CLINICAL REVIEW

Application Type	NDA
Submission Number	22-310
Submission Code	S-001
Letter Date	June 25, 2008
Stamp Date	June 25, 2008
PDUFA Goal Date	December 25, 2008
Reviewer Name	Dragos Roman
Review Completion Date	December 15, 2008
Established Name	Bicalutamide
(Proposed) Trade Name	Casodex
Therapeutic Class	Antiandrogen
Applicant	AstraZeneca Pharmaceuticals
Priority Designation	P
Formulation	oral
Dosing Regimen	
Indication	treatment of gonadotropin-independent precocious puberty in familial male-limited precocious puberty (testotoxicosis)
Intended Population	boys with precocious puberty due to testotoxicosis

Table of Contents

1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

Given that the bicalutamide/anastrozole regimen evaluated in this NDA in boys with familial male-limited precocious puberty ("testotoxicosis") failed to demonstrate efficacy, it should not be approved in this patient population.

1.2 Recommendation on Postmarketing Actions

1.2.1 Risk Management Activity

None.

1.2.2 Required Phase 4 Commitments

None.

1.2.3 Other Phase 4 Requests

The applicant has committed to submit in Annual Reports adverse events collected in the extension phase of the clinical trial D6873C00047.

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

On April 17, 2003, the Agency issued to AstraZeneca a Pediatric Written Request (WR) for the study of bicalutamide (an antiandrogen) and anastrozole (an aromatase inhibitor) in patients with testotoxicosis. The rationale for this regimen is that androgen receptor blockade with bicalutamide and reduction of androgen aromatization to estrogens with anastrozole would suppress the manifestations of precocious puberty, such as virilization and accelerated linear growth, universally observed in patients with testotoxicosis. The safety and efficacy of bicalutamide and anastrozole were evaluated in Study D6873C00047, a one-year, open-label, single-arm clinical trial conducted in 14 boys with testotoxicosis[1]. Although at first inspection the number of patients treated in this clinical trial (14 enrolled, 13 completers) appears

[1] The WR included two additional studies conducted in healthy adult volunteers that established bioequivalence between two different pediatric and adult formulations of bicalutamide (Study D6873C00003) and anastrozole (Study D6873C00002).

remarkably small, it should be recognized that testotoxicosis is a condition of exceedingly low prevalence, estimated at 1-9 boys per 1,000,000. Placed in the historical context of clinical studies conducted to date in boys with testotoxicosis, this study is numerically the largest (other case series reported to date do not exceed 10 patients) but not the longest, as several published studies report efficacy data for extended periods of time (including even final height).

For the patients enrolled in Study D6873C00047 the diagnosis of testotoxicosis was based on a combination of clinical and biochemical criteria. Both treatment-naïve and previously-treated patients were enrolled[2]. Bicalutamide was titrated with the goal of selecting a dose that resulted in serum drug concentrations within the range that had been associated with androgen receptor blockade in adult studies. The selected anastrozole dose was also the result of drug titration, with the goal of achieving estrogen suppression, as well as anastrozole serum levels within a range that had been shown to be safe in adults. Efficacy analyses focused on endpoints that measured changes in clinical signs and symptoms of precocious puberty, such as linear growth acceleration, bone age advancement, acne lesions, aggressive behavior, as well as biochemical changes of sex hormone serum concentrations. Safety assessments were standard.

1.3.2 Efficacy

As indicated by the primary efficacy analysis, the regimen of bicalutamide and anastrozole evaluated in Study D6873C00047 was not efficacious in reducing the accelerated growth rate associated with androgen excess in this group of 14 patients with testotoxicosis. The mean growth velocity decreased only minimally after 12 months of treatment (1.6 cm) and this change was not statistically significant (p=0.278)[3]. Treatment-naïve patients responded somewhat better (2.84 cm reduction in growth velocity) and, although the change failed to reach statistical significance, it showed a favorable trend (p=0.053) [4]; however, even this treatment effect is of limited clinical significance, in particular when viewed in the context of efficacy data published to date with other regimens. Specifically, the changes of growth rate observed in this clinical trial were inferior to those reported in an NIH study of 10 patients treated with another antiandrogen/aromatase inhibitor combination (spironolactone/testolactone) or in another case series of 5 patients treated with ketoconazole. In these previously published reports growth velocity reduction was both statistically significant and clinically meaningful (approximately 50% reduction in baseline growth velocity after one year of treatment). On a positive note, the bicalutamide/anastrozole combination appeared to stabilize and even reduce some of the manifestations of virilization, in that it maintained the same Tanner stage in most patients for the duration of the trial and appeared to reduce the aggressive behavior associated with androgen

[2] Seven treatment-naïve patients and 6 previously-treated patients completed the trial.
[3] For the 13 completers, the mean growth rate was 10.81 cm/year at baseline and it changed by Month 12 to 9.19 cm/year. When growth rate was expressed as a SD score, the mean change from baseline of -0.07 SD was not statistically significant either (p=0.882).
[4] The change in growth rate expressed as a SD score (-0.74) did not indicate as strong a trend, however (p=0.139). For the previously treated group, the observations were numerically very similar to those made for the entire cohort.

excess[5]. All the above listed efficacy-related statements have to be considered within the restrictive evidentiary boundaries imposed by a study that did not have a control arm.

1.3.3 Safety

No distinctive safety signals were identified in this one-year study of 14 patients. There were no deaths, no serious adverse events and no trial discontinuations due to adverse events (one patient was lost for follow-up).

Although almost all patients[6] experienced at least one adverse event, most adverse events were either mild or moderate in intensity (the only two AEs severe in intensity were gynecomastia and furuncle). The most frequently reported adverse events were gynecomastia (50%), central precocious puberty (42.9%[7]), vomiting (35.7%), pyrexia and headache (3% each). Adverse events that occurred in 2% of patients were infectious croup, gastroenteritis, nasopharyngitis, tonsillitis, upper respiratory tract infection, abdominal pain, nausea, acne, and conjunctivitis.

Adverse events that were judged to be possibly related to either anastrozole or bicalutamide occurred in 6 (42.9%) patients. Headache (1 patient or 7.1%) was the only adverse event that was considered possibly related to anastrozole. All others were considered possibly related to bicalutamide: gynecomastia (6 patients or 42.9%), central precocious puberty (2 patients or 14.3%)[8], breast tenderness (14.3%), breast pain (1 patient or 7.1%), asthenia (7.1%), increased ALT (7.1%), increased AST[9] (7.1%), and musculoskeletal chest pain (7.1%). All the events of "breast tenderness" or "breast pain" occurred in patients who also experienced gynecomastia.

Absence of a control group makes certain attribution of adverse events to any specific treatment extremely difficult. Given this major limitation, it is reasonable to assert that most of the adverse events observed in the trial are either due to common infectious diseases of childhood (the largest number of adverse events in this trial), or are coincidental with the bicalutamide/anastrozole treatment. This statement is based on the fact that many of these adverse events are not secondary to any known mechanisms of action of either Casodex or Arimidex, as currently described in their respective labels. Given the known pharmacodynamic effects of the bicalutamide/anastrozole combination, gynecomastia, breast tenderness, and breast pain are adverse events likely to be drug-related. Another one is central precocious puberty, an event that is expected in association with persistent sex steroid exposure.

[5] In addition, it decreased the number of acne lesions in the few patients who had such lesions at baseline (and it did not allow the development of new acne lesions other then occasionally in patients who did not have such manifestations at baseline).
[6] 13/14 patients or 92.9%.
[7] Changed to 50% following the 4-month safety update..
[8] Changed to 3(21.4%) following the 4-month safety update.
[9] ALT and AST elevations were mild and resolved despite continuation of the treatment.

1.3.4 Dosing Regimen and Administration

Study D6873C00047 did not establish an efficacious dose regimen of bicalutamide/anastrozole combination. The specific dose regimen evaluated failed despite successful titration of bicalutamide to serum concentrations within a range known to induce androgen blockade in adult males with prostate cancer, and despite suppressing serum estrogen to levels below the limit of detectability of the assay utilized in this study. These results are puzzling given that a similar regimen of a presumably less potent antiandrogen and aromatase inhibitor was quite successful both short-term and long-term (Lescheck et al.), as was the case of a recently published report of two patients treated with the same bicalutamide/anastrozole regimen for 44 months and 17 months, respectively (Kreher NC et al.). Whether bicalutamide titration to different serum concentrations or some other modification of the current regimen would improve efficacy, it remains to be explored in further investigations.

1.3.5 Drug-Drug Interactions

Due to the small size of the dataset no explorations for drug-disease interactions were done.

1.3.6 Special Populations

No studies were conducted in patients with renal or hepatic failure.

2 INTRODUCTION AND BACKGROUND

2.1 Product Information

Bicalutamide is a non-steroidal antiandrogen that competitively inhibits the action of endogenous androgens by binding to cytosol androgen receptors in the target tissues; it is approved under the brand name Casodex for the treatment of metastatic carcinoma of the prostate in association with a luteinizing hormone-releasing hormone (LHRH) analogue. Bicalutamide is a racemic mixture of 2 enantiomers (R- and S- bicalutamide). The (R)-enantiomer is responsible for the anti-androgenic activity and, at steady-state, it accounts for 99% of the total circulating enantiomers.

Anastrozole is a non-steroidal aromatase inhibitor that suppresses the conversion of endogenous androgen to estrogen and thus lowers the serum estradiol concentrations; it is approved for the treatment of breast cancer under the brand name Arimidex.

2.2 Currently Available Treatment for Indications

There is no approved treatment regimen for the indication of familial male-limited precocious puberty, also referred to as testotoxicosis. Several pharmacological interventions have been used off label to control the manifestations of androgen excess seen in testotoxicosis. As illustrated in the following table[10], some of them have been administered successfully both short- and long-term. It is worth mentioning that the combination of an androgen receptor blocker and an aromatase inhibitor in patients with testotoxicosis has already been used successfully in the NIH study of Leschek et al[11].

[10] From Reiter EO and Norjavaara E: Testotoxicosis: Current viewpoint. Pediatric Endocrinology Reviews, (30 2, 7786, 2005.

[11] Leschek et al. Six-year results of spironolactone and testolactone treatment of familial male-limited precocious puberty with addition of deslorelin after central puberty onset. J Clin Endocrinol Metab 84: 175-178, 1999.

Table 4: Treatment approaches used in testotoxicosis (54)

Treatment	Mean decrease in height velocity over first year (cm)	Mean improvement in final height vs predicted pre-treatment height (cm)	Potential disadvantages
Ketoconazole	6.066	+8.0, p<0.01 (66)	Hepatotoxicity Rash Gastrointestinal disorders Worsening of gynecomastia
MPA	≤3.067	N/A	Cushingoid side effects
CPA	Single case, data not given (64)	N/A	Suppression of plasma cortisol Adrenal insufficiency
Spironolactone	5.8, p=ns (68)	N/A	Weak anti-androgen Metabolic acidosis Hyperkalemia Hyponatremia
Testolactone	7.1, p<0.05 (68)	N/A	Weak aromatase inhibitor
Spironolactone and testolactone	8.2, p<0.0569	+12.9 (after 6 years of treatment), p<0.005 (70)	Weak aromatase inhibitor and weak anti-androgen Spironolactone adverse events

CPA, cyproterone acetate; MPA, medroxyprogesterone acetate

2.3 Availability of Proposed Active Ingredient in the United States

Both bicalutamide and anastrozole are approved and available drug products in the US (refer to Section 2.1).

2.4 Important Issues With Pharmacologically Related Products

Liver toxicity has been a safety concern with some of the androgen receptor blockers (e.g. flutamide). According to the current Casodex label, liver injury has been reported in adults during the postmarketing phase. Therefore, periodic measurement of serum transaminases during Casodex treatment, in particular during the first months of treatment, is recommended.

One major theoretical concern regarding the use of aromatase inhibitors in children is the effect that estrogen suppression may have on bone mineral density and bone mass during growth, which is a time of active bone development.

2.5 Presubmission Regulatory Activity

The Pediatric Written Request for the study of bicalutamide and anastrozole in patients with testotoxicosis was issued on April 17, 2003, and was amended 6 times following multiple written communications and teleconferences with the applicant[12].

2.6 Other Relevant Background Information

None.

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC (and Product Microbiology, if Applicable)

Both bicalutamide and anastrozole are approved drug products.

3.2 Animal Pharmacology/Toxicology

Both bicalutamide and anastrozole are approved drug products. In response to this Written Request the applicant has conducted a 90-day oral toxicity study in juvenile male rats with assessment and recovery of reproductive function (Study 0514GR). This study has been reviewed by the Agency's pharmacology and toxicology staff prior to the initiation of the clinical trial and was the basis for supporting the pediatric doses selected.

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

The sources of clinical data are constituted primarily by the clinical study reports detailed in this NDA (refer to Section 4.2, below) and subsequent information requests issued during the review process. Published medical literature has been used for placing the results of the submitted clinical studies in scientific and clinical context.

[12] The dates of the amendments were as follows: February 13, 2004 for Amendment #1, May 7, 2004 for Amendment #2, October 1, 2004 for Amendment #3, April 8, 2005 for Amendment #4, February 7, 2008 for Amendment #5, and May 8, 2008 for Amendment #6.

4.2 Tables of Clinical Studies

Table 1 Listing of clinical studies

Type of study	Study	Location of study report	Objectives of the study	Study design and type of control	Test product; dosage regimen; route of administration	Number of subjects	Diagnosis of patients	Duration of treatment	Study status; type of report
Bio-availability	0003	Module 5.3.1.1	Relative bioavailability	Open label crossover	Bicalutamide 50 mg marketed tablet and 2 x 25 mg dispersible tablets; oral	30	Healthy adult male volunteers	Single dose	Complete; Full
Bio-availability	0002	Module 5.3.1.1	Relative bioavailability	Open label crossover	Anastrozole 1 mg marketed tablet and 1 mg dispersible tablet; oral	28	Healthy adult male volunteers	Single dose	Complete; Full
Efficacy	0047	Module 5.3.5.2	Safety and efficacy	Open label	Bicalutamide dispersible tablet; o.d.; oral and anastrozole dispersible tablet; o.d.; oral. Doses tailored for each patient	14 treated	Prepubertal boys with testotoxicosis	12 months	Complete; Full

o.d. Once daily.

4.3 Review Strategy

This review has focused on the efficacy and safety data of Study D6873C00047, the only clinical study of this NDA conducted in the population of interest (boys with testotoxicosis).

4.4 Data Quality and Integrity

The data presented appeared complete and the datasets interpretable. There were no inconsistencies between different sections of the review. Overall, this submission was acceptable and reviewable.

4.5 Compliance with Good Clinical Practices

The applicant states that "[t]he study was performed in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with ICH/Good Clinical Practice and applicable regulatory requirements and the AstraZeneca policy on Bioethics." The applicant also indicates that IRB or IEC committee approval was thought for the clinical protocol and any subsequent changes, and that patient/guardian consent was obtained before conducting any study procedure.

4.6 Financial Disclosures

The applicant submitted a signed FDA Form 3454 certifying that (1) AstraZeneca has not entered into any financial arrangement with the listed investigators whereby the value of the compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a), (2) none of the investigators had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.(b), and (3) no listed investigator was the recipient of significant payments of other sorts as defined in CFR 54.2 (f).

