CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-310

STATISTICAL REVIEW(S)

12/17/08

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/Serial Number:	22-310
Drug Name:	Casodex
Indication(s):	gonadatropin-independent precocious puberty in boys with testotoxicosis
Applicant:	Astra Zeneca
Date(s):	Submitted June 25, 2008
Review Priority:	Priority (pediatric)
Biometrics Division:	Biometrics 2
Statistical Reviewer:	J. Todd Sahlroot, Ph.D.
Concurring Reviewers:	Tom Permutt, Ph.D.
Medical Division:	Metabolic and Endocrine Products (DMEP)
Clinical Team:	Dragos Roman, M.D. (Reviewer)
	Mary Parks, M.D. (Team Leader and Division Director)
Project Manager:	Jennifer Johnson
Keywords	NDA submission, clinical studies, pediatric exclusivity

Table of Contents

1. **EXECUTIVE SUMMARY** 3

1.1 CONCLUSIONS AND RECOMMENDATIONS 3
1.2 BRIEF OVERVIEW OF CLINICAL STUDIES 3
1.3 STATISTICAL ISSUES AND FINDINGS 4

2. **INTRODUCTION** 5

2.1 OVERVIEW 5
2.2 DATA SOURCES 5

3. **STATISTICAL EVALUATION** 5

3.1 EVALUATION OF EFFICACY 5

4. **LABELLING RECOMMENDATIONS** 8

APPENDIX 9

1. EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

In a small open-label study submitted in response to an FDA pediatric Written Request (WR), the combination of Casodex (bicalutamide) and Arimidex (anastrozole) failed to significantly reduce growth velocity in 13 boys with testotoxicosis. The median change in growth velocity after 12 months was -2.8 cm/year from a retrospective pre-study rate of 10.8 cm/year (mean change = -1.6 cm/yr, 95% CI = (-4.8, 1.7)). In the subgroup of patients without previous testotoxicosis treatment (n=7), the primary analysis population identified in the WR for assessing growth, the mean change in growth velocity was close to nominal statistical significance (-2.8 cm/yr, p=.053). Mean changes were null in previously treated patients.

There was a strong linear relationship between pre-study growth rate and change in growth rate from pre-study (Pearson r = -0.94). Patients with higher pre-study rates had greater reductions in growth while on treatment.

The sponsor proposed labeling for the product without an indication. Recommendations for labeling can be found in Section 4.

1.2 Brief Overview of Clinical Studies

The sponsor submitted one open-label study of combination Casodex (bicalutamide) and Arimidex (anastrozole) for the treatment of gonadatropin-independent precocious puberty in boys with testotoxicosis. The study was submitted in response to an FDA pediatric WR. The primary objective concerned the combined effect of Casodex and Arimidex on the change in growth velocity from pre-study growth velocity after 12 months of treatment.

Enrolled patients had to be naïve to anti-androgen therapy. To increase enrollment, subsequent protocol amendments relaxed this restriction to allow specific prior treatment with ketoconazole, spironolactone, anastrozole or other aromatase inhibitors. In the Final Report, the sponsor considered all enrolled patients to be treatment-naïve and therefore equated the entire study population to the "treatment naïve" population specified in the WR. The Medical Officer considers only those patients not previously treated for testotoxicosis (7 of 13 patients) to be the "treatment naïve" subset in the WR. I will use the Medical Officer (and WR definition) of treatment naïve in this review.

Dosing was specific to each patient with the goal of achieving clinically appropriate serum estradiol and plasma bicalutamide concentrations.

Table 1 shows major study characteristics. A patient was a completer if he received a minimum of 300 days of study treatment over the previous 12 months and had 12

months of safety and efficacy data. Thirteen of the 14 patients exposed to treatment were completers by this definition.

Table 1: Study characteristics

# cntrs	Total n/ completers	Population Age, race	Design	primary endpoint key secondary endpts	Dur of Trt
10 centers in 3 cntries	14/13 One patient received treatment but did not have on-trt height data	Boys with testotoxicosis treated for gonadatropin-independent precocious puberty 14 boys ages 2 to 9 (mean 3.9 yr) 12/14 caucasian Previous testotoxicosis trt (completers): No n=7 Yes n=6	Uncontrolled open label retrospective collection of pre-study height data	Change from pre-study in growth velocity (cm/yr) at 12 months <u>Key secondary</u> Other growth measures Bone age Testicular volume Tanner stage	12 months

1.3 Statistical Issues and Findings

I've presented growth rate changes as both means and medians. Data for all endpoints were roughly normally distributed. Medians are shown for comparative purposes.

Two patients (5101 and 5102) were twins. As would be expected, their growth data were very similar and should not be considered as independent. Removing either of their data from statistical analyses did not alter the overall conclusions.

Despite its small size, the trial was designed to have adequate power on the primary endpoint in the subset of naïve patients, i.e., those without prior testotoxicosis treatment. Sample size calculations are shown in the Appendix. Power was calculated for 12 scenarios (3 growth velocities x 2 SD x 2 powers). All but two of the scenarios required at most 5 patients.

Pre-study height data were collected retrospectively. The rules regarding the selection of relevant pre-study data were identified prospectively in the study protocol.

