODEX)	Dispersible 2 x 25 mg tablets
t_{max} (h)		
N	29	30
Median	36.0	48.0
Minimum	9.0	12.0
Maximum	48.0	72.0
AUC_{0-t} (ng.h/mL)		
N	29	30
Geometric mean	204100	188500
CV (%)	26.67	23.75
$t_{½}$ (h)		
N	27	29
Mean	135.2	131.1
SD	26.53	24.97
CL/F (L/h)		
N	27	29
Mean	0.1254	0.1354
SD	0.0362	0.0259
V_{ss}/F (L)		
N	27	29
Mean	24.82	25.70
SD	4.564	3.718

AUC_{0-t} = Area under plasma concentration time curve from zero to the time of the last quantifiable concentration
CL/F = Plasma clearance following oral dosing
CV= Coefficient of variation
N = Number of volunteers
SD = Standard deviation
t_{max} = Time to Cmax
$t_{½}$ = Elimination half-life
V_{ss}/F = Volume of distribution at steady state following oral dosing

Plasma concentrations of S-bicalutamide were appreciably lower than those of R-bicalutamide at all sampling time-points. Beyond 72 hours the S-bicalutamide plasma concentrations fell below the limit of quantification for all profiles and the extrapolated portion of the S-bicalutamide AUC accounted for more than 10% of the total. C_{max} data for S-bicalutamide were only between around 4 – 11% of the corresponding R-

bicalutamide C_{max} values. The plasma concentration-time profile of S-bicalutamide and the range of values for C_{max}, AUC(0-t) and T_{max} S-bicalutamide was comparable between the two formulations.

Table 4: Summary of PK parameters for S-bicalutamide

Variable	Marketed 50 mg tablet (CASODEX)	Dispersible 2 x 25 mg tablets
C_{max} (ng/mL)		
N	29	30
Geometric mean	60.40	43.65
CV (%)	32.83	26.84
AUC_{0-t} (ng.h/mL)		
N	29	30
Geometric mean	1566	1441
CV (%)	33.41	27.93
t_{max} (h)		
Median	3.00	4.00
Minimum	1.00	1.00
Maximum	24.00	24.00

AUC_{0-t}, area under plasma concentration time curve from zero to the time of the last quantifiable concentration
Cmax, maximum plasma concentration
CV, coefficient of variation
N, number of volunteer
t_{max}, time to Cmax

Summary of pharmacokinetic results

The plasma pharmacokinetics of R-bicalutamide following a single oral dose of either a 50 mg marketed tablet (CASODEX) or 2 x 25 mg dispersible tablets was assessed in healthy adult male volunteers. The confidence intervals of treatment ratios for both parameters are comparable and lie well within 0.8 – 1.25, thus the exposure of the two formulations can be considered to be similar.

Summary of safety results

There were no deaths, serious adverse events (SAEs), discontinuations due to AEs, or other significant adverse events (OAEs) reported during this study. There were no clinically significant findings related to clinical laboratory evaluations, vital signs, ECG or physical observations.

Conclusions

Bicalutamide exposure following a single oral dose of either a 50 mg marketed tablet (CASODEX) or 2 x 25 mg dispersible tablets can be considered to be similar on the basis of comparison of R-bicalutamide AUC and C_{max} in healthy adult volunteers. There were no new safety issues identified during this study and both the study drugs are well tolerated.

4.2.2 Clinical Study D6873C00002

Title: An Open-label, Randomised, Single-centre, Cross-over, Phase I Study to Determine the Relative Bioavailability of Anastrozole 1 mg When Administered Orally as Dispersible Tablet and Marketed Tablet (ARIMIDEX™) in Healthy Male Volunteers.

Investigator and Study Center(s)

Michael Davies MD, FRCS
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Deborah Sandell MB, DA
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STUDY SPONSOR:

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Cheshire, SK10 4TG, UK

BIOANALYTICAL ANALYSIS:

Analysis of pharmacokinetic samples
(b) (4)

STUDY PERIOD: 02 September 2004 (First volunteer enrolled) – 10 November 2004 (Last volunteer completed)

Objective:
The primary objective of the study was to determine the relative bioavailability of anastrozole when administered as a dispersible oral 1 mg tablet compared with the marketed oral 1 mg tablet (ARIMIDEX) in healthy adult male volunteers

The secondary objectives of the study were:

- To characterize and compare the pharmacokinetics of anastrozole 1 mg, when administered as dispersible oral 1 mg tablet and marketed oral 1 mg tablet (ARIMIDEX) in healthy adult male volunteers.