5 CLINICAL PHARMACOLOGY

5.1 Pharmacokinetics

Pharmacokinetic (PK) information following oral administration of bicalutamide and/or anastrozole was collected in all three studies included in this supplement (refer to Section 4.2 for study description). Studies # 1 and # 2 of the WR were bioequivalence studies conducted in healthy adult volunteers, while Study # 3 (Study D6873C00047) was a clinical study conducted in children with testotoxicosis). Studies # 1 and # 2 demonstrated that two 25-mg dispersible tablets of bicalutamide are bioequivalent to the marketed 50-mg bicalutamide tablet (Study D6873C00003 or Study # 1 of the WR) and that a dispersible 1-mg tablet of anastrozole is bioequivalent to the marketed 1-mg anastrozole tablet (Study D6873C00002 or Study # 2 of the WR). For a critical review of these two studies refer to the clinical pharmacology review.

Due to the rarity of testotoxicosis, the applicant did not conduct a PK pediatric study but rather collected pediatric PK information in the clinical study D6873C00047 and used such data to guide further dosing. An Advisory Panel evaluated the PK data obtained from each cohort of 4 patients and made recommendations as to whether the bicalutamide and/or anastrozole dose should be escalated. Thus, following analysis of the PK information generated from the first group of 4 patients, the panel recommended that the starting bicalutamide daily dose be increased from 12.5 mg to 25 mg while holding the starting daily anastrozole dose at 0.5 mg. Following the next 4 patients, the starting bicalutamide dose was further increased to 50 mg and the anastrozole dose was maintained at 0.5 mg/day. Following the third 4-patient cohort it was recommended that the latter regimen be maintained for the remainder of the trial. In this trial both bicalutamide and anastrozole were titrated to goal. For anastrozole, the goal was to reach a steady-state dose that suppressed the serum estradiol concentration to <10 pmol/L or 2.7 pg/mL. As already stated, the starting dose of anastrozole was 0.5 mg daily[13]; the planned ascending daily doses at the beginning of the trial were 0.5 mg, 1 mg, 2 mg, 4 mg, and 8 mg. The anastrozole doses reached at the end of the trial were 0.5 mg (10 patients) and 1 mg (4 patients).

[13] Anastrozole dosing was initially started 2 weeks before bicalutamide dosing, in case the starting dose of 0.5 mg proved insufficient to reduce estradiol level and needed to be increased to 1 mg. However, contrary to expectations, the serum estradiol concentrations were low at baseline and on treatment. Subsequently the initial 2-week period of anastrozole alone was discontinued.

As previously indicated, bicalutamide was initiated at a dose of 12.5 mg daily (approximately 0.5 mg/kg) and subsequently titrated toward a serum bicalutamide concentration of 5-15 µg/mL (this range is associated with androgen blockade in adults). The planned ascending daily doses of bicalutamide were 12.5 mg, 25 mg, 50 mg, 100 mg, and 150 mg. The final doses of bicalutamide were 12.5 mg (1 patient), 25 mg (1 patient), 50 mg (8 patients) and 100 mg (4 patients).

The pharmacokinetics of R-bicalutamide following the titration period are displayed in applicant's Table 31 (for most patients maintenance doses were reached at Day 56 of the trial). The descriptive statistics indicate a range of values around the titration goal of 5-15 µg/mL. For critical review of these data refer to the Clinical Pharmacology review.

Table 31 Summary of plasma concentrations (µg/mL) of R-bicalutamide: Safety set

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					

Patient E0003004 was lost to follow up before Day 56 and so did not provide data for this table. Patient E0003002 did not provide a sample at Day 140.
CV Coefficient of variation

The pharmacokinetics of anastrozole plasma concentrations are summarized in applicant's Table 32; in order to provide a similar format to that presented for bicalutamide, the data are presented from Day 56 onward. The trough anastrozole concentrations ranged from 15.82-25.70 ng/mL. For a critical review of these data refer to the clinical pharmacology review.

Table 32 Summary of plasma concentrations (ng/mL) of anastrozole: Safety set

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					

Patient E0003004 was lost to follow up before Day 56 and so did not provide data for this table. At Day 56 and Day 84 no sample was available for Patients E0054003 and E0054004. At Day 112 no sample was available for E0003002 and E0003003. At Day 140 no sample was available for Patients E0002001, E0003002, E0009001, E0054003 and E0054004.
CV Coefficient of variation

5.2 Pharmacodynamics

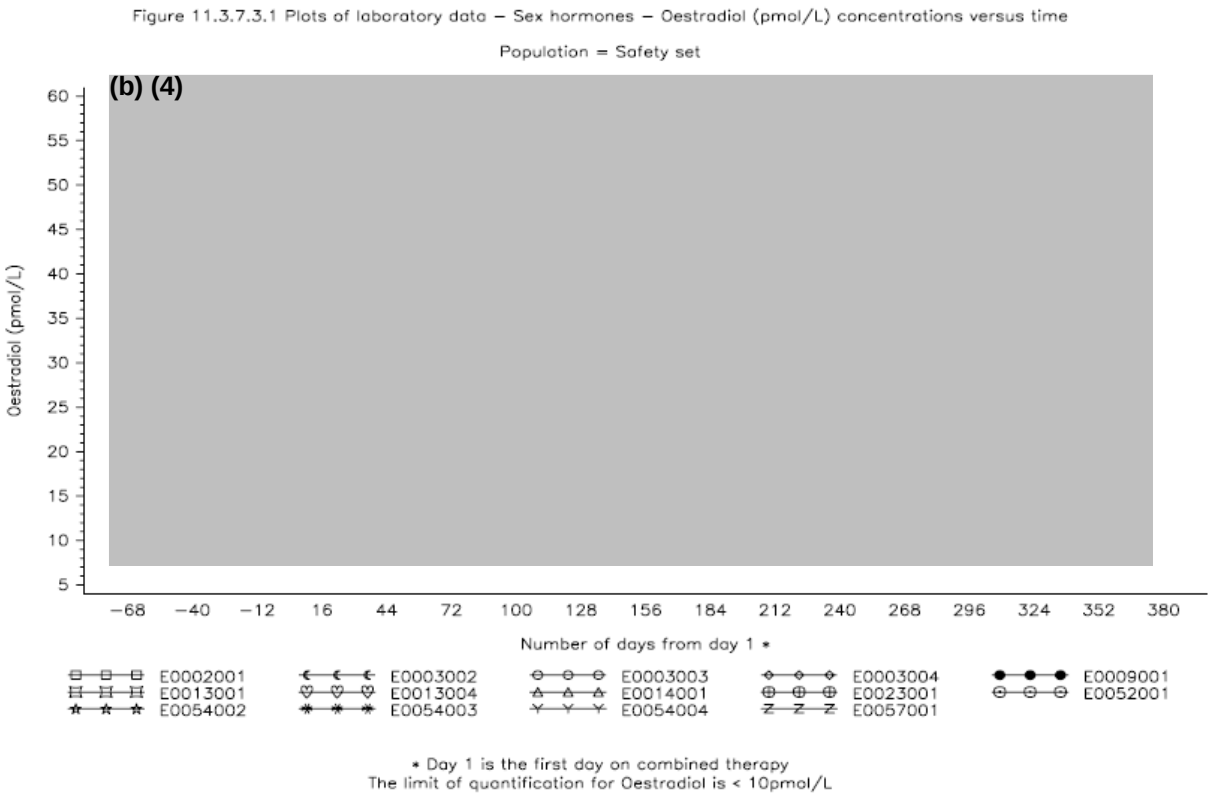
The most important pharmacodynamic endpoint evaluated in the clinical trial (Study D6873C00047) was the serum estradiol concentration, a direct measure of testosterone aromatization. Serum estradiol concentrations are summarized in applicant's Table 33, which includes data from Day 56 onward. Prior to study initiation it was anticipated that estrogen levels would be elevated on treatment due to anastrozole mediated suppression of testosterone aromatization. However, the estradiol serum concentrations observed remained close to the lower limit of quantification of the assay.

Table 33 Summary of serum oestradiol concentrations (pmol/L): Safety set

Summary statistic	Day 56	Day 84	Day 112	Day 140	Month 12
N	11	11	12	8	13
Mean	9.58	9.45	9.18	9.32	9.32
SD	1.33	0.88	0.00	0.39	0.51
Median	9.18	9.18	9.18	9.18	9.18
Min	(b) (4)				
Max					

Note that 9.18 pmol/L is the LOQ for the assay.

Individual plasma estrogen levels are illustrated in applicant's Figure 11.3.7.3. Although several estrogen peaks are present in this figure, it should be emphasized that they are measurement errors due to a problem with the solvent used for extraction (subsequent replacement of the solvent with another batch resulted in resolution of the issue.).



5.3 Exposure-Response Relationships

There were no formal analyses attempting to correlate the pharmacokinetic information with the clinical response. It is worth mentioning, however, that visual inspection of the serum bicalutamide concentration profile did not identify any differences in drug serum levels between patients who responded or those who did not respond to treatment.

6 INTEGRATED REVIEW OF EFFICACY

6.1 Indication

The proposed indication is the treatment of gonadotropin-independent precocious puberty in boys with familial male-limited precocious puberty (testotoxicosis).

6.1.1 Methods

6.1.2 General Discussion of Endpoints

Several efficacy endpoints evaluated in this study (e.g. growth rate, bone age/chronological age ratio) are standard efficacy assessments in clinical trials that evaluate agents that suppress or accelerate linear growth. Other endpoints (Tanner stage, testicular volume) are objective measurements that parallel those of clinical practice. Generally speaking, the efficacy endpoints selected for the clinical study were modeled after those of the NIH clinical study of Leschek et al.

6.1.3 Study Design

Study objectives

The objective of study D6873C00047 (Study # 3 of the WR) was to assess the efficacy of a bicalutamide/anastrozole combination regimen on clinical manifestations of precocious puberty (e.g. growth rate, rate of bone age maturation, predicted adult height, signs and symptoms of virilization) in boys with testotoxicosis. In addition, safety data as well as pharmacokinetic information for both bicalutamide and anastrozole were collected.

Study design

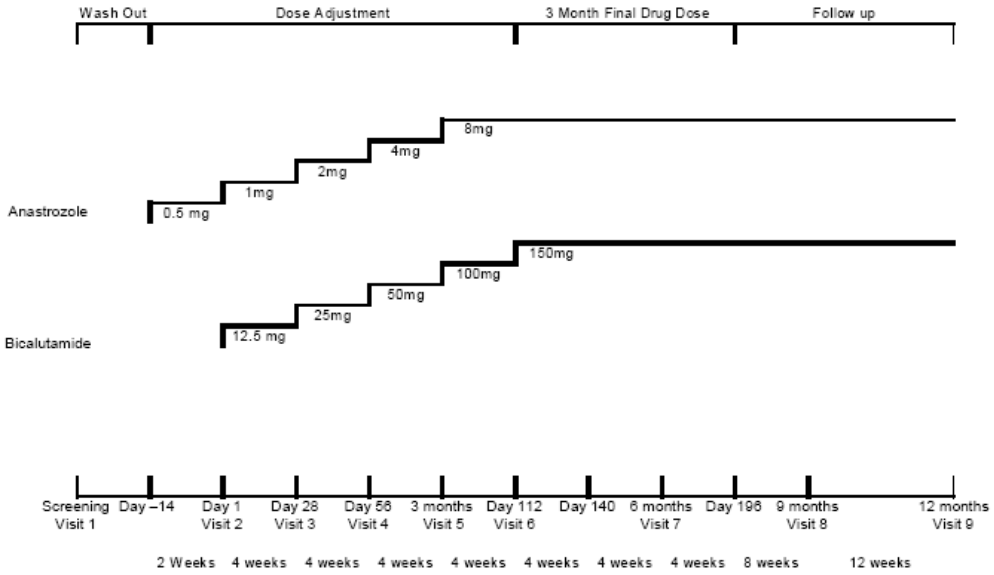
The study was a multi-center, open-label, single-arm, baseline-controlled, phase II clinical trial of 12 month duration. The study enrolled 14 patients in 10 centers in three countries: India (3 patients from 2 centers), United Kingdom (1 patient from 1 center) and United States (10 patients from 7 centers[14]). The first patient was enrolled on November 22, 2004 and the last patient completed the study on May 7, 2008. It is worth mentioning that testotoxicosis is an exceedingly rare condition and none of the largest case-series published to date studied more than 10 patients each.

As described already in Section 5.1, a PK study was nested in the clinical study. Pharmacokinetic data were reviewed by an Advisory Panel for every set of 4 patients and dose adjustments were made based on this information. Study medication was to be titrated in each patient based on a plasma drug level of 5-15 μg/mL for bicalutamide and a serum estradiol level <10 pmol/L (or 2.7 pg/mL) for anastrozole (anastrozole dose escalation was to be stopped once a plasma anastrozole concentration of 350 ng/mL or a daily dose of 8 mg was reached). Both drugs were administrated in ascending order (12.5 mg, 25 mg, 50 mg, 100 mg, 150 mg for bicalutamide and 0.5 mg, 1 mg, 2 mg, 4 mg, 8 mg for anastrozole. Both study drugs were to be taken orally, once-daily at the same time each day in the morning, preferably at breakfast. If central precocious puberty (CPP) developed during the study, treatment with a gonadotropin-releasing

[14] Two patients were transferred from an existing US center to a new US center during the study.

hormone (GnRH) agonist was to be initiated. Retrospective pre-study height data for ≥ 6 months (and, if available, bone age data[15]) were to be collected prior to initiating treatment. The study design and the sequence of treatment periods are diagrammed in applicant's Figure 1.

Figure 1 **Study flow chart (representation of a patient requiring all 4 dose adjustments for both products during the first 12 months of study treatment)**



Information regarding the investigational products used during the clinical trial regarding dosage form, strength, formulation and batch number is summarized in applicant's Table 7.

[15] Original x-rays were centralized and independently read at the **(b) (4)** .

Table 7 Details of investigational products

Investigational Product	Dosage form and strength	Formulation Number	Batch number
ZD1033 Anastrozole	Tablet 0.5mg	F13134	2000074188, 2000074316, 2000076954, 2000083387, 2000085468, 2000086183, 2000090154, 2000091451, 2000094717, 2000096273, 2000098521, 2000098985, 2000099116, 2000100871, 2000103897, 2000104393, 2000106389, 2000107596, 2000108017, 2000109470, 2000109666, 2000114010.
ZD1033 Anastrozole	Tablet 1mg	F13135	2000074313, 2000090733, 2000111841, 2000111641.
ZD7054 Bicalutamide	Tablet 12.5mg	F13126	2000074315, 2000076956, 2000086188, 2000090156, 2000100878, 2000109653.
ZD7054 Bicalutamide	Tablet 25mg	F13127	2000074194, 2000074318, 2000084400, 2000086209, 2000089203, 2000094708, 2000096403, 2000098688, 2000099280, 2000100873, 2000103975, 2000104370, 2000105836, 2000109472, 2000109653, 2000109656, 2000109658, 2000109856, 2000112382, 2000114009

Inclusion and exclusion criteria

In order to be enrolled in the clinical trial patients had to meet the following inclusion criteria:

- male ≥ 2 years of age
- diagnosis of testotoxicosis based on clinical features of progressive precocious puberty, symmetrical testicular enlargement, advanced bone age[16], pubertal levels of serum testosterone, prepubertal pattern of gonadotropin secretion following GnRH stimulation, absence of other causes of testosterone excess[17]
- written informed consent of parent/ legal guardian and patient assent.