- To ensure the safety of volunteers, and their tolerability to anastrozole.

Study Design:
This study was a single centre, randomised, open-label, two-period cross-over study in 28 healthy adult male volunteers. The study consisted of two treatment periods (Periods I and II). Each volunteer received two single oral doses of anastrozole (one in each Period). In Period I volunteers were randomised to receive a single oral dose of either

- 1 mg marketed anastrozole tablet (ARIMIDEX), or
- 1 mg dispersible anastrozole tablets

In Period II volunteers crossed over to receive the formulation not received in Period I. Volunteers were kept in the Clinical Pharmacology Unit (CPU) from the evening before each dose of anastrozole until at least 24 hours following dosing. The dose was taken at the same approximate time in both periods. In each Period, samples for PK analysis were collected over a 10 day interval. There was a minimum 21-day washout period between doses. Each volunteer returned for a post-study medical examination within the 14 days following the last PK sample in Period II. For each subject, 16 blood samples were withdrawn for the assessment of anastrozole concentrations in plasma over a 10-day period.

Study Population:
Twenty eight healthy adult male volunteers were enrolled in this study. The mean age was 38.9 years (range 19 to 57 years), mean height was 177.4 cm (range 156 to 189 cm) and mean weight was 80.79 kg (range 60.0 to 107.0 kg). The body mass index for the study population was 25.68 (range 19.3 to 30.0). All volunteers completed the study. All 28 volunteers were non-smokers at entry to the study.

Bioanalytical Analysis:
Quantitative assessment of anastrozole concentration in human plasma was done employing a validated HPLC-MS/MS method. Samples were extracted using a liquid-liquid extraction procedure. Extracted samples were (b) (4) (b) (4) analyzed by HPLC with an (b) (4) mass spectrometer. The calibration curves were analysed at anastrozole concentrations of 0.1, 0.250, 1.0, 2.5, 10.0, 25, 50, 60 ng/mL. The lower limit of quantification (LOQ) for anastrozole was 0.1 ng/mL. Between-batch precision (%CV) results for QC samples

prepared at low, medium, and high QC concentrations of anastrozole was less than or equal to 11.0 % and accuracy (%Bias) ranged from -1.0 to -0.4 %. Between-batch precision (%CV) results of the calibration standards of anastrozole were less than 4 % and accuracy (%Bias) ranged from -0.8 to 1.0 %.

Data Analysis:
PK analysis anastrozole plasma concentration data was performed by non-compartmental analysis. The relative bioavailability of the dispersible tablet in each individual volunteer was determined from the ratios of the AUC and C_{max} of anastrozole obtained following dosing of the dispersible tablet to the AUC and C_{max} of anastrozole obtained following dosing of the marketed tablet. ANOVA was used to compare the log transformed AUC and C_{max} between the dispersible tablet and marketed tablet. The results were presented in terms of the geometric least square means (glsmeans) for each formulation, the relative bioavailability (i.e. the ratios of glsmeans of dispersible 1 mg tablets versus marketed 1 mg tablet), and the associated 90% confidence intervals. Secondary PK parameter were calculated wherever the data allowed. The following secondary pharmacokinetic (PK) variables for anastrozole were determined: Time to reach the maximum plasma concentration (t_{max}), area under plasma concentration-time curve from zero to time t (AUC_{0-t}), terminal rate constant (λz), terminal half-life ($t_{1/2}$), total apparent drug clearance (CL/F), and volume of distribution at steady state (V_{ss}/F).

Pharmacokinetics Results:
Plasma concentrations of anastrozole were comparable after administration of the marketed and dispersible tablets to fasted volunteers. The relative bioavailability, as assessed by the ratios of the dispersible tablet to the marketed tablet was 0.98 (90% CI: 0.96 – 1.01) from comparison of AUC and 0.98 (90% CI: 0.94 – 1.02) from comparison of C_{max}. Thus the exposure of the two formulations can be considered to be similar.

There were four protocol deviations where patient took concomitant medication during the course of study. However, none of the subject took any medications between 72 hours before dosing and 24 hours after dosing. Although all subjects were included in the analysis, a separate analysis was also carried out according to the protocol. No marked difference in parameters values between the two analyses was observed.