In the early versions of the protocol patients had to be treatment-naïve. This restriction was later removed and patients previously treated with ketoconazole, spironolactone and/or an aromatase inhibitor were allowed enrollment after being appropriately washed off for 15 days or 4 half-lives (whichever was longer).

Patients were excluded from the trial if they had any of the following:

- evidence of central precocious puberty as demonstrated by a GnRH stimulation test
- serum concentration of total or direct bilirubin, GGT, AST or ALT greater than 1.5 times the upper limit of normal (>1.5X ULN) for age
- serum concentration of creatinine >1.5X ULN for age.

[16] Defined as bone age of at least 12 months greater than chronological age.
[17] Undetectable plasma β-human chorionic gonadotropin (β-HCG), normal levels of 17-hydroxyprogesterone (17-OHP), and normal levels of dehydroepiandrosterone sulphate (DHEAS).

Efficacy endpoints, datasets analyzed, and statistical plan

The primary efficacy analysis was the change in growth rate after 12 months of treatment relative to the growth rate during the pre-study period[18].

The secondary analyses were the following:

- the change in growth rate after 6 months of treatment relative to the growth rate during the pre-study period
- the change in rate of bone age maturation after 6 and 12 months of treatment relative to the rate of bone age maturation during the pre-study period for patients with retrospective bone age data
- the change in bone age to chronological age ratio after 6 and 12 months of treatment relative to the same ratio at baseline
- the number and percentage of patients who achieved and/or maintained growth rates between the 5th and the 95th percentile for chronological age at 3, 6, 9 and 12 months of treatment
- the change in predicted adult height (PAH) after 12 months of treatment compared to baseline PAH.

Additional assessments included:

- an evaluation of testicular volume and Tanner staging at 6 and 12 months of treatment
- counting the number of acne lesions
- an assessment of aggressive behavior using the Children's Aggression Scale - Parent Version (CAS-P) questionnaire at 3, 6 and 12 months of treatment
- descriptive statistics of the plasma concentrations of R-bicalutamide, anastrozole, and serum concentrations of estradiol.

The datasets analyzed were:

- the "all treated" population (13 patients), which included patients who received bicalutamide/anastrozole treatment and had at least one on-treatment height measurement
- the "protocol-valid" population (13 patients), which was defined in Amendment # 1 as including patients who met the inclusion/exclusion criteria, had efficacy and safety data at the end of 12 months and had received a minimum of 300 days of study therapy (i.e. had approximating 80% compliance)[19].
- the safety population (14 patients)

At the request of the Division, the applicant presented the efficacy data for two subsets of the "all treated" dataset: treatment-naïve (7 patients) and previously treated (6 patients).

[18] The pre-study period was to be ≥ 6 months. Height measurements were standardized during the trial; a calibrated stadiometer was used for morning measurements at each visit.

[19] A patient was described as having "efficacy and safety data at the end of 12 months" if they had a retrospective height measurement, a baseline height measurement, a height recorded at the 12 ±2 month assessment, and a completed adverse event form at 3, 6, 9 and 12 month visits.

Protocol amendments

The study had two protocol amendments that are summarized in Table 1. In addition, there were four minor administrative changes that clarified the starting dosing recommendations of the Advisory Panel, and the site for central reading of the bone age X-rays.

Table 1: Protocol Amendments

Amendment number (and date)	Content of the amendment
Amendment # 1 (March 11, 2005)	• Clarified the definition of evaluable patient • Added another secondary endpoint (bone age to chronological age ratio) • Updated procedures for study drug escalation • Added evaluations of predicted adult height in children < 6 years of age using the Roche- Wainer-Thissen Stature Prediction Model • Expanded the drug safety evaluation • Clarified the bone age inclusion criteria • Allowed inclusion of patients previously treated with ketoconazole and spironolactone if treated for less than 12 months and if appropriately washed out.
Amendment # 2 (July 26, 2005)	• Clarified that retrospective height data should be at least 6 months prior to study entry. • Clarified how GnRH agonists were to be used of for the treatment of CPP • Allowed ketoconazole and spironolactone treated patients to be enrolled even if treated for > 12 months as long as a drug washout was done.

Source: text.

Patient disposition

Of the 24 patients initially considered for treatment, 10 were screening failures and only 14 patients received the study drugs. Patient disposition is summarized in Table 2. Only one patient did not complete the 12 month period of treatment (this patient was lost to follow-up). All 13 patients who completed the study entered an extension phase and 12 of them were continuing treatment at the time of the study report.

Table 2: Summary of patient disposition

Patients who received treatment	14 (100 %)
Patients who completed 12 months of treatment	13 (92.9 %)
Patients who discontinued treatment/study prematurely	1 (7.1 %)

Demographic and other baseline characteristics

The major demographic characteristics are summarized in applicant's Table 19. The mean age at baseline was 3.9 years (range 2 to 9 years) with about two thirds of patients being between 2 and 5 years of age, and one third of them being between 5 and 10 years. The vast majority of patients were Caucasian (85.7%).

Table 19 Summary of demographic characteristics: Safety set

Demographic characteristic	Number (%) of patients N=14
Age (years)	
n	14
Mean	3.9
SD	1.9
Median	3.5
Min	2
Max	9
Age group (years) n (%)	
n	14
≥2 - <5	9 (64.3)
≥5 - <10	5 (35.7)
Race n (%)	
n	14
Caucasian	12 (85.7)
Black	1 (7.1)
Other	1 (7.1)
Ethnic group n (%)	
N	14
Hispanic/Latino	1 (7.1)
African/American	1 (7.1)
Asian	3 (21.4)
Not applicable	9 (64.3)

Data derived from Table 11.1.4

The baseline growth characteristics for each of the 14 patients who received bicalutamide/anastrozole treatment are displayed in applicant's Table 20. The mean growth rate was 11.37 cm/yr (this corresponds to a growth rate SD score of +0.52). Growth rates ranged from 4.15 to 18.92 cm/year (-1.99 to 2.97 SD score). Bone ages ranged from 4.77 to 13.63 years and were markedly advanced in all patients. The bone age to chronological age ratio at baseline ranged from 1.29 to 3.01. The mean weight at baseline was 23.43 ± 5.55 kg (range of 17.2 to 34.7 kg). A positive family history of testotoxicosis was elicited in 8/14 (57.1%) patients; 8 patients (57.1%) had a confirmed genetic diagnosis of testotoxicosis. Six patients (42.9%) had

received previous therapy for testotoxicosis. Two patients (E0054003[20] and E0054004[21]) had previously received ketoconozole, two other patients (E0054002[22] and E0057001[23]) had previously received anastrozole, patient E0003002[24] had previously received spironolactone, and patient E0009001[25] had previously received spironolactone and anastrozole combination.

Table 20 Clinical features of patients at start of treatment: Safety set

Patient	CA (years)	BA (years)	Height (cm)	Height (SD units)	Growth rate (cm/year)	Growth rate (SD units)
E0002001	5.1	10.51	133.3	5.02	12.26	0.72
E0003002 [a]	5.6	10.72	123.4	1.85	9.37	0.40
E0003003	5.2	9.9	131.4	4.46	14.15	2.97
E0003004	3.6	7.61	112.0	2.71	18.92	1.92
E0009001 [a]	2.8	6.97	101.0	1.94	15.65	0.94
E0013001	5.2	10.71	125.4	3.16	6.61	-0.01
E0013004	3.4	10.23	114.2	4.01	9.69	-0.05
E0014001	3.9	9.26	113.2	2.51	10.08	0.33
E0023001	9.4	13.63	139.5	0.77	9.93	0.45
E0052001	2.4	4.77	100.4	3.03	16.03	1.5
E0054002 [a]	3.0	7.6	107.0	3.16	11.33	0.16
E0054003 [a]	4.7	6.24	101.3	-1.44	4.15	-1.99
E0054004 [a]	4.7	6.07	101.5	-1.40	4.23	-1.95
E0057001 [a]	3.4	7.93	112.2	3.49	17.07	1.91

[a] Patient had previously received treatment for testotoxicosis
CA Chronological age; BA Bone age; SD Standard deviation.

6.1.4 Efficacy Findings

Primary efficacy analysis

The protocol-specified primary efficacy analysis was a comparison of growth rate at Month 12 with baseline growth rate. The results of this comparison are summarized in Table 3. The 13 protocol completers had a mean baseline growth rate of 10.81 cm/year which changed minimally by Month 12 to 9.19 cm/year. This change from baseline of -1.62 cm/year (95% CI -4.72 to

[20] Patient E0054003 received ketoconazole for 855 days.
[21] Patient E0054004 received ketoconazole for 855 days.
[22] Patient E0054002 received anastrozole for 177 days.
[23] Patient E0057001 received anastrozole for 135 days.
[24] Patient E0003002 received spironolactone for 148 days.
[25] Patient E0009001 received spironolactone and anastrozole for 127 days.

1.48) did not reach statistical significance (p=0.278). When growth rate was expressed as a SD score, the mean change from baseline of -0.07 SD (95% CI: -1.15 to 1.00) was not statistically significant either (p=0.882). Similar results were observed when the same analysis was applied to treatment-naïve and to previously-treated patients separately. For the latter group, the observations were numerically very similar to those made for the whole group. For treatment-naïve patients, the mean change of -2.84 cm/year almost reached statistical significance (p=0.053) but the change in growth rate expressed as a SD score (-0.74) did not indicate as strong a trend (p=0.139).

Table 3: Change in growth rate at Month 12

	Baseline	Month 12	Change from baseline	P -value
All treated patients (primary efficacy analysis) N=13				
Growth rate (cm/year) Mean (SD)	10.81 (4.22)	9.19 (1.92)	-1.62 (5.13)	p=0.278
Growth rate SD score Mean (SD)	0.41 (1.36)	0.34 (0.62)	-0.07 (1.78)	p=0.882
Previously treated patients N=6				
Growth rate (cm/year) Mean (SD)	10.30 (5.50)	10.10 (2.13)	-0.20 (6.85)	P=0.947
Growth rate SD score Mean (SD)	-0.09 (1.58)	0.61 (0.72)	0.70 (2.17)	P=0.468
Treatment naïve patients N=7				
Growth rate (cm/year) Mean (SD)	11.25 (3.15)	8.41 (1.43)	-2.84 (3.13)	P=0.053
Growth rate SD score Mean (SD)	0.84 (1.07)	0.11 (0.43)	-0.74 (1.14)	P=0.139

Source: Tables 11.2.1.7, Table 23, Table 11.2.1.11, Table 11.2.1.13

Growth rate and bone age/chronological ratio at Months 6 and Month 12

Table 4 presents summary statistics for growth rate and rate of bone age maturation at Months 6 and Months 12. The changes in mean growth rate at Month 6 were, in general, either minimal changes from baseline or intermediary changes to those noted at Month 12. The baseline bone age/chronological age ratio for the whole group was 2.06 and changed minimally on treatment: 1.97 after 6 months treatment and 1.82 after 12 months treatment (the mean change from baseline was –0.09 after 6 months and –0.24 after 12 months).

Table 4: Efficacy summary: growth rate on trial and bone age/chronological age ratio

Endpoint	**Baseline** Mean (SD)	**Month 6** Mean (SD)	**Change from baseline to Month 6** Mean (SD)	**Month 12** Mean (SD)	**Change from baseline to Month 12** Mean (SD)
All patients (n= 13)					
Growth rate (cm/yr)	10.81 (4.22)	10.11 (2.63)	-0.70 (5.77)	9.19 (1.92)	-1.62 (5.13)
Growth rate (SD score)	0.41 (1.36)	0.27 (0.45)	-0.14 (1.67)	0.34 (0.62)	-0.07 (1.78)
BA/CA ratio	2.06 (0.51)	1.97 (0.46)	-0.09 (0.14)	1.82 (0.35)	-0.24 (0.18)
Previously treated patients (n= 6)					
Growth rate (cm/yr)	10.30 (5.50)	10.99 (3.36)	0.69 (7.94)	10.10 (2.13)	-0.20 (6.85)
Growth rate (SD score)	-0.09 (1.58)	0.44 (0.55)	0.52 (2.05)	0.61 (0.72)	0.70 (2.17)
BA/CA ratio	1.99 (0.58)	1.86 (0.53)	-0.12 (0.12)	1.74 (0.39)	-0.25 (0.22)
Treatment-naïve patients (n= 7)					
Growth rate (cm/yr)	11.25 (3.15)	9.36 (1.73)	-1.89 (3.23)	8.41 (1.43)	-2.84 (3.13)
Growth rate (SD score)	0.84 (1.07)	0.14 (0.34)	-0.71 (1.12)	0.11 (0.43)	-0.74 (1.14)
BA/CA ratio	2.12 (0.48)	2.06 (0.42)	-0.07 (0.15)	1.89 (0.33)	-0.23 (0.16)

Source; Tables 25, 25, and 27 of the Clinical Study Report.
NA= not available.
BA.CA = bone age/chronological age ratio.

Predicted adult height

It is important to recognize that prediction methods for adult height have not been validated in patients with testotoxicosis. Therefore, the analyses summarized in this section have purely an exploratory value. The applicant used two methods for the calculation of predicted adult height: Bayley -Pinneau and Roche-Wainer-Thissen. Since the Bayley -Pinneau method applies only to children with a bone age ≥7 years, this analysis could be conducted only in 9 of the 13 patients who met this age criterion. The mean PAH for these 9 boys at baseline was 163.19 cm; it increased to 168.65 cm at 12 months, the mean change from baseline to Month 12 being 6.21 cm.

In addition to the Bayley -Pinneau analysis, the applicant conducted another exploratory analysis using the Roche-Wainer-Thissen stature prediction model. This included 12 of the 13 patients (one patient was excluded because his parents did not provide consent for their height to be used). According to this method, the mean PAH at baseline was 184.68 cm and at 12 months was 186.06 cm; the mean change from baseline at Month 12 was 1.38 cm. There were minor variations in the previously-treated and the treatment-naïve patients for both predictive analyses.

Changes in signs and symptoms of virilization

Signs and symptoms of virilization were evaluated during the trial through measurements of testicular volume, Tanner staging, and CAP-S Children's Aggression Scale (all summarized in Table 5) and acne lesion count. For all patients, the mean testicular volume increased from 6.08 mL at baseline to 7.54 mL at Month 6 and 8.77 at Month 12. The mean Tanner stage remained stable with minimal changes. Aggression was measured using the Children's Aggression Scale-Parent Version (CAS-P), a 33-item questionnaire which measures five domains: verbal aggression, aggression against objects and animals, provoked physical aggression, unprovoked physical aggression, and use of weapons. The mean CAS-P total score was 15.66 at baseline and decreased at 10.77 after 3 months, 10.22 after 6 months and 7.71 after 12 months treatment.