Sponsor's PK analyses for secondary parameters of anastrozole were similar for both formulations with T_{max} ranging from 0.5-4.0 hours, $t_{1/2}$ ranging from 30-70 hours

Table 1: Primary PK parameters of Anastrozole

Variable	1 mg marketed tablet	1 mg dispersible tablet
AUC (ng.h/mL)		
N	28	28
Geometric mean	648.9	638.3
CV (%)	19.73	19.17
C_{max} (ng/mL)		
N	28	28
Geometric mean	12.46	12.15
CV (%)	17.41	17.41

AUC = Area under the plasma concentration-time curve from zero to infinity
C_{max} = Maximum plasma concentration
CV= Coefficient of variation
N = Number of volunteers

Table 2: Statistical comparison of primary pharmacokinetics parameters for Anastrozole after oral administration of marketed 1 mg ARIMIDEX tablet and 1 mg dispersible tablet

Variable	1 mg dispersible tablet glsmean[a] (N = 28)	1 mg marketed tablet glsmean[a] (N =28)	Relative bioavailability	90% CI lower limit	90% CI upper limit
AUC (ng.h/mL)	638.35	648.87	0.984	0.962	1.006
C_{max} (ng/mL)	12.15	12.46	0.975	0.935	1.017

[a] Geometric least squares mean
CI = confidence interval

Table 3: Secondary PK parameters for Anastrozole

Variable	1 mg marketed tablet	1 mg dispersible tablet
t_{max} (h)		
Median	1.000	1.000
Minimum	0.500	0.500
Maximum	4.00	4.00
AUC_{0-t} (ng.h/mL)		
N	28	28
Geometric mean	620.2	610.3
CV (%)	18.02	17.03
$t_{½}$ (h)		
N	28	28
Mean	46.44	46.99
SD	9.62	9.77
CL/F (L/h)		
N	28	28
Mean	1.57	1.59
SD	0.3071	0.3016
V_{ss}/F (L)		
N	28	28
Mean	97.16	99.53
SD	12.34	13.59

AUC_{0-t} = Area under plasma concentration time curve from zero to the time of the last quantifiable concentration
CL/F = Plasma clearance following oral dosing
CV= Coefficient of variation
N = Number of volunteers
t_{max} = Time to Cmax
$t_{½}$ = Elimination half-life
V_{ss}/F = Volume of distribution at steady state following oral dosing

Summary of pharmacokinetic results

The plasma pharmacokinetics of anastrozole following a single oral dose of either a 1 mg marketed tablet (ARIMIDEX) or 1 mg dispersible tablets was assessed in healthy adult male volunteers. The confidence intervals of treatment ratios for both parameters are comparable and lie well within 0.8 – 1.25, thus the exposure of the two formulations can be considered to be similar.

Summary of safety results
There were no deaths, serious adverse events (SAEs), discontinuations due to AEs, or other significant adverse events (OAEs) reported during this study. There were no clinically significant findings related to clinical laboratory evaluations, vital signs, ECG or physical observations.

Conclusions
Anastrozole exposure following a single oral dose of either a 1 mg marketed tablet (ARIMIDEX) or 1 mg dispersible tablets can be considered to be similar on the basis of comparison of anastrozole AUC and C_{max} in healthy adult volunteers. There were no new safety issues identified during this study and both the study drugs are well tolerated

4.2.3 Clinical Study D6873C000047

Title: An Open-label Non-comparative, Multi-centre Study To Assess The Efficacy And Safety Of Bicalutamide When Used In Combination With Anastrozole For The Treatment Of Gonadotropin-independent Precocious Puberty In Boys With Testotoxicosis ((BATT – bicalutamide anastrozole treatment for testotoxicosis)

Investigator and Study Center(s)

Patients were enrolled at 14 centres in 6 countries but were allocated to treatment in only 9 centres in 3 countries as follows: India (2 centres), United Kingdom (1 centre) and United States (6 centres). Two patients who were allocated treatment transferred from one US centre to a new US centre during the study and so patients were treated at 10 centres in total.

STUDY SPONSOR:

AstraZeneca
Alderley Park
Macclesfield
Cheshire, SK10 4TG, UK

BIOANALYTICAL ANALYSIS:

Analysis of pharmacokinetic samples
AstraZeneca
Alderley Park
Macclesfield
Cheshire, SK10 4TG, UK

STUDY PERIOD: 02 September 2004 (First volunteer enrolled) – 10 November 2004 (Last volunteer completed)

Objective:
The primary objective of this study was to assess the efficacy of bicalutamide when used in combination with anastrozole in terms of a reduction in growth rate after 12 months treatment of precocious puberty in boys with testotoxicosis.

The secondary objectives of the study were:

1) To investigate the efficacy of bicalutamide when used in combination with anastrozole in terms of:
    - a reduction in growth rate after 6 months treatment
    - a reduction in bone age maturation rate after 6 and 12 months treatment
    - normalization of growth rate
    - increase in predicted adult height (PAH) after 12 months treatment
    - reduction of signs and symptoms of virilization

2) To assess the safety and tolerability of bicalutamide when used in combination with anastrozole in terms of:
    - gynaecomastia and breast pain adverse events (AEs)
    - all other AEs, withdrawals and laboratory data.

3) To assess pharmacokinetic and pharmacodynamic parameters in achieving an optimal dose of study treatment.

Study Population:
A total of 14 male subjects with a diagnosis of testotoxicosis were enrolled in this study. The age of the subject at the time of enrollment ranged from 2 to 9 years. Their growth rates ranged from 4.15 to 18.92 cm/year (-1.99 to 2.97 SD above the normal rate for boys of the same age). Their bone ages of these subjects ranged from 4.77 to 13.63 years and their ratio of bone age to chronological age at baseline ranged from 1.29 to 3.01. The boys average testicular volume ranged from 3 to 11 mL, their pubic hair stages ranged from 1 to 4 on the Tanner scale and their testes and scrotum development had reached Tanner stage 2 to 4. Eight patients had a male relative with a history of early sexual development. Six of the 14 patients had previously been treated for testotoxicosis.

Table 1: Demographics of the enrolled patients.

Demographic characteristic	Number(%) of patients N=14
Age (years)	
n	14
Mean	3.9
SD	1.9
Median	3.5
Minimum	2
Maximum	9
Age group (years)	
n	14
>=2 - <5	9 (64.29)
>=5 - <10	5 (35.71)
Sex n(%)	
n	14
Male	14 (100.00)
Race n(%)	
n	14
Caucasian	12 (85.71)
Black	1 (7.14)
Other	1 (7.14)
Ethnic group n(%)	
n	14
Hispanic/Latino	1 (7.14)
African-American	1 (7.14)
Asian	3 (21.43)
Not Applicable	9 (64.29)

Study Design and Dose Regimen:
This was a multi-centre, open-label, non-comparative, observational phase II study to investigate the efficacy and safety of bicalutamide in combination with anastrozole for the treatment of testotoxicosis (familial male-limited precocious puberty). Patients were to be given study drugs (bicalutamide and anastrozole) daily for 12 months through individual titration to optimal doses of each drug independently and to be followed up at 3 monthly intervals at 3, 6, 9 and 12 months. After 12 months, all study patients (on or off treatment) were to be followed up annually until they attained their final adult height.

Arimidex (anastrozole) and Casodex (bicalutamide) orodispersible tablets were given orally once daily. The dosing of anastrozole and bicalutamide was independently tailored for each patient. Anastrozole and bicalutamide dose revisions were driven by serum estradiol and plasma bicalutamide concentrations, respectively. Doses of each drug were iteratively adjusted until a dose was reached that gave steady-state trough serum estradiol concentrations of <10 pmol/L (2.7 pg/mL) and R-bicalutamide (the active isomer of bicalutamide) trough plasma concentrations within the range 5-15 µg/mL. Anastrozole

dose escalation was stopped once a plasma anastrozole concentration of 350 ng/mL or a daily dose of 8 mg was reached.

Rationale for dose selection: Clinical data in adults with prostrate cancer have shown that CASODEX at a dose of 50 mg daily provides effective androgen receptor blockade as demonstrated by significant falls in prostate specific antigen (PSA) and improvement in clinical outcome occurring with Casodex usage at this dose. The plasma mean plasma concentration of bicalutamide after daily 50 mg single dose administration to adult males was observed to be 10 μg/mL, with a typical range of 5- 15 μg/mL. Since the exposure of 5-15 μg/mL is shown to be effective in having anti-androgenic effect in adults this exposure window was also chosen for pediatric patients with testotoxicosis. The starting dose of Casodex was 12.5 mg, with dose being titrated up to 150 mg based on observed plasma R-bicalutamide concentrations on Day 21 or later.

Boys with testotoxicosis were expected to have elevated serum estradiol concentrations because of the conversion of excess testosterone to estradiol. Dose selection and titration of Arimidex is based on the plasma estradiol concentrations. The plasma oestradiol concentrations were kept below10 pmol/L as this represents the plasma estradiol concentration in boys at early puberty. Although the serum estradiol concentrations were not elevated at enrollment, patients were started on lowest dose of Anastrozole (0.5 mg).