Table 5: Summary of testicular volume, Tanner staging, and CAS-P score at baseline, Month 6, and Month 12

Assessment	**Baseline** Mean (SD)	**Month 6** Mean (SD)	**Change from baseline to Month 6** Mean (SD)	**Month 12** Mean (SD)	**Change from baseline to Month 12** Mean (SD)
All patients (n= 13)					
Testicular volume (mL) Mean (SD)	6.08 (2.78)	7.54 (2.93)	1.46 (2.29)	8.77 (2.12)	2.69 (2.51)
Tanner stage (testes and scrotum) Mean (SD)	3.00 (0.74)	2.92 (0.79)	-0.08 (0.51)	3.25 (0.45)	0.25 (0.45)
Tanner stage (Pubic hair) Mean (SD)	2.62 (0.77)	2.31 (0.95)	-0.31 (0.63)	2.15 (0.99)	-0.46 (0.52)
CAS-P Total Score (Median)	15.66 (12.02)	10.22 (8.86)	-5.44 (9.24)	7.71 (7.30)	-7.95 (5.91)
Previously treated patients (n= 6)					
Testicular volume (mL) Mean (SD)	4.75 (1.89)	7.08 (2.11)	2.33 (1.97)	8.00 (1.41)	3.25 (1.08)
Tanner stage (testes and scrotum) Mean (SD)	2.40 (0.55)	2.60 (0.89)	0.20 (0.45)	3.00 (0.00)	0.60 (0.55)
Tanner stage (Pubic hair) Mean (SD)	2.33 (0.82)	2.17 (0.98)	-0.17 (0.75)	1.67 (0.82)	-0.67 (0.52)
CAS-P Total Score (Median)	14.50 (11.47)	13.96 (8.17)	-0.54 (10.00)	8.13 (6.51)	-6.37 (5.56)
Treatment-naïve patients (n= 7)					
Testicular volume (mL) Mean (SD)	7.21 (3.03)	7.93 (3.61)	0.71 (2.41)	9.43 (2.49)	2.21 (3.33)
Tanner stage (testes and					

scrotum) Mean (SD)	3.43 (0.53)	3.14 (0.69)	-0.29 (0.49)	3.43 (0.53)	0.00 (0.00)
Tanner stage (Pubic hair) Mean (SD)	2.86 (0.69)	2.43 (0.98)	-0.43 (0.53)	2.57 (0.98)	-0.29 (0.49)
CAS-P Total Score (Median)	16.65 (13.30)	7.01 (8.69)	-9.64 (6.54)	7.35 (8.42)	-9.30 (6.28)

Source: Tables 28, 29, and 30.

According to Appendix 12.2.6.7 of the Clinical Study report, only 5 patients (38.5%) had acne lesions at baseline and all had reductions in the acne count by Month 12[26]. Of the nine patients without acne lesions at baseline three developed a few acne lesions at Month 12[27].

Individual growth rates

The individual growth rates and change from baseline in growth rates at Month 12 are presented in applicant's Table 24. Nine out of 13 patients experienced a reduction in growth rate at Month 12. There was marked variability of responses that does not seem to correlate with the treatment status (naïve vs. non-naïve). For instance, both the patients with the largest and those with the smallest reductions in growth rate are a mixture of previously-treated and treatment -naïve[28]. In addition, a visual inspection of the individual bicalutamide serum profiles following titration through the end of the treatment period does not suggest a link between the growth rate reduction (or lack thereof) and the serum bicalutamide level; most patients, responders and non-responders alike, had serum levels of bicalutamide < 10 μg/ml).

[26] Patient E0003003 had 3 lesions at baseline and none at Month 12; patient E0013004 had 12 lesions at baseline and 6 at Month 12; patient E0023001 had 10 lesions at baseline and 1 at Month 12; patient E0052001 had 30 lesions at baseline and none at Month 12; patient E0057001 had 4 lesions at baseline and none at Month 12.
[27] Patients E0003002 and E0023001developed one lesion each at Month 12; patient E0054003 developed 4 acne lesions at Month 12.
[28] Two of the patients who responded particularly poorly were twins (patients E0054003 and E0054004). For them the growth rate at baseline was <5 cm/year or approximately 2 SD below the normal growth rate for boys of the same age and increased 3 to 4-fold by 3 months. Both had previously been treated for their testotoxicosis with ketoconazole for a period >2 years and they had also been treated previously with hydrocortisone for adrenocortical insufficiency.

Table 24 Listing of change in growth rates (cm/year) at 12 months ordered by baseline growth rate (ascending)

Patient	Baseline growth rate (cm/year)	Growth rate at 12 months (cm/year)	Change in growth rate (cm/year)	Previously treated for testotoxicosis
E0054003	(b) (4)			Yes
E0054004				Yes
E0013001				No
E0003002				Yes
E0013004				No
E0023001				No
E0014001				No
E0054002				Yes
E0002001				No
E0003003				No
E0009001				Yes
E0052001				No
E0057001				Yes

Individual growth rate SD scores, rates of bone age maturation, and predicted adult height changes are further summarized in applicant's Table 21.

Table 21 List of changes in growth rate, bone maturation rate and predicted adult height: All treated

Patient	Days on treatment[c] Anastrozole/ bicalutamide	Growth rate (cm/year)		Growth rate (SD units)		Bone age maturation rate		Ratio of BA/CA		PAH (B&P) (cm)		PAH (RWT) (cm)	
		Baseline	12 months	Baseline	12 months	Baseline	12 months	Baseline	12 months	Baseline	12 months	Baseline	12 months
E0002001							(b) (4)						
E0003002 [b]													
E0003003													
E0003004 [b]													
E0009001 [a]													
E0013001													
E0013004													
E0014001													
E0023001													
E0052001													
E0054002 [a]													
E0054003 [a]													
E0054004 [a]													
E0057001 [a]													

[a] Patient had previously received treatment for testotoxicosis
[b] Excluded from the AT population due to no height measurement following treatment
[c] Number of tablets in days calculated from the total days of tablets dispensed minus the total days of tablets returned across all visits up to month 12 from the first day of combined dosing (Day 1).
BA bone age; CA chronological age; PAH predicted adult height; B&P Bayley and Pinneau method; RWT Roche-Wainer-Thissen predicted stature model.
NC Not Calculated; NR Not Recorded; SD Standard deviation.

Individual changes in testicular volume

Testicular volume at baseline and the change in testicular volume to Month 12 are summarized in Table 6 (all patients had testicular volumes measured with an orchidometer). Highlighted in yellow are patients who were treatment-naïve at enrolment. At baseline, the average testicular volumes were between 3 to 11 mL. The changes were variable and did not follow any specific pattern (they ranged from reductions of -3 to increases of 7 cm; it is conceivable that the reductions in size may represent measurement errors).

Table 6: Change in testicular volume

Patient ID	Left testicular volume (ml)		Right testicular volume (ml)		Average testicular volume (ml)		Change in average testicular volume at Month 12
	Baseline	Month 12	Baseline	Month 12	Baseline	Month 12	
E0002001				(b) (4)			
E0003002							
E0003003							
E0003004							
E0009001							
E0013001							
E0013004							
E0014001							
E0023001							

E0052001	(b) (4)
E0054002	
E0054003	
E0054004	
E0057001	

Source: Appendix 12.2.6.5
NA= not available.

Individual changes in Tanner staging

Tanner staging at baseline and the change in Tanner staging at Month 12 are summarized in Table 7. At baseline, the Tanner stages for pubic hair were between 1 and 4 and the Tanner stages for testes and scrotum were between 2 to 4. Five patients had no changes at Month 12; for the other patients the changes minimal.

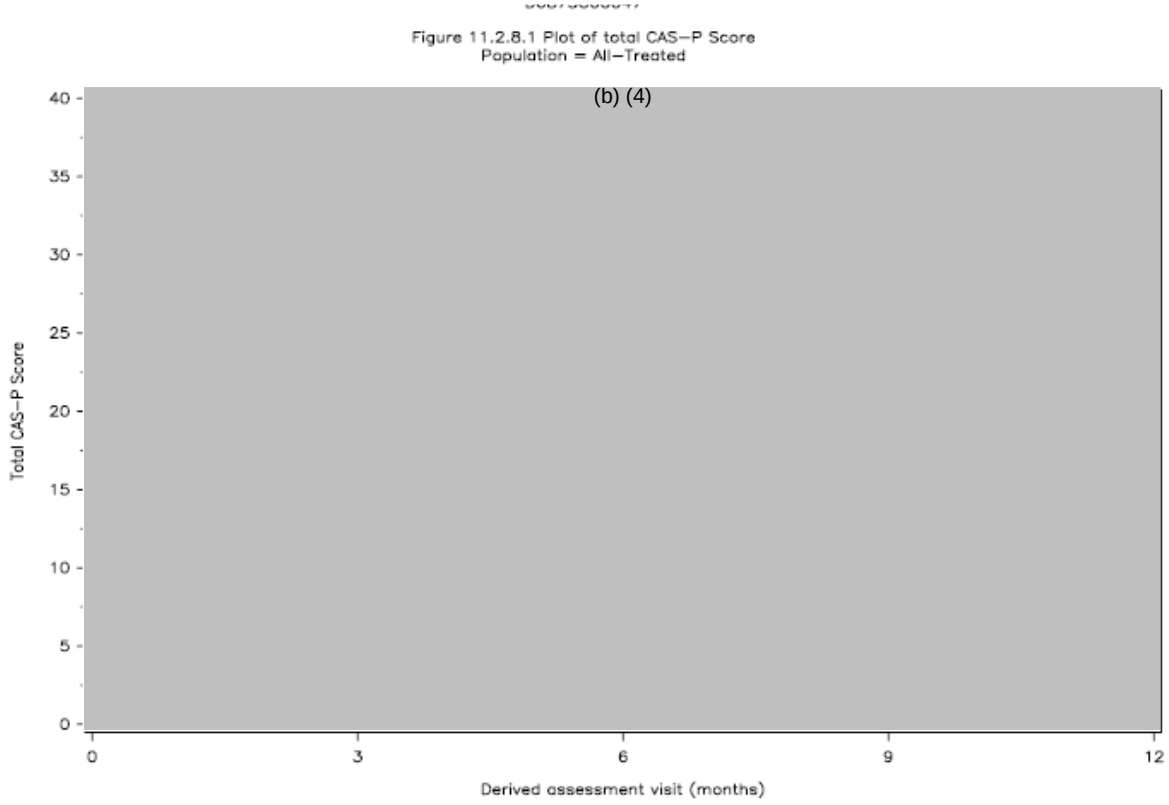
Table 7: Change in Tanner staging at Month 12

Patient ID	Tanner stage (testes and scrotum)		Tanner stage (pubic hair)	
	Baseline	Change from baseline	Baseline	Change from baseline
E0002001	(b) (4)			
E0003002				
E0003003				
E0003004				
E0009001				
E0013001				
E0013004				
E0014001				
E0023001				
E0052001				
E0054002				
E0054003				
E0054004				
E0057001				

Source: Appendix 12.2.6.5
NA= not available

Individual changes in CAS-P scores

Individual changes Total CAS-P scores are presented graphically in Figure 11.2.8.1. At Month 12, 12/13 (92.3%) patients had shown reductions in CAS-P total score.



Comparison of efficacy with published studies

For a description of the published studies that report various pharmacological interventions in boys with testotoxicosis refer to Section 8.6 of this review. Table 8 compares the efficacy data from clinical trial D6873C00047 with that of the NIH trial of spironolactone/testolactone combination (10 patients) and that of the case series of Soriano-Guillen et al. (5 patients, all treated with ketoconazole)[29]. These studies were selected because they provided efficacy data for the Month 12 timepoint and assessed similar efficacy endpoints to those of Study D6873C00047 (results of a third case series of 10 patients treated with ketoconazole and cyproterone could not be included because the one-year data were not presented[30]). The bicalutamide/anastrozole combination compares unfavorably with both the spironolactone/testolactone combination and with the ketoconazole treatment. This is a surprising observation given the fact that spironolactone is a weak antiandrogen and that anastrozole (a 3rd generation aromatase inhibitor) is expected to be more potent than testolactone.

Table 8: Comparison of growth velocity across clinical studies conducted in patients with testotoxicosis

Study	Growth velocity (cm/yr)			Growth velocity (SD score)		
	Baseline	Month 12	Change from	Baseline	Month 12	Change from

[29] Soriano-Guillen L et al. Adult height after ketoconazole treatment in patients with familial male limited precocious puberty. J Clin Endocrinol Metab 90: 147-151, 2005.
[30] Almeida MQ et al. Long-term treatment of familial male limited precocious puberty (testotoxicosis) with cyproterone acetate or ketoconazole. Clinical Endocrinology, 69, 93-98 (2008).

			baseline to Month 12			baseline to Month 12
Leschek et al.	16.11	7.5	-8.6	6.9	1.1	-5.8
Soriano-Guillen et al.	12	6	-6	5.8	0	-5.8
NDA (all patients)	10.81	9.19	-1.62	0.41	0.34	-0.07
NDA (pretreated patients)	10.3	10.10	-0.20	-0.09	0.61	0.70
NDA (treatment naïve patients)	11.25	8.41	-2.84	0.84	0.11	-0.74

A comparison of main baseline characteristics of the patients enrolled in the three studies described above does not reveal any differences in baseline chronological age and bone age characteristics. The only clear discrepancy was related to baseline growth velocity, which was greater in both published studies. Testosterone levels were elevated in all studies (and comparable between Study D6873C00047 and the Leschek et al. study. Of interest, the patients enrolled in the NIH study were genetically homogeneous (they all had the same mutation of the LH receptor: D578G); this was not the case for any of the other two studies[31].

Table 9: Comparison of baseline characteristics across clinical studies

Study	CA	BA	BA minus CA	Growth velocity (cm/yr)	Growth velocity (SD score)	Total testosterone	Genetics of LH mutations
Leschek et al.	4.3	9.6	5.3	16.1	6.9	11.6 nmol/L (316 ng/dl)	Single mutation
Soriano-Guillen et al.	4.9	8.8	3.9	12.8	5.6	17.9 nmol/L (5.1 ng/ml)	2 mutations
NDA (all patients)	3.9	8.7	4.8	10.81	0.41	9.62 nmol/L	Not described

CA= chronological age; BA = bone age.

6.1.5 Clinical Microbiology

Not applicable.

[31] Although the specific LH receptor mutations of the patients enrolled in Study D6873C00047 was not described for the patients identified with mutations, they are likely to be heterogeneous because this was an international study.

6.1.6 Efficacy Conclusions

The regimen of bicalutamide and anastrozole evaluated in Study D6873C00047 was not efficacious in reducing the accelerated growth rate associated with androgen excess in this cohort of 14 patients with testotoxicosis. The mean growth velocity decreased only minimally after 12 months of treatment (1.6 cm) and this change was not statistically significant. Treatment-naïve patients fared somewhat better (a mean 2.84 cm reduction in growth velocity) but even this change failed to reach statistical significance and was not clinically meaningful. The efficacy changes observed in this clinical trial were inferior to those reported for other case series such as an NIH study of 10 patients treated with another antiandrogen/aromatase inhibitor combination (spironolactone/testolactone) or another case series of 5 patients treated with ketoconazole. In these published case series the reduction in growth velocity was both statistically significant and clinically meaningful (approximately 50% reduction in baseline growth velocity after one year of treatment).

Bicalutamide/anastrozole treatment appeared to stabilize and even reduce some of the manifestations of virilization, in that it maintained the same Tanner stage in most patients and reduced the aggressive behavior observed in testotoxicosis patients. In addition, it decreased the number of acne lesions in the few patients who had such lesions at baseline (and did not allow the development of acne other then occasionally in patients who did not have such manifestations prior to treatment initiation). All such statements have to be placed in the evidentiary context of a study that did not have a control arm.

It is not clear why the study did not demonstrate a significant reduction in growth velocity over the interval measured. A possible explanation may be that, despite expectations to the contrary, this bicalutamide/anastrozole regimen is not efficacious in testotoxicosis and that an effective dose for one or both drugs has not been established in this patient population. Although unlikely, it is possible that the titration phase may have been too long and, given the period of total treatment of 12 months, it may not have been enough to observe the full effect of the treatment combination. One has also to consider that the adult range of bicalutamide serum concentrations of 5-15 μg/ml may nor be extrapolabable to children with testotoxicosis or that the current treatment regimen which resulted in serum bicalutamide levels in the medium range may be more effective if it targets bicalutamide concentrations that reach the upper range. Finally, differences in clinical responses between published clinical studies and Study D6873C00047 may be due to differences in the underlying LH receptor mutations, an issue not explored in this NDA.

7 INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

7.1.1 Deaths

No deaths were reported in this study.

7.1.2 Other Serious Adverse Events

No serious adverse events were reported in this study while patients were on study drugs.

7.1.3 Dropouts and Other Significant Adverse Events

None of the 14 patients who received study drugs discontinued the study because of an adverse event.

7.1.3.1 Overall profile of dropouts

Not applicable (no patient discontinued the trial due to an adverse event).

7.1.3.2 Adverse events associated with dropouts

Not applicable (no patient discontinued the trial due to an adverse event).

7.1.3.3 Other significant adverse events

There were no other significant adverse events.[32]

7.1.4 Other Search Strategies

Due to the small size of the dataset no other analyses were conducted.

[32] The study defined significant adverse events as "adverse events of particular clinical importance" other than SAEs and AEs leading to discontinuation of patients from the study treatment. They were supposed to be identified as such by the Medical Advisers during the evaluation of safety data for the clinical study report.

7.1.5 Common Adverse Events

7.1.5.1 Eliciting adverse events data in the development program

According to the study protocol, adverse events were collected at baseline, Month 1, Month 3, Month 6, Month 9, and Month 12. Gynecomastia and breast pain were ascertained prospectively.

7.1.5.2 Appropriateness of adverse event categorization and preferred terms

Visual review of Appendix 12.2.7.1 entitled "listing of adverse events" indicates appropriate conversion of the investigators' terms to MedDRA preferred terms.

7.1.5.3 Incidence of common adverse events

The applicant reports that 13/14 (92.9%) of patients experienced at least one adverse event and that there was a total of 90 AEs reported for the duration of the study. Table 10 lists the number and percentage of patients who experienced ≥ 2 adverse events. Gynecomastia, acne, and central precocious puberty are the only adverse events that can be related mechanistically to the study drugs and/or the underlying condition. Central precocious puberty is an anticipated event in patients with prolonged exposure to elevated sex steroid hormone levels as are acne (a common sign of virilization) and gynecomastia. All other adverse events presented in Table 10 represent common infectious conditions (e.g. infectious croup, gastroenteritis, nasopharyngitis, etc.), or other nonspecific signs or symptoms of childhood illnesses (e.g. pyrexia, headache, nausea).

Table 10: Adverse event occurring in ≥ 2 patients

Adverse event (preferred term)	Number (%) of patients with event
Gynecomastia	7 (50.0)
Central precocious puberty	6 (42.9)*
Vomiting	5 (35.7)
Pyrexia	3 (21.4)
Headache	3 (21.4)
Croup infectious	2 (14.3)
Gastroenteritis	2 (14.3)
Nasopharyngitis	2 (14.3)
Tonsillitis	2 (14.3)
Upper respiratory tract infection	2 (14.3)
Abdominal pain	2 (14.3)
Nausea	2 (14.3)
Acne	2 (14.3)
Conjunctivitis	2 (14.3)

. Source: Table 39, Clinical Study Report.
*Changed to 7(50%) with the 4-month safety update.

Most adverse events were either mild or moderate in intensity. According to applicant's Table 11.3.2.7, there were only 2 adverse events judged as severe in intensity: gynecomastia and furuncle. Severe and moderate adverse events are listed in Table 11. In general, they suggest a pattern similar to that describe in Table 10 and describe common pediatric infectious diseases or clinical consequences of excess sex steroid hormone levels due to the underlying testotoxicosis or therapeutic intervention.

Table 11: Adverse events considered moderate of severe in intensity

Adverse event (preferred term)	Number (%) of patients with event
Adverse events "severe" in intensity	
Gynecomastia	1 (7.1)
Furuncle	1 (7.1)
Adverse events "moderate" in intensity	
Precocious puberty	5 (35.7)
Gynecomastia	4 (28.6)
Pyrrexia	1 (7.1)
Acne	1 (7.1)
Breast tenderness	1 (7.1)
Nasopharyngitis	1 (7.1)
Tonsillitis	1 (7.1)
Eosinophilia	1 (7.1)
Labyrinthitis	1 (7.1)
Pyoderma	1 (7.1)
Seasonal allergy	1 (7.1)
Skin laceration	1 (7.1)
Staphylococcal abscess	1 (7.1)
Stridor	1 (7.1)
Varicella	1 (7.1)

*Source: Table 11.3.2.7.

Table 12 summarizes the number and percentage of patients who experienced adverse events that were judged treatment-related. Specifically, 6 (42.9%) patients reported 16 adverse events possibly related to either anastrozole or bicalutamide. There was only one adverse event (headache) that was considered possibly related to anastrozole. Adverse events possibly related to bicalutamide were gynecomastia, central precocious puberty[33], breast tenderness, breast pain, asthenia, increased ALT, increased AST, and musculoskeletal chest pain. All three adverse events of breast tenderness and breast pain occurred in patients who had ongoing gynecomastia (nterestingly, none of the study patients had gynecomastia or breast pain at baseline). The elevation of transaminases[34] was reported in one patient 107 days after starting the treatment and was described as mild (the enzyme elevations returned to normal without discontinuation of the

[33] Six events of central precocious puberty (CPP) were recorded during the trial (two of them were considered "treatment related". The number of patients who developed CPP over 12 months (6/14 patients) was higher than that reported by Leschek et al 1999. The development of CPP was descried to have occurred in these patients on treatment days 106, 168, 169, 206, 365, and 375.
[34] Patient E0057001

study drugs). All other treatment-related AEs (asthenia, musculoskeletal pain, and headache) were mild in intensity.

Table 12: Adverse events judged treatment-related*

Adverse event (preferred term)	Number and % of patients with adverse event (N=14)		
	Anastrozole	Bicalutamide	Either Treatment
Any patients with treatment-related AE	1 (7.1)	6 (42.9)	6 (42.9)
Gynecomastia	0	6 (42.9)	6 (42.9)
Breast tenderness	0	2 (14.3)	2 (14.3)
Breast pain	0	1 (7.1)	1 (7.1)
Precocious puberty**	0	2 (14.3)***	2 (14.3)
Asthenia	0	1 (7.1)	1 (7.1)
ALT increased	0	1 (7.1)	1 (7.1)
AST increased	0	1 (7.1)	1 (7.1)
Musculoskeletal chest pain	0	1 (7.1)	1 (7.1)
Headache	1 (7.1)	0	1 (7.1)

*Patients with multiple events with the same preferred term are counted only once under the maximum reported causality.
** Central precocious puberty per investigator, mapped as "precocious puberty" using MedDRA dictionary
***3 (21.4%) following the 4-month safety update.

7.1.5.4 Common adverse event tables

Refer to Section 7.1.5.3.

7.1.5.5 Identifying common and drug-related adverse events

Absence of a control group makes identification of drug-specific adverse events extremely difficult. It is reasonable, however, to assume that most adverse events that are due to common infectious diseases of childhood are coincidental and have no connection with the treatment (this is consistent with the lack of mechanistic association of such events with both drugs studied, and with the extensive adult experience reflected in the current Casodex and Arimidex labels) Other adverse events (such as vomiting, headache, abdominal pain) reflect common symptoms encountered in childhood illnesses. As described previously, gynecomastia and breast tenderness/pain are likely to be drug-related, as is central precocious puberty, an event that is expected to be seen following persistent sex steroid exposure.

7.1.5.6 Additional analyses and explorations

Due to the absence of a control group and the small size of the dataset no additional analyses were conducted.

7.1.6 Less Common Adverse Events

Adverse events that occurred in only one patient were (by preferred term): ear infection, furuncle, labyrinthitis, lower respiratory tract infection, otitis externa, pyoderma, respiratory tract infection viral, rhinitis, sinusitis, staphylococcal abscess, varicella, viral infection, breast pain, abdominal pain upper, diarrhea, asthenia, fatigue, eosinophilia, lymphadenopathy, microcytosis, fall, skin laceration, sunburn, café au lait spots, skin hyperpigmentation, cough, stridor, seasonal allergy, alanine aminotransferase increased, aspartate aminotransferase increased, decreased appetite, musculoskeletal chest pain, and crying. Due to the absence of a control group and given the small size of the dataset no attempts were made to further characterize these adverse events.

7.1.7 Laboratory Findings

7.1.7.1 Overview of laboratory testing in the development program

Laboratory testing consisted in sex hormone measurements and standard hematology and chemistry analytes. The former included measurements of total and free testosterone, luteinizing hormone, follicle stimulating hormone, inhibin B, estrone (in addition, β-HCG, 17-OHP and DHEAS were measured at screening,). The latter included full blood count, electrolytes (sodium and potassium), renal tests (urea, creatinine) and liver function tests (bilirubin, gamma GT, AST and ALT). Most laboratory measurements were done at baseline, Month 6 and Month 12. Serum estradiol was an exception; being used for the titration of anastrozole, it was measured with higher frequency particularly during the first half of the study. Laboratory abnormalities were not to be reported as adverse events unless they met the definition criteria for SAEs or if they resulted in study discontinuation. If an abnormal laboratory value was associated with clinical signs and symptoms, the latter were reported as adverse events and the associated laboratory results were considered “additional information”.

7.1.7.2 Selection of studies and analyses for drug-control comparisons of laboratory values

Not applicable (there was only one clinical study).

7.1.7.3 Standard analyses and explorations of laboratory data

7.1.7.3.1 Analyses focused on measures of central tendency

Summary statistics for the main hematology analytes are presented in Table 13. There were no clinically meaningful changes in any of the analytes characterized.

Table 13: Summary statistics for main hematology analytes

Analyte	Baseline	Month 3*	Month 6**	Month 9	Month 12
Hemoglobin (g/L)					
N	14	13	12	13	13
Mean (SD)	131.50 (7.74)	129.46 (6.59)	128.33 (8.26)	130.08 (7.90)	125.23 (6.22)
Minimum	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)
Maximum					
WBC (109/L)**					
N	14	13	12	13	13
Mean (SD)	9.06 (5.50)	7.79 (3.41)	7.73 (3.82)	7.31 (2.73)	6.55 (2.37)
Minimum	(b)	(b)	(b)	(b)	(b)
Maximum	(4)	(b) (4)	(4)	(4)	(4)
Platelet count (109/L)**					
N	14	12	12	13	12
Mean (SD)	342.64 (103.71)	297.33 (52.54)	301.08 (72.36)	297.38 (78.30)	296.25 (99.73)
Minimum	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)
Maximum					

*Day 84
**Day 168
Source: Table 11.3.7.1.

Summary statistics for liver function tests[35] are presented in Table 14. No clinically significant changes were observed for the duration of the trial.

Table 14: Summary statistics for liver function tests

Analyte	Baseline	Month 3*	Month 6**	Month 9	Month 12
AST U/L					
N	14	11	10	12	13
Mean (SD)	29.57 (8.37)	31.18 (12.27)	25.20 (3.94)	29.75 (5.89)	26.46 (3.48)
Minimum	(b)	(b)	(b)	(b)	(b)
Maximum	(4)	(4)	(4)	(4)	(4)
ALT U/L					
N	14	11	10	13	13
Mean (SD)	16.79 (3.53)	22.09 (24.45)	14.40 (2.01)	18.15 (6.22)	15.77 (3.54)
Minimum	(b)	(b)	(b)	(b)	(b)
Maximum	(4)	(4)	(4)	(4)	(4)
GGT U/L	14	11	10	13	13
Mean (SD)	10.07 (3.15)	9.73 (3.13)	8.50 (3.63)	9.15 (3.26)	10.00 (3.74)
Minimum	(b)	(b)	(b)	(b)	(b)
Maximum	(b)	(4)	(4)	(4)	(4)
Total Bilirubin umol/L					

[35] Range of normal values are as follows: AST: 20-60 IU/L; ALT: 5-45 IU/L. GGT: 2-49 U/L; total bilirubin 3-21 umol/L

N	14	11	10	13	13
Mean (SD)	5.00 (2.69)	5.91 (2.07)	6.80 (3.26)	6.23 (2.92)	6.00 (2.48)
Minimum	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)
Maximum					

*Day 84
**Day 168
Source; Table 11.3.7.3.

Summary statistics for electrolytes and renal function tests[36] are presented in Table 15. There were no clinically meaningful changes during the trial.

Table 15: Summary statistics for electrolytes and renal function tests

Analyte	Baseline	Month 3*	Month 6**	Month 9	Month 12
Sodium mmol/L					
N	14	11	10	13	13
Mean (SD)	140.00 (2.77)	139.73 (3.10)	140.60 (2.01)	140.31 (1.55)	139.85 (1.68)
Minimum	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)
Maximum					
Potassium mmol/L					
N	14	10	10	13	12
Mean (SD)	4.29 (0.28)	4.43 (0.36)	4.22 (0.40)	4.21 (0.27)	4.18 (0.22)
Minimum	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)
Maximum					
BUN mmol/L					
N	10	7	8	9	9
Mean (SD)	4.86 (1.11)	5.00 (1.62)	5.22 (1.22)	4.76 (0.94)	4.68 (1.19)
Minimum	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)
Maximum					
Creatinine umol/L	14	13	13	13	13
Mean (SD)	44.64 (9.64)	42.62 (6.20)	44.00 (8.22)	46.08 (3.95)	41.92 (8.34)
Minimum	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)
Maximum					

*Day 84
**Day 168
Source; Table 11.3.7.3.

Sex hormones (sex steroids and gonadotropins)

Sex steroids and gonadotropins were measured at baseline, Month 6, and Month 12. Estradiol had additional measurements during the titration phase of the trial because estradiol serum levels were used to guide anastrozole dose titration.

[36] Range of normal values are as follows: Sodium: 132-147 mmol/L; potassiun: 3.5 to 5.5 mmol/L; BUN: 1.43-8.57 mmol/L; creatinine: 18-44 umol/l for ages 1-5 years and 18-62 umol/L for ages 6-10 years.

The mean serum total testosterone concentrations[37] were above the upper limit of normal at baseline and at all subsequent timepoints evaluated in the clinical trial, consistent with the underlying diagnosis of testotoxicosis and precocious puberty (Table 16). They increased during the clinical trial at both Month 6 and Month 12 (changes from baseline of 8.23 nmol/L and 5.20 nmol/L, respectively). Consistent with the observations made for total testosterone, the mean free testosterone concentrations were above the upper limit of normal at baseline and they increased on treatment at Month 6 and Month 12 (changes from baseline of 2.62 pg/ml and 1.39 pg/ml, respectively).

Contrary to expectations, the mean serum concentrations of estrogens were not elevated at baseline; they remained in the normal range for the duration of the trial (the estradiol concentrations declined slightly during the trial while the estrone concentrations increased somewhat)[38].