Bioanalytical Analysis: Quantitative assessment of anastrozole and R-bicalutamide concentration in human plasma was done employing a validated HPLC-MS/MS method (b) (4) R-Bicalutamide plasma samples were extracted using a liquid-liquid extraction procedure. Extracted samples were analyzed by chiral HPLC with an (b) (4) mass spectrometer. The calibration curves were analyzed at R-bicalutamide concentrations of 40, 80, 200, 1000, 5000, 9000, 10000 ng/mL. The lower limit of quantification (LOQ) for bicalutamide was 40 ng/mL. Between-batch precision (%CV) results for QC samples prepared at low, medium, and high QC concentrations of R-bicalutamide was between 5.9 to 9.8 % and accuracy ranged from 99.5 % to 101.9 %. A between-batch precision (% CV) result of the calibration standards of R-bicalutamide was between 4.5 to 10.7 % and accuracy ranged from 98.7 to 102%.

Anastrozole plasma samples were extracted using a (b) (4) . Extracted samples were analyzed by HPLC with an (b) (4) mass spectrometer. The calibration curves were analyzed at anastrozole concentrations of 1, 2, 5, 10, 50, 100, 250 and 500 ng/mL. The lower limit of quantification (LOQ) for bicalutamide was 1 ng/mL. Between-batch precision (%CV) results for QC samples prepared at low, medium, and high QC concentrations of anastrozole was between 6.1to 8.6 % and accuracy ranged from 99.1 % to 103.2 %. A between-batch precision (% CV) result of the calibration standards of anastrozole was between 2.7 to 9.4 % and accuracy ranged from 98.1 to 101.5%.

Pharmacokinetic Results: The mean trough plasma concentrations for R-bicalutamide remained in the pre-specified concentration range of 5- 15 µg/mL. For the 13 patients who were stabilised for bicalutamide, (i.e., attained their potential therapeutic dose), 8 patients were on 50 mg, 4 patients on 100 mg, 1 patient on 12.5 mg bicalutamide. The final stabilised dose for anastrozole was 0.5 mg for 10 patients and 1 mg for 3 patients.

Table 1: Summary of plasma concentration of R-bicalutamide (µg/mL) in pediatric patients.

Summary statistic	Day 56	Day 84	Day 112	Day 140	Month 12
N	13	13	13	12	13
Geometric mean	7.01	7.80	8.01	8.11	8.51
CV (%)	34.7	22.1	40.4	28.8	31.7
Median	6.97	7.51	7.39	8.20	8.46
Min	(b) (4)				
Max					

Table 2: Summary of plasma concentration of Anastrozole (ng/mL) in pediatric patients.

Summary statistic	Day 56	Day 84	Day 112	Day 140	Month 12
N	11	11	11	8	13
Geometric mean	22.13	17.99	15.82	25.70	18.40
CV (%)	68.7	74.5	64.2	75.1	65.7
Median	19.8	15.5	13.6	26.3	13.9
Min	(b) (4)				
Max					

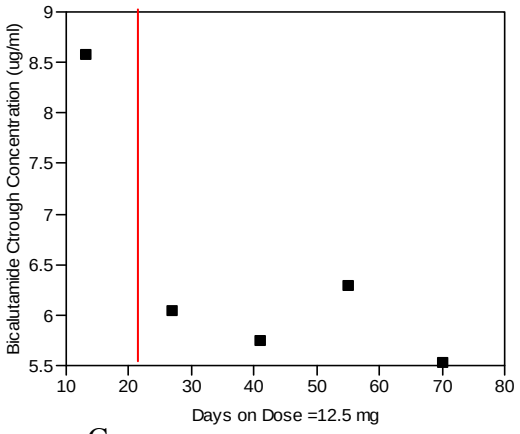
Reviewer's Comments

1) In Adults, once daily dosing of 50 mg Casodex resulted in mean steady state concentration of 8.939 ± 3.5 µg/mL. The steady state C_{trough} plasma concentration in pediatric patients can be considered comparable to the mean steady state plasma concentrations that were observed in adults (Table 1).
2) In Caucasian postmenopausal women, once daily dosing of 1 mg Arimidex resulted in mean steady state trough concentration of 25.7 ng/mL. In pediatric patients the mean steady state C_{trough} plasma concentration was found to be 18.4 ng/mL at Month 12 (Table 2). These differences in trough concentration between adults and pediatric patients can be explained partly because they were targeted to achieve different estradiol concentrations (i.e., <10 pmol/L for pediatric population and <3.7 pmol/L in adults). In addition, in pediatric patient the doses were titrated to keep the estradiol concentration below pre-pubertal estradiol concentration while the adult data came from 1 mg administration.

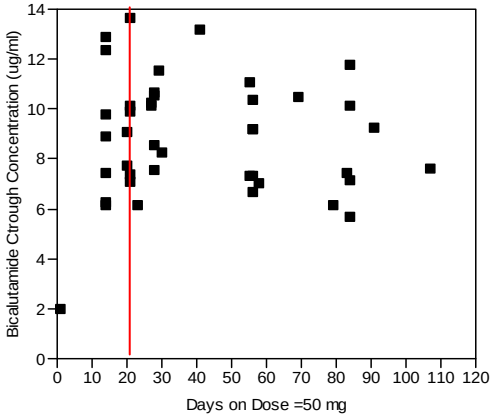
3) The steady-state R-bicalutamide and anastrozole concentrations appeared to be attained in the majority of patients by Day 21 and Day 8, respectively, following once a day dosing (Fig. 1).

Figure 1: Steady State C_{trough} concentration at various doses of bicalutamide, A (12.5 mg), B (50 mg), C (100 mg) and anastrozole D (0.5 mg) and E (1.0 mg). Red line represents Day 21 in figures A, B, C and Day 8 in figures D and E.

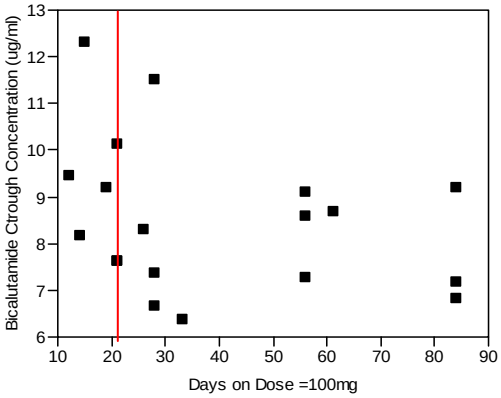
A.



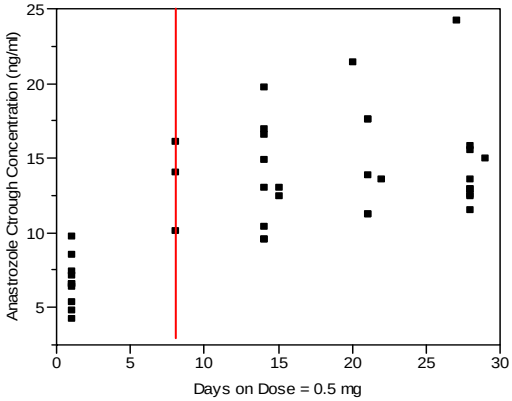
B.



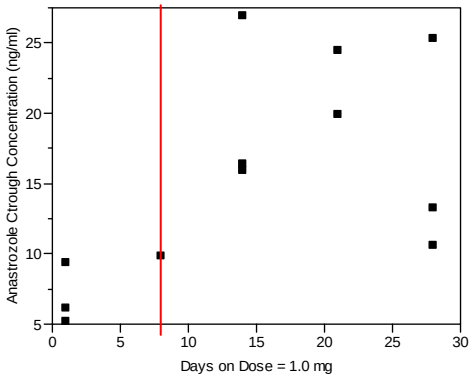
C.