At baseline, the mean levels of LH were below the lower limit of normal[39] and in the prepubertal range, and remained so throughout the study[40]. The mean serum concentration of FSH at baseline was only slightly above the lower limit of the normal and stayed in the normal range throughout the study[41].

Table 16: Descriptive statistics for sex hormones

Analyte	Baseline	Month 6	Change from baseline to Day Month 6	Month 12	Change from baseline to Month 12
Total Testosterone (nmol/L)					
N	14	12	12	13	13
Mean (SD)	9.62 (7.22)	18.15 (8.96)	8.23 (8.97)	14.80 (8.43)	5.20 (8.52)
Range	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)
Free Testosterone pg/mL)					
N	13	12	11	13	12
Mean (SD)	5.71 (4.87)	8.69 (6.56)	2.62 (6.37)	7.07 (5.25)	1.39 (5.84)
Range	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)
Estradiol (pmol/L)					
N	14	9	9	13	13

[37] Normal levels of total testosterone were as follows: 0-0.52 nmol/L for children aged 1-3 years; 0-1.31nmol/L for children 4-8 years; 0.69-9.03 nmol/L for children 9-11 years of age. Normal levels of free testosterone were 0-0.49 pg/ml for children 1-10 years of age.
[38] The applicant reports that "there was a problem with the estradiol assay" and that some measurements were erroneously reported to be " unexpectedly high" for the period of February to May 2007. Refer also to Section 5.2.
[39] Normal LH range is 1.5-9.3 U/L.
[40] Only one patient had an elevated LH level at 2.7 U/L; this was patient E0023001 who developed central precocious puberty.
[41] Normal FSH range is 0.3-4.6 U/L.

Mean (SD) Range	10.62 (2.65) (b) (4)	9.18 (0.00) (b) (4)	-0.28 (0.85) (b) (4)	9.32 (0.51) (b) (4)	-1.41 (2.85) (b) (4)
Estrone (pg/L) N Mean (SD) Range	 11 10.27 (10.39) (b) (4)	 12 17.25 (11.87) (b) (4)	 9 6.33 (6.02) (b) (4)	 13 13.31 (4.42) (b) (4)	 10 3.00 (13.15) (b) (4)
LH (U/L) N Mean (SD) Range	 14 0.13 (0.08) (b) (4)	 12 0.64 (0.78) (b) (4)	 12 0.52 (0.70) (b) (4)	 13 0.36 (0.25) (b) (4)	 13 0.23 (0.25) (b) (4)
FSH (U/L) N Mean (SD) Range	 14 0.40 (0.27) (b) (4)	 12 0.73 (0.55) (b) (4)	 12 0.35 (0.55) (b) (4)	 13 0.69 (0.80) (b) (4)	 13 0.28 (0.88) (b) (4)

Source: Table 11.3.7.6.

Individual testosterone and estradiol concentrations at baseline, Month 6 (Day 168) and Month 12 are presented in Table 17. Highlighted in yellow are patients who treatment-naive. With the exception of patient E0023001 all patients had above-normal serum testosterone concentrations at baseline[42]; with one exception (patient E0052001 at Month 6), all testosterone measurements during the trial were above normal. Most individual changes reflected the changes observed for the mean values, i.e. serum testosterone values increased on treatment. The vast majority of estrogen serum concentrations was low at baseline and remained low at both Month 6 and Month 12.

Table 17: Individual testosterone and estradiol concentrations

Patient ID	Total testosterone (nmol/L)			Estradiol (pmol/L)		
	Baseline or Day 1 *	Month 6	Month 12	Baseline or Day 1 *	Month 6	Month 12
E0002001	(b) (4)					
E0003002						
E0003003						
E0003004						
E0009001						
E0013001						
E0013004						
E0014001						
E0023001						
E0052001						
E0054002						
E0054003						
E0054004						
E0057001						

Source: Appendix 12.2.8.9

[42] This patient had, reportedly, an elevated total testosterone level prior to baseline measured locally (all on-trial testosterone measurements were centralized).

*Baseline measurement for total testosterone and pre-dosing measurement for estradiol.
NA = not available.
#Measurement at 140 days.
"H" indicates a value of total testosterone above the normal range.

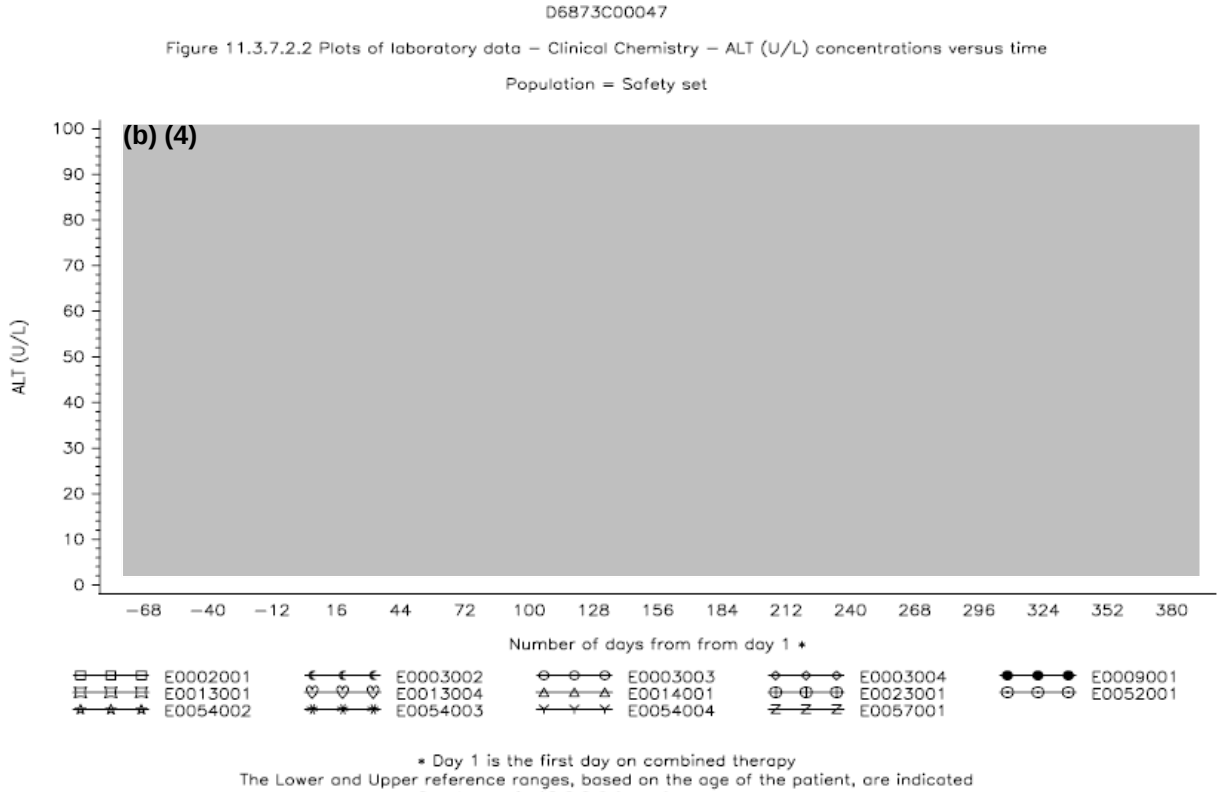
7.1.7.3.2 Analyses focused on outliers or shifts from normal to abnormal

Hematology and standard chemistries

Review of Appendices 12.2.8.2 through 12.2.8.6 (Listing of individual hematology analytes for the safety population) did not reveal any consistent pattern of hematology abnormalities. Occasional out of range measurements were observed but they were either small or of no clinical consequence.

Review of Appendix 12.2.8.7 (Listing of individual hepatic biochemistry results) identified one patient with mild elevations of ALT on the following occasions: Day 84 (95 U/L, slightly above 2X ULN[43]), Day 112 (83 U/L and 59 U/L on repeat), and Day 140 (58 U/L, respectively). This patient had normal ALT levels at baseline and on three occasions prior to the observed ALT elevation; ALT levels normalized on trial despite continued treatment (three normal levels on Day 196, Month 9, and Month 12). There were no associated bilirubin or GGT elevations. The individual ALT concentrations during the trial are illustrated in Applicant's Figure 11.3.7.22.

[43] Normal range for ALT: 5-45 U/L.



Review of Appendix 12.2.8.8 (Listing of individual urea, creatinine, and electrolytes individual results) did not reveal any consistent pattern of abnormalities. Occasional out of range measurements were observed but they were either mild or of no clinical consequence. Approximately 50% of patients had minor creatinine elevations on one or more occasions without associated BUN elevations or adverse events. These minor creatinine elevations are very likely a consequence of the testosterone-induced increase in muscle mass observed in boys with testotoxicosis and indicate that the standard normal range of creatinine of prepubertal children may not be appropriate for this patient population.

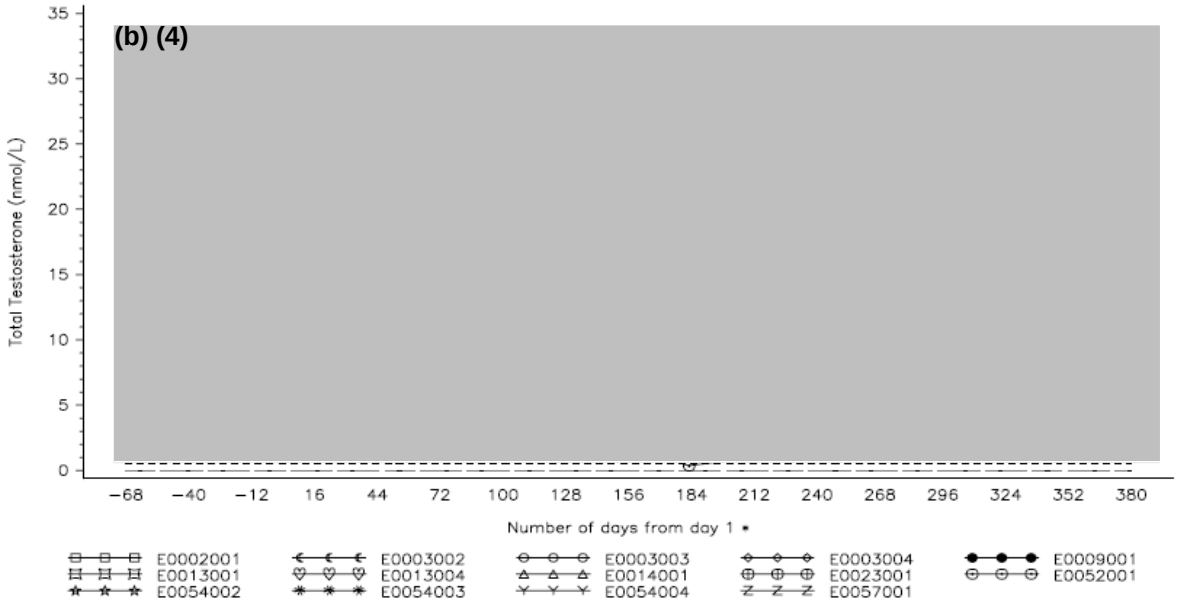
Sex hormones

The individual measurements in total testosterone during the clinical trial are illustrated in applicant's Figure 11.3.7.3.3. Individual estrogen values were discussed in Section 5.2 and also listed in Table 17.

D6873C00047

Figure 11.3.7.3.3 Plots of laboratory data – Sex hormones – Total Testosterone (nmol/L) concentrations versus time

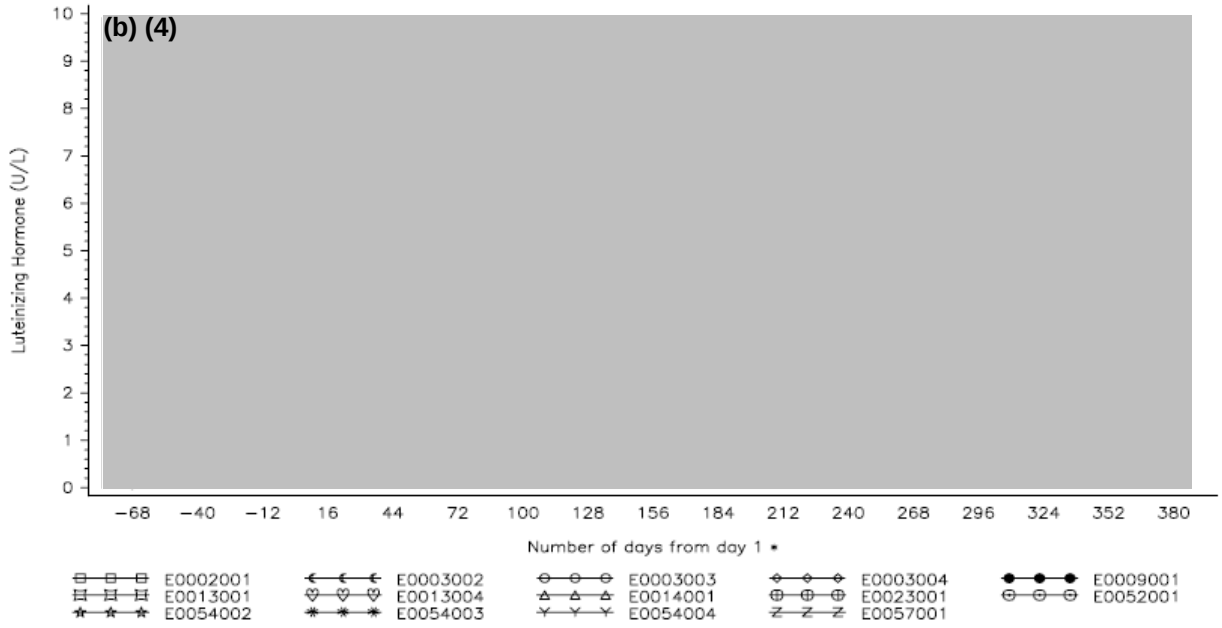
Population = Safety set



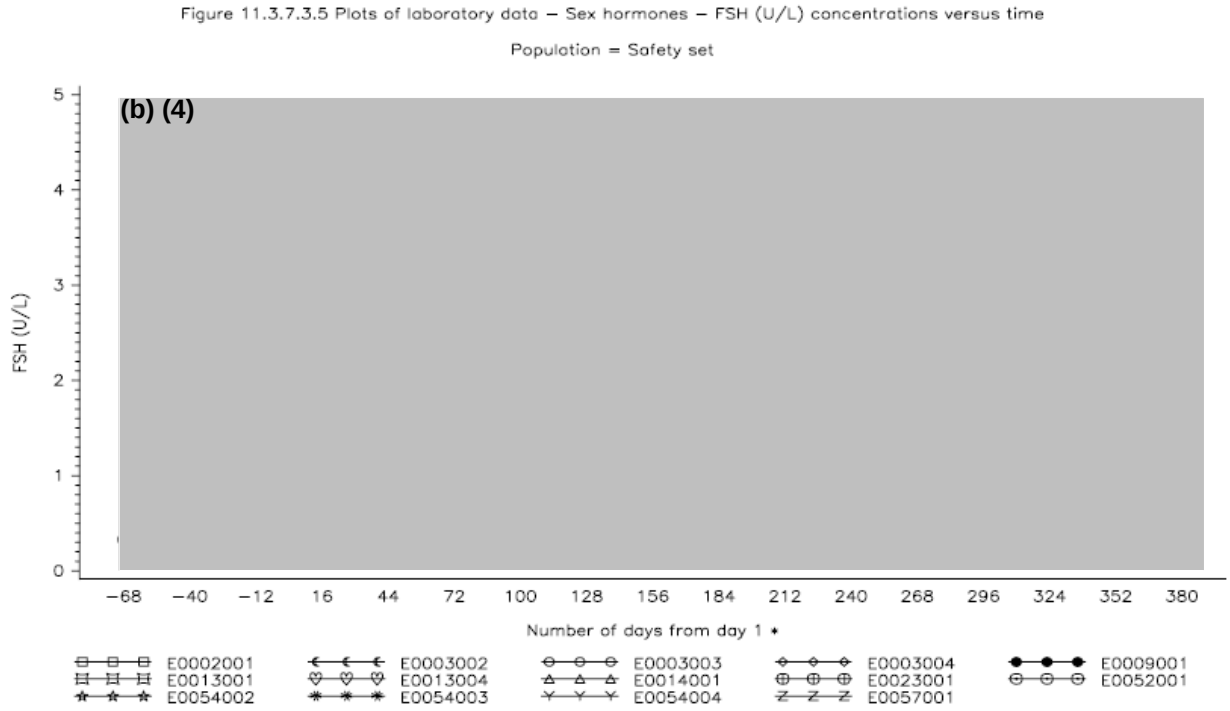
The individual measurements for luteinizing hormone (LH) during the clinical trial are illustrated in applicant's Figure 11.3.7.3.4.