D

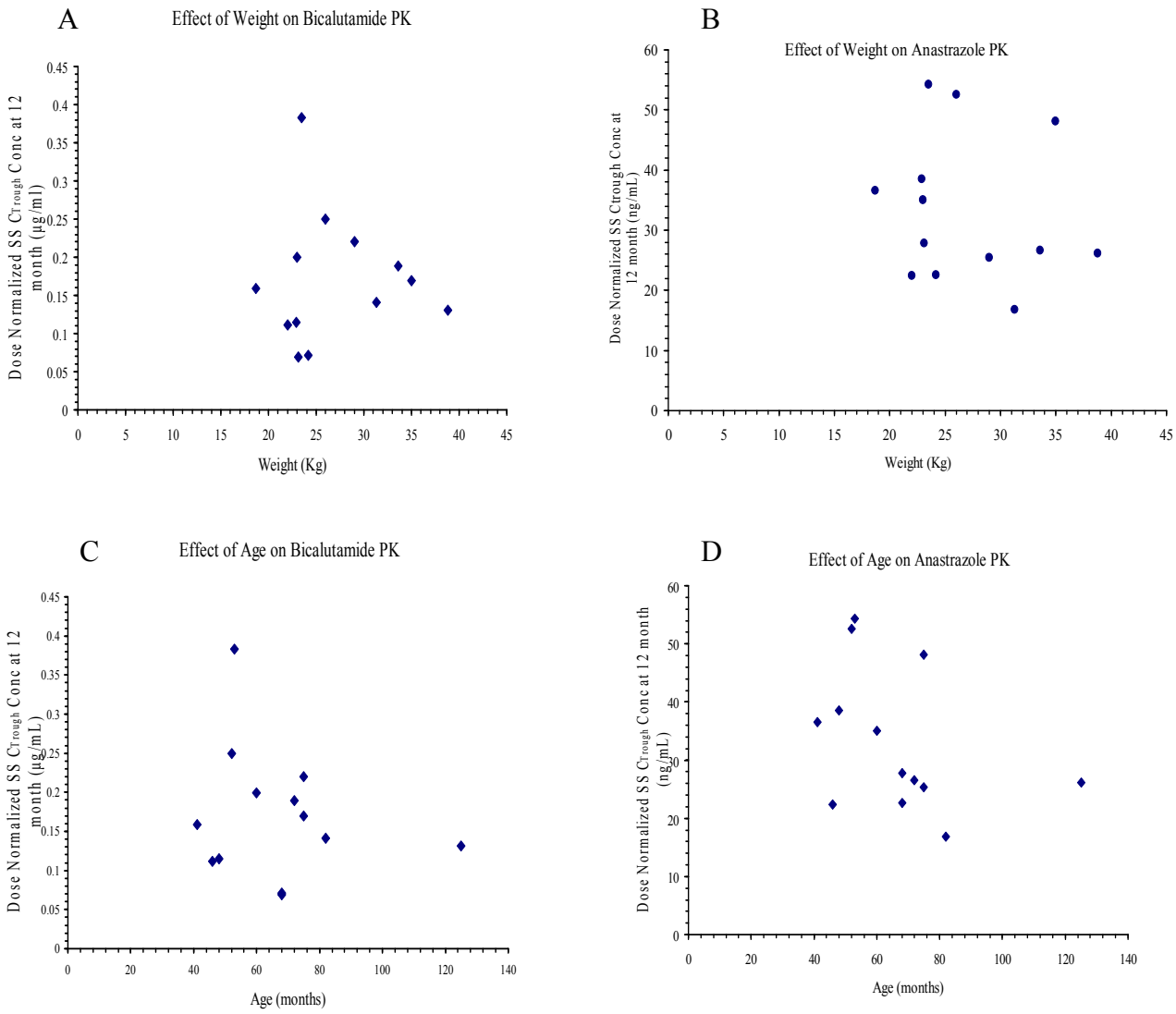


E.



Due to the limited number of sample size no definitive conclusion on the effect of age and body weight on steady state C_{trough} concentrations of bicalutamide and anastrozole can be drawn (Fig. 2). However, in previous review of NDA 22-214 by Dr. Manoj Khurana, it was found that body weight is an important covariate for the determination of clearance and volume of distribution of anastrozole in pediatric patients.

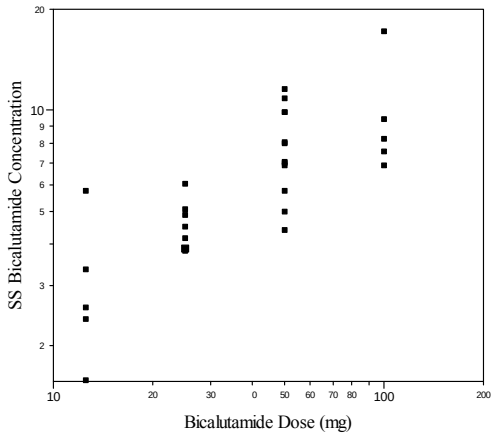
Figure 2: Effect of weight on dose normalized steady state C_{trough} concentration of bicalutamide (A) and anastrozole (B). Effect of age on dose normalized steady state C_{trough} concentration of bicalutamide (C) and anastrozole (D).



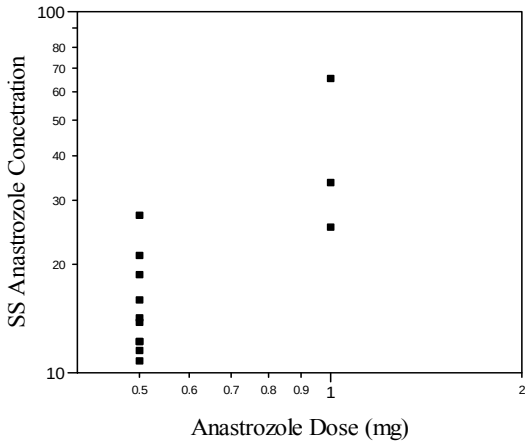
Dose Proportionality: Sponsor claims that the (b) (4)

Figure 3: Steady State C_{trough} Concentration of bicalutamide (A) and anastrozole (B) at different doses.

A



B



Reviewer's Comment: This reviewer does not agree with the sponsor's claim of (b) (4) in their proposed labeling for the following reasons:

1) Proportional increases of trough plasma concentrations for R-bicalutamide and anastrozole do not add any insight in describing the pharmacokinetic property of the drugs.

2) The number of subjects evaluated at each dose is quite limited and unbalanced. In bicalutamide dose proportionality evaluation there were 5 subjects at 12.5 mg, 7 subjects at 25 mg, 12 subjects at 50 mg and 5 subjects at 100mg. In case of Anastrozole there were only 3 patients on 1mg and 10 patients on 0.5 mg

3) No standard evaluation of the dose-proportionality or dose-linearity of the pharmacokinetics of bicalutamide and anastrozole has been performed in pediatric subjects by the sponsor. When this reviewer performed the dose proportionality evaluation of entire data set available, despite the limited data, dose proportionality was not demonstrated (Table-3).
The power model used for the dose proportionality assessment:
$Log_e(parameter) = a + b*Log_e(dose) + error$ where, a is the intercept and b is the slope.

-

Table 3: Dose proportionality evaluation of Bicalutamide and Anastrozole

Drug	Parameter	Slope	90%-CI
Bicalutamide	C_{trough}	0.60	0.45-0.75
Anastrozole	C_{trough}	1.73	1.23-2.24

Efficacy Analysis: The primary efficacy variable in this application is change in growth rate (cm/year) after 12 months of treatment with bicalutamide and anastrozole. Efficacy analysis was done by measuring the height of the patients at ≥ 6 months pre-study period, at baseline and after 12 months of treatment. Growth rate at baseline is derived from retrospective data as follows:
GR_B (cm/year) = [height (cm) at baseline – height (cm) at ≥ 6 months pre-study period]/ time interval in years between baseline and pre-study assessment. Change in growth rate after 12 months of the treatment can be obtained by difference in the growth after 12 months (GR_{12} cm/year) and growth rate at baseline (GR_B cm/year).

Several other secondary variables such as rate of change of bone age, bone age to chronological age ratio, normalization of growth rate after 3, 6, 9 and 12 months, change in predicted adult height, change in testicular volume and change in tanner staging were also assessed. Radiographs were used to assess the bone age. Normalization of growth rate was assessed by checking whether the patient's height was within 5^{th} and 95^{th} percentiles compared to the reference population at months 3, 6, 9 and 12 months. Predicted adult height was calculated from the bone age using the Bayley and Pinneau Method. Testicular volume of both testes was measured using either ultrasound or an orchidometer. Development of secondary sexual characteristics was recorded by assigning tanner stages to external genitalia and pubic hair distribution. The number of acne lesions on the face and body was counted by visual inspection and the change in acne lesions and counts were studied at 3, 6 and 12 months. The children's aggression scale - parent version (CAS-P) is a questionnaire designed to assess severity, frequency, pervasiveness and diversity of aggressive, as distinct from nonaggressive, disruptive behaviors. The CAS-P questionnaire was completed at baseline, 3, 6, and 12 months.

Efficacy Results:
The primary efficacy endpoint of this study was to assess the efficacy of bicalutamide when used in combination with anastrozole in terms of the change in the growth rate after 12 months of treatment in boys with testotoxicosis. The clinical efficacy trial failed to meet the primary efficacy endpoint. Please see the review by the medical officer, Dr. Dragos Roman for details.

No exposure response relationship can be drawn from this study.

Reviewer's Comment:

1) Exposure-response or dose-response relationship can not be drawn in this study because of the fact that the number of subject evaluated in this study was very limited to make any meaningful interpretation.

2) This study failed to show a statistically significant change in growth rate at 12 months. However, there are some trends suggesting that the effects are greater for the patients with higher growth rate at baseline. Since the number of subjects in, this study was small, this phenomenon can not be ascertained with confidence.

3) There are also some indications that the patients who are previously treated for testotoxicosis showed a lesser effect as compared to patients who do not receive any therapy before. Due to limited sample size, this phenomenon can not be confirmed.

4.3 Pediatric Written Request

Written Request Amendment #6 (pgs 56-64) have been removed. See the Pediatric Therapeutics section of FDA.gov for a copy.

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/s/

Ritesh Jain
12/15/2008 01:11:44 PM
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Sally Choe
12/15/2008 01:23:50 PM
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