Figure 11.3.7.3.4 Plots of laboratory data – Sex hormones – Luteinizing Hormone (U/L) concentrations versus time

Population = Safety set



The individual measurements of follicle stimulating hormone (FSH) during the clinical trial are illustrated in applicant's Figure 11.3.7.3.5.



7.1.3.3.3 Marked outliers and dropouts for laboratory abnormalities

There were no marked outliers of laboratory abnormalities.

7.1.7.4 Additional analyses and explorations

7.1.7.5 Special assessments

7.1.8 Vital Signs

Data on vital signs were not collected routinely in this study.

7.1.9 Electrocardiograms (ECGs)

ECG data were not collected routinely in this study.

7.1.10 Immunogenicity

Not applicable. Neither bicalutamide nor anastrozole is a protein therapeutic.

7.1.11 Human Carcinogenicity

Both Casodex and Arimidex are approved products. Refer to the current Casodex and Arimidex labels.

7.1.12 Special Safety Studies

No special safety studies were conducted and none are recommended.

7.1.13 Withdrawal Phenomena and/or Abuse Potential

There is no clinical or mechanistic evidence of withdrawal phenomena and/or abuse potential for bicalutamide or anastrozole in any of the population studied to date.

7.1.14 Human Reproduction and Pregnancy Data

Both Casodex and Arimidex are approved products. Refer to the current Casodex and Arimidex labels.

In response to the Agency's request, a 90-day oral toxicity study with assessment and recovery of reproductive function was conducted in juvenile male rats (Study 0514GR). The results of this study have been reviewed (see pharmacology and toxicology review in DFS) and found to support the doses evaluated in clinical trial D6873C00047.

7.1.15 Assessment of Effect on Growth

Refer to the efficacy section for details (linear growth has been the primary efficacy endpoint in clinical trial D6873C00047.

7.1.16 Overdose Experience

There were no cases of accidental overdose in the clinical trial.

7.1.17 Postmarketing Experience

Not applicable (neither bicalutamide nor anastrozole is not approved in children).

7.2 Adequacy of Patient Exposure and Safety Assessments

7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

7.2.1.1 Study type and design/patient enumeration

Refer to Section 6.1.3

7.2.1.2 Demographics

Refer to Section 6.1.3

7.2.1.3 Extent of exposure (dose/duration)

Descriptive statistics regarding the exposure to bicalutamide and anastrozole during the study are summarized in applicant's Table 36. The mean duration of actual exposure to bicalutamide was 329.6 days (range of 25 to 383 days). For anastrozole, the mean duration of actual exposure was 337.1 days (range 40-383 days)[44].

Table 36 Summary of duration of exposure (days): Safety set

Duration (days)	Anastrozole (0.5 or 1 mg) N=14		Bicalutamide (12.5 to 100 mg) N=14	
	Total exposure	Actual exposure	Total exposure	Actual exposure
n	14	14	14	14
Mean	339.6	337.1	334.6	329.6
SD	86.40	87.30	88.98	89.68
Median	365.0	362.0	365.0	349.0
Range	43 - 380	40 - 383	29 - 366	25 - 383

Total exposure = last dose date – first dose date + 1
Actual exposure = last dose date - first dose date + 1 accounting for dose interruptions based on tablet counts
The duration of exposure includes the titration phase when patients received lower doses.

[44] The anastrozole exposure was longer because in the early stages of the trial patients were started on anastrozole prior to bicalutamide treatment initiation out of concern that bicalutamide may elevate testosterone, and subsequently estrogen, to undesired levels. Once this concern was not confirmed both drugs were initiated at the same time.

Following titration, the final daily doses of bicalutamide (applicant's Table 37) were 12.5 mg (1 patient), 25 mg (1 patient), 50 mg (8 patients) and 100 mg (4 patients). The final daily doses of anastrozole were 0.5 mg (10 patients) and 1 mg (4 patients).

Table 37 Summary of final stabilised dose of anastrozole (mg) and final stabilised dose of bicalutamide (mg): Safety set

Anastrozole final dose (mg)	Number (%) of patients N=14 Bicalutamide final dose (mg)			
	12.5	25	50	100
0.5	0 (0.0)	0 (0.0)	7 (50.0)	3 (21.4)
1	1 (7.1)	1 (7.1)	1 (7.1)	1 (7.1)

7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

7.2.2.1 Other studies

None.

7.2.2.2 Postmarketing experience

None known in patients with testotoxicosis.

7.2.2.3 Literature

7.2.3 Adequacy of Overall Clinical Experience

Given the rarity of the disease the number of patients studied (14 *in toto* with 7/14 treatment-naïve) is comparable to the largest datasets published to date in the medical literature for patients with testotoxicosis.

7.2.4 Adequacy of Special Animal and/or In Vitro Testing

Refer also to Section 7.1.14.

7.2.5 Adequacy of Routine Clinical Testing

Clinical testing was extensive and consisted in physical exams, recording of adverse events, and laboratory assessments. Physical exams also included counting of the number of acne lesions, testicular volume measurements, Tanner staging, and breast pain/gynecomastia evaluations. Standard adverse event collections were completed at scheduled visits (i.e. baseline, Month 1, Month 3, Month 6, Month 9, Month 12) and at additional timepoints as dictated by supplementary PK assessments due to bicalutamide/ anastrozole dose changes. GnRH testing

was performed at baseline, end of study and, if necessary, in between if onset of central puberty was suspected. Laboratory testing included sex hormone measurements[45] and standard hematology and chemistry analytes[46]. Radiological exams to calculate the bone age were performed at baseline, Month 6, and Month 12.

7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup

Refer to the Casosex and Arimidex labels.

7.2.7 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study

Not applicable. Both Casodex and Arimidex are approved drugs.

7.2.8 Assessment of Quality and Completeness of Data

The data appeared complete. There were no inconsistencies between different datasets and data sources.

7.2.9 Additional Submissions, Including Safety Update

Several submissions were presented to the Agency in response to information requests. The data included in these submissions is implicitly and/or explicitly included in various sections of this clinical review.

A 4-month safety update was submitted on October 21, 2008. It summarizes safety information accumulated from May 7, 2008 (the cut-off date for the NDA) through August 31, 2008. It includes data collected in 12/13 patients who completed Study D6873C00047 and continued the extension phase of the study. There were no deaths, serious adverse events, discontinuations due to adverse events, or other significant adverse events. There were five new adverse events reported, all mild or moderate in intensity (applicant's Table 4). The only AE that was considered to be related to the study treatment was central precocious puberty, an adverse event already described in the initial NDA dataset. The safety information provided by the 4-month safety update was consistent with that of the original NDA.

[45] They included total and free testosterone, luteinizing hormone, follicle stimulating hormone, inhibin B, estradiol, estrone, β-HCG, 17-OHP and DHEAS.
[46] They included full blood count, electrolytes (sodium and potassium), renal tests (urea, creatinine) and liver function tests (bilirubin, gamma GT, AST and ALT).

Table 4 Listing of AEs with an onset date between the cut-off for the NDA and the cut-off for the 4MSU: Safety set

Patient	MedDRA Preferred Term	CTC grade (Intensity)	Days from Day 1 when the AE started	Duration	Considered related to bicalutamide and/or anastrozole
E0003002	Sinus Congestion[a]	Mild	709	5 days	No
E0013001	Precocious puberty[a, b]	Moderate	656	Ongoing	Yes
E0014001	Eosinophilia	Mild	771	Ongoing	No
E0052001	Otitis media	Moderate	617	15 days	No
	URTI	Mild	622	4 days	No

[a] These events had a start date before the cut-off for the NDA but were not reported to AstraZeneca until after the cut-off and were not included in the NDA.
[b] Investigator text was "central precocious puberty" for which MedDRA preferred term is "precocious puberty"
URTI Upper Respiratory Tract Infection

7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

The major limitation of this dataset is the low patient exposure (14 patients enrolled, 13 completers treated for 12 months) and the absence of a control group. Within these limits imposed by the rarity of the disease and the exploratory nature of the study, one can assert that no distinct safety signals were identified. Although the absence of a control group makes certain attribution of adverse events to any specific treatment extremely difficult, it is reasonable to assert that most of the adverse events observed in the trial were either due to common infectious diseases of childhood or were coincidental with the bicalutamide/anastrazole treatment. This statement is based on the fact that many of these adverse events are not secondary to any known mechanisms of action of either Casodex or Arimidex as currently described in their respective labels. Given the known pharmacodynamic effects of the bicalutamide/anastrozole combination, gynecomastia, breast tenderness, and breast pain are adverse events likely to be drug-related. Another one is central precocious puberty, an event that is expected in association with persistent sex steroid exposure.

7.4 General Methodology

7.4.1 Pooling Data Across Studies to Estimate and Compare Incidence

Not applicable.

7.4.1.1 Pooled data vs. individual study data

Not applicable.

7.4.1.2 Combining data

Not applicable.

7.4.2 Explorations for Predictive Factors

Due to the small size of the dataset no explorations for predictive factors were done.

7.4.2.1 Explorations for dose dependency for adverse findings

Due to the small size of the dataset no explorations for dose dependency were done.

7.4.2.2 Explorations for time dependency for adverse findings

Due to the small size of the dataset no explorations for time dependency were done.

7.4.2.3 Explorations for drug-demographic interactions

Due to the small size of the dataset no explorations for drug-demographic interactions were done.

7.4.2.4 Explorations for drug-disease interactions

Due to the small size of the dataset no explorations for drug-disease interactions were done.

7.4.2.5 Explorations for drug-drug interactions

Due to the small size of the dataset no explorations for drug-drug interactions were done.

7.4.3 Causality Determination

Refer to Section 7.3.

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

The bicalutamide and anastrozole doses evaluated in Study D6873C00047 were not effective in reducing the accelerated growth rate associated with androgen excess in patients with testotoxicosis. This occurred despite successfully titrating bicalutamide to serum drug concentration within the range of 5-15 µg/ml, which is known to induce androgen blockade in adult males with prostate cancer, and in spite of maintaining low serum estrogen concentrations with the anastrozole regimen selected. These observations are puzzling given that a similar regimen of a presumably less potent antiandrogen and aromatase inhibitor was quite successful both short-term and long-term (Lescheck et al.). Whether bicalutamide titration to higher serum concentrations, or some other modification of the current regimen would be successful, remains to be explored in further investigations.

8.2 Drug-Drug Interactions

Due to the small size of the dataset no explorations for drug-disease interactions were done.

8.3 Special Populations

No studies were conducted in patients with renal or hepatic failure.

8.4 Pediatrics

Under PREA, a waiver should be issued for the study of children < 2 years of age or > 12 years. Patients over 12 years are expected to be in puberty and therefore should not be treated with bicalutamide. The number of patients with testotoxicosis below 2 years of age is expected to be so low that conducting a clinical trial in this age group would be a practical impossibility.

8.5 Advisory Committee Meeting

There were no Advisory Committee Meetings for this application.

8.6 Literature Review

Testotoxicosis is an extremely rare disease with an estimated prevalence of 1-9 boys per 1,000,000[47]. Not surprisingly there are relatively few publications about testotoxicosis (mostly

[47] According to estimate published on Orphanet at http://www.orpha.net//consor/cgi-bin/OC_Exp.php?Lng=GB&Expert=3000).

case reports, occasional reviews and basic science investigations into the molecular defects of the condition) and no randomized clinical trials. Regarding therapeutical interventions in testotoxicosis, there are three case-series which represent the largest datasets published to date in this condition (about 10 patients per case-series); they will be briefly summarized next. Emphasis will be placed for efficacy data at the end of the first year of study (a duration comparable to that of Study D6873C00047).

Leschek et al. Six-year results of spironolactone and testolactone treatment of familial male-limited precocious puberty with addition of deslorelin after central puberty onset. J Clin Endocrinol Metab 84: 175-178, 1999.

This study, published in 1999, summarizes the NIH experience accumulated with 10 patients treated with an antiandrogen (spironolactone) and an aromatase inhibitor (testolactone) for 6 years. All patients had an activating mutation of the LH receptor (D578G). The baseline characteristics for the patients described are summarized in Table 1, below. Mean chronological age was 4.3 years (range: 2.3 years to 5.6 years). Bone age was markedly advanced with a mean of 9.6 years (range: 4 to 13.5 years). All patients had markedly accelerated growth rates (all were > +2 SD) with a mean growth rate SD score of + 7.8 (range: 3.4 to 12.5) and a mean growth rate of 16 cm/year (range: 9.8 to 20.7).

TABLE 1. Clinical features of 10 boys with familial male precocious puberty at start of treatment with spironolactone and testolactone

Patient no.	CA (yr)	BA (yr)	Ht (cm)	Ht (SD units)	Growth rate (cm/yr)	Growth rate (SD units)
1	5.6	13	125.0	+2.4	9.8	+3.4
2	5.2	12.5	134.6	+5.1	13.8	+7.0
3	4.6	13.5	129.3	+4.9	20.7	+12.5
4	3.8	10	123.3	+5.2	15.9	+7.4
5	2.3	4	99.6	+2.9	20.1	+7.7
6	4.8	9	111.2	+0.6	14.2	+6.9
7	4.1	9	117.5	+3.2	16.5	+8.2
8	3.5	6	108.2	+2.2	13.8	+5.3
9	4.3	8	115.4	+2.3	18.4	+10.1
10	4.5	11.5	116.6	+2.3	17.7	+9.6

CA, Chronological age; BA, bone age.

At the end of the first year of treatment the following efficacy observations were made:

- the mean growth rate decreased from 16.1 ±1.1 cm/yr to 7.5 ± 0.6 cm/yr ($P < 0.005$), which corresponds to greater than 50% reduction. Similarly, growth velocity SD score decreased from 6.9 ± 1.0 to 1.1 ± 0.4 ($P <0.005$).
- the rate of bone maturation decreased from 2.5 ± 0.3 to 1.7 ± 0.3 ($P<0.005$)
- predicted adult height did not change significantly

- testosterone was in the male adult normal range before treatment (316 ± 28 ng/dL) and remained in the adult range throughout treatment; estrogen levels were not provided
- seven of the 10 boys had acne that improved by the 6-month visit
- two of the four boys whose parents complained of aggressive behavior before treatment improved within 6 months of treatment.

Additional data are presented beyond one year of treatment (up to 5 years).

- the regimen of spironolactone and testolactone resulted in statistically significant reductions in growth velocity relative to baseline for up to 6 years of treatment
- predicted adult height reach statistically significant improvements beginning with Year 4 and continued so through Year 6 of treatment
- testosterone remained in the adult range for 6 years of study with some variations (reductions) from baseline[48]
- safety profile was acceptable (gastrointestinal upset was noted with testolactone but it resolved spontaneously without dose reduction).

Soriano-Guillen L et al. Adult height after ketoconazole treatment in patients with familial male limited precocious puberty. J Clin Endocrinol Metab 90: 147-151, 2005.

This single center study describes the long-term efficacy of ketoconazole (an antifungal which also inhibits adrenal and testicular androgen biosynthesis) on five patients with testostosticosis treated for 5–10 years and followed to adult height. Baseline characteristics for this group of patients are summarized in Table 1 of the publication (below). Mean chronological age at treatment initiation was 4.9 years (range: 3.5 to 6 years). Other baseline features included: a mean growth rate of 12.8 cm ± 2.8 cm (range: 10-14 cm), a mean growth velocity SDS of + 5.6, a mean serum testosterone concentration of 5.12 ng/ml (17.9 nmol/L), and a bone age that was advanced by 1-5.7 years over chronological age (mean 3.9 years).

TABLE 1. Characteristics of FMPP patients before treatment

Patient no.	1	2[a]	3[a]	4[a]	5[a]
Age at onset of symptoms (yr)	2.3	5.6	6	3.1	4
LH receptor mutation	M398T	M398T	M398T	I542L	I542L
Age at treatment initiation (yr)	4.8	6	6	3.5	4.3
Bone age − chronological age (yr)	5.7	5.3	4	3.6	1
Height (SDS)	4.0	2.2	1.0	4.0	2.8
Growth velocity (cm/yr)	13	14	10	13	10
Growth velocity (SDS)	6.5	7.8	3.8	5.8	4.0
Unilateral testicular volume (ml)[b]	7	8	7	9	11
Pubic hair stage	P2	P3	P2	P3	P2
Serum testosterone (ng/ml)[c]	6.5	5.6	1.5	7.4	4.6
Plasma LH (basal/peak after GnRH, IU/liter)	0.3/0.8	0.6/2.8	0.8/0.3	0.5/0.5	0.5/0.5
Plasma FSH (basal/peak after GnRH, IU/liter)	0.5/0.7	0.6/1.2	0.4/1.6	0.5/0.5	0.5/0.5

[a] Patients 2 and 3, and 4 and 5, respectively, are brothers.
[b] The largest of two testes.
[c] To convert the values for testosterone to nmol/liter, multiply by 3.5.

[48] In a preliminary report from the same group that included 8 patients, testosterone levels were 10.4 ± 1 at baseline and remained practically unchanged at the end of one year of treatment (11.8 ± 0.7 mmol/L). (Laue L et al. Treatment of familial male limited precocious puberty with spironolactone, testolactone, and deslorelin. J Clin Endocrinol Metab 76: 151-155, 1993).

The following observations were made at the end of the first year of treatment:

- growth velocity decreased from 12 ± 2.8 cm/yr before treatment to 6 ±3.5 cm/yr (approximately 50% reduction)
- growth velocity SDS decreased from 5.8 ± 2.8 before treatment to 0 ± 2.3 (and remained stable thereafter)
- bone age minus chronological age did not change significantly (reductions were observed with the 2nd and subsequent years)
- testosterone level, which was in the pubertal range before treatment (5.6 ± 3.4 ng/ml; 19.6 ±12.2 nmol/liter), decreased during ketoconazole treatment to 0.2 ±0.5 ng/ml (0.7 ± 1.7 nmol/liter).

Data presented beyond one year of treatment indicated a decelerated growth rate, a progressive and persistent reduction in the difference between the bone age and chronological age, a normalized final height (-1.7 to - 1.1 SDS) , and a significant increase in adult height when compared to pretreatment predicted adult height (range of 5-13 cm). Tolerance was acceptable (one patient had asymptomatic ALT elevation up to 102 IU/L that resolved without interruption of treatment).

Almeida MQ et al. Long-term treatment of familial male limited precocious puberty (testotoxicosis) with cyproterone acetate or ketoconazole. Clinical Endocrinology, 69, 93-98 (2008).

This Brazilian multicenter case-series reports efficacy data from 10 patients with testotoxicosis treated with one of two regimens: cyproterone acetate or ketoconazole. The main baseline characteristics and efficacy on treatment are summarized in Table 1, below. The mean chronological age at the start of treatment was 4.1 years (range 1.3 –7.9 years) and 4.2 years (2.4–6.4 years) for patients treated with cyproterone acetate[49] and ketoconazole, respectively.

[49] An agent that to antagonizes androgen action at the receptor level, also known to induce suppression of the pituitary gonadotropin secretion in patients with gonadotropin-dependent precocious puberty

Table 1. Phenotype of Brazilian boys with FMPP before and after treatment with cyproterone acetate or ketoconazole

	Initial evaluation				Post-treatment							
Patient	CA (years)	BA (years)	BA/CA	Height (cm/SDS)	CA (years)	BA (years)	BA/CA	Height (cm/SDS)	Target height range (cm)	LHCGR mutation	Treatment	Duration (years)
1	5·9	13	2·2	144/5·9	11·1	Adult	1·4	176/0·3	Adopted	A568V	Cyproterone‡	5·3
2	2·8	6	2·1	103/3	10·7	15·5	1·5	164/–0·7	162·4–179·4	T577I	Cyproterone†§	8
3*	1·3	1	0·8	83/1·3	2·3	2	0·9	95/	162·4–179·4	T577I	Cyproterone	1·5
4	2·8	6	2·1	113/6·2	8·5	15	1·8	161/–0·8	169–186	L457R	Cyproterone§	4·5
5	7·9	13·5	1·7	143/2·8	16·3	Adult	1·0	159/–2·2	NA	A568V	Cyproterone†	5
6	4·0	6	1·5	107/1·3	9	10	1·1	145/1·8	NA	M571I	Ketoconazole	4
7	3·4	6	1·8	103/1·95	15	Adult	1·1	160/–2·6	161·5–178·5	L368P	Ketoconazole†	14
8	2·4	4	1·7	94/1·3	15	Adult	1·1	160/–2·6	161·5–178·5	L368P	Ketoconazole†	11
9	4·7	7	1·5	118/4·0	7·8	11	1·4	136/–0·8	163·5–180·5	M571I	Ketoconazole	3·1
10	6·4	13	2·0	136/3·7	15	Adult	1·1	164/–1·6	153·5–170·5	A568V	Ketoconazole	8

CA, chronological age; BA, bone age; SDS, standard deviation score; NA, not available.
Patients 2 and 3 were siblings, as were patients 7 and 8.
*Patient 3 was diagnosed after familial screening.
†Combined treatment with leuprolide acetate depot; ‡medroxyprogesterone acetate (3 years); §anastrozole.

Efficacy data are presented for timepoints beyond one year of treatment and the main ones are summarized in the following figures. Of interest is the fact that one patient (patient 4, who had the LH receptor mutation L457R mutation) did not show improvement in height after 2 years of combined therapy with cyproterone acetate(and anastrozole. The authors propose that "differences in the phenotypic expression and therapeutic results might be explained by some peculiarities of LHCGR-activating mutations".

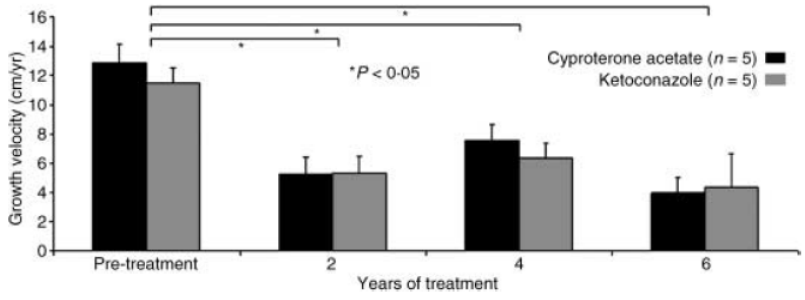


Fig. 1 Growth velocity (cm/year) obtained during treatment with cyproterone acetate ($n = 5$) or ketoconazole ($n = 5$) in boys with familial male-limited precocious puberty (FMPP) were compared to pretreatment values in each group. $^*P < 0{\cdot}05$.

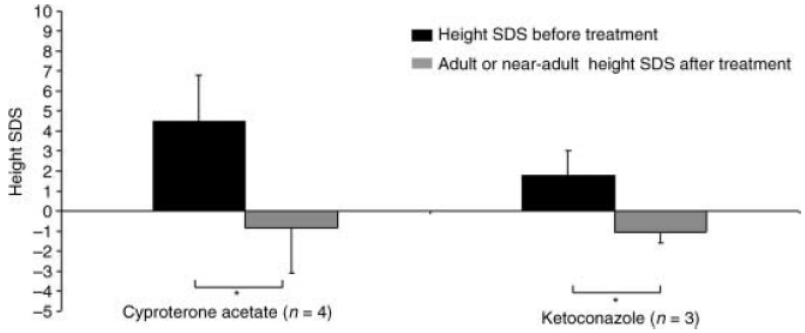


Fig. 2 Height SDS before therapy and adult or near-adult height SDS in boys with familial male-limited precocious puberty (FMPP) treated with cyproterone acetate ($n = 4$) or ketoconazole ($n = 3$). $^*P < 0{\cdot}05$.

Kreher NC et al. Treatment of familial male limited precocious puberty with bicalutamide and anastrozole. J Pediatr 2006; 149; 416-20. J Clin Endocrinol Metab 84: 1136-1140, 1999.

Although this article is a report of only two patients, it is of interest because both patients were treated with the same regimen (bicalutamide and anastrozole) that was used in Study D6873C00047. The first patient (Case1) was a 6-month-old boy, with advanced bone age (8.5 years), rapid linear growth (9.1 cm/y (+3.3 SD)), an elevated testosterone level (8.1 nmol/L or 233 ng/dL), and undetectable estradiol levels (<92 pmol/L). The second patient (Case 2) was a 4-year-old boy with accelerated growth velocity 13.4 cm/y (+6.0 SD), advanced skeletal maturation (ΔBA/ΔCA = 4.7), elevated testosterone (15.0 nmol/L or 434 ng/dL), and an estradiol level of (<92 pmol/L or <25 pg/mL).

Patient 1 received 44 months of treatment with bicalutamide (50 mg per day) and anastrozole (1 mg per day). Over 1 year of treatment growth velocity decreased from 9.1 cm/y (+3.3 SD) to 4.7 cm/y (-0.9 SD). In addition, ΔBA/ΔCA was reduced, testosterone levels remained stable (8.4 nmol/L or 291 ng/dL) and there was no detectable change in estrodial levels.

Patient 2 received 17 months of treatment with bicalutamide/anastrozole (doses not specified). During treatment growth velocity normalized from 13.4 cm/y (+6.0 SD) to 7.1 cm/y (+0.7 SD), ΔBA/ΔCA decreased, virilization manifestations and inappropriate behavior improved; there was no change in total testosterone (22.0 nmol/L or 635 ng/dL) or estrogen.

The authors conclude that "the combination of bicalutamide and anastrozole has resulted in impressive clinical results [..] and improvement in height potential without any reported side effects."

8.7 Postmarketing Risk Management Plan

None recommended (the indication should not be approved).

8.8 Other Relevant Materials

None.

9 OVERALL ASSESSMENT

9.1 Conclusions

The bicalutamide/anastrozole regimen evaluated in this NDA in boys with testotoxicosis failed to demonstrate efficacy. There were no safety signals associated with this regimen that were identified during this 12-month study.

9.2 Recommendation on Regulatory Action

Non-approval.

9.3 Recommendation on Postmarketing Actions

None**.**

9.3.1 Risk Management Activity

None.

9.3.2 Required Phase 4 Commitments

None.

9.3.3 Other Phase 4 Requests

The applicant has committed to submit in Annual Reports adverse events collected in the extension phase of the clinical trial D6873C00047.

9.4 Labeling Review

The proposed labeling is in general acceptable, but the information provided is too detailed. A more concise version is provided in the Appendix.

9.5 Comments to Applicant

See labeling changes in Section 10.2.

10 APPENDICES

10.1 Review of Individual Study Reports

Not applicable (there was only one clinical study).

10.2 Line-by-Line Labeling Review

8.4. Pediatric Use

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

REFERENCES

Almeida MQ et al. Long-term treatment of familial male limited precocious puberty (testotoxicosis) with cyproterone acetate or ketoconazole. Clinical Endocrinology, 69, 93-98 (2008).

Aziz. AA et al. Testotoxicosis: gonadotrophin-independent male sexual precocity. Postgrad Med J, 68, 225-228, 1992.

Bertelloni S et al: Long-term outcome of familial male limited precocious puberty. Horm Res; 48: 235-239 1997.

Clark PA and Clarke WL. Testotoxicosis. An unusual presentation and novel gene mutation. Clinical Pediatrics , 1995, 271-274.

Egli CA et al. Pituitary gonadotropin-independent male-limited utosomal dominant sexual precocity in nine generations: Familial testotoxicosis. J Pediatr 106:33, 1985.

Kreher NC et al. Treatment of familial male limited precocious puberty with bicalutamide and anastrozole. J Pediatr 2006; 149; 416-20. J Clin Endocrinol Metab 84: 1136-1140, 1999.

Kremer H et al. A limited repertoire of mutations of the luteinizing hormone (LH) receptor gene in familial and sporadic patients with male LH-independent precocious puberty.

Laue L et al. Treatment of familial male limited precocious puberty with spironolactone and testolactone. N Engl J Med 1989; 320: 496-502.

Laue L et al. Treatment of familial male limited precocious puberty with spironolactone, testolactone, and deslorelin. J Clin Endocrinol Metab 76: 151-155, 1993.

Leschek et al. Six-year results of spironolactone and testolactone treatment of familial male-limited precocious puberty with addition of deslorelin after central puberty onset. J Clin Endocrinol Metab 84: 175-178, 1999.

Lim YL and Low LCK. Familial testotoxicosis in a Chinese family. Eur j Pediatr, 153: 241-244, 1994.

Reiter EO and Norjavaara E: Testotoxicosis: Current viewpoint. Pediatric Endocrinology Reviews, (30 2, 7786, 2005.

Soriano-Guillen L et al. Adult height after ketoconazole treatment in patients with familial male limited precocious puberty. J Clin Endocrinol Metab 90: 147-151, 2005.

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

/s/

Dragos Roman
12/15/2008 10:03:02 AM
MEDICAL OFFICER

Mary Parks
12/15/2008 10:45:26 AM
MEDICAL OFFICER
I concur with Dr. Roman's conclusion on efficacy and safety of this application. Although no indication is granted, labeling will be approved to include the findings from this application to better inform healthcare providers.