2. INTRODUCTION

2.1 Overview

Testotoxicosis, or familial male-limited precocious puberty, is a luteinizing hormone-releasing hormone-independent form of isosexual precocious puberty resulting from an activating mutation at the luteinizing hormone receptor. The condition is rare. Affected boys usually begin pubertal development by 2 to 3 years of age, resulting in rapid growth and bone maturation, progressive virilization and ultimately, premature epiphyseal fusion and short stature in adulthood. The imbalance in the ratio of estrogen to androgen levels can also result in transient gynecomastia and breast pain.

There is no approved treatment for testotoxicosis. The rationale for using Casodex and Arimdex together is that of combining an anti-androgen to block testosterone activity (e.g., Casodex) and an aromatase inhibitor (e.g., Arimidex) to inhibit estrogen production in testotoxicosis.

2.2 Data Sources

Raw data
\\Cdsesub1\EVSPROD\NDA022310\0000\m5\53-clin-stud-rep\535-rep-effic-safety-stud\request-for-pediatric-exclusivity-01\5352-stud-rep-uncontr\d6873c00047\crt\datasets

Study report
\\Cdsesub1\EVSPROD\NDA022310\0000\m5\53-clin-stud-rep\535-rep-effic-safety-stud\request-for-pediatric-exclusivity-01\5352-stud-rep-uncontr\d6873c00047

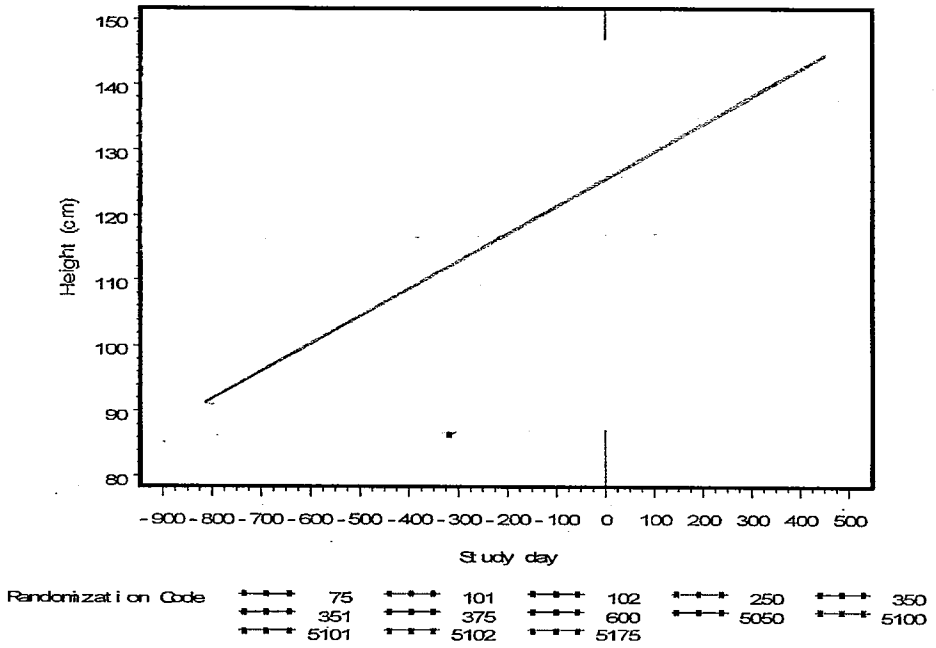
3. STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

Height

On-study height was measured (prospectively) at months 0, 3, 6, 9 and 12. Pre-study height data were obtained retrospectively. Patients were required to have at least one height measurement ≥ 6 months before starting treatment. If there were multiple such height measurements, the most recent height measured 6 months before treatment was used to calculate a pre-study growth rate. The selected heights for patients were measured anywhere from 6 months and 2-1/2 years before treatment. All raw height data are shown in Figure 1.

Figure 1
Retrospective and prospective height measurements
By previous treatment (N=black, Y=blue)



b(4)

Primary endpoint -- Growth velocity

The primary efficacy endpoint was the change from pre-study in growth velocity (cm/yr) at 12 months. Table 2 shows growth rates in cm/yr and SD units. (Data verified by this reviewer.) A patient's growth rate in SD units was calculated by taking the annualized difference of heights in SD (age-adjusted) units. Each height was standardized by subtracting the mean of the same-age population from the patient's value and dividing by the standard deviation of the population.

Table 2. Annualized growth rates

Efficacy Measure	Analysis set	Pts (%) with growth reduction[5]	Means			Median Change [2]	P-value (95% CI) [3]
			Base	On-trt	Change [1]		
Growth rate (cm/yr)	All treated (n=13)	9/13 (69%)	10.8	9.2	-1.6	-2.8	.33 (-4.8, 1.7)
	Previous trt (n=6)	4/6 (67%)	10.3	10.1	-0.2	-2.6 [4]	.99 (-7.5, 7.6)
	No prev trt (n=7)	5/7 (71%)	11.2	8.4	-2.8	-2.8	.053 (-5.7, 0.1)
Growth rate SDS (SD units)	All treated (n=13)	9/13 (69%)	0.4	0.3	-0.1	-0.4	.85 (-1.2, 1.0)
	Previous trt (n=6)	4/6 (67%)	-0.1	0.6	+0.7	-0.2 [4]	.47 (-1.6, 3.0)
	No prev trt (n=7)	5/7 (71%)	0.8	0.1	-0.7	-0.4	.14 (-1.8, 0.3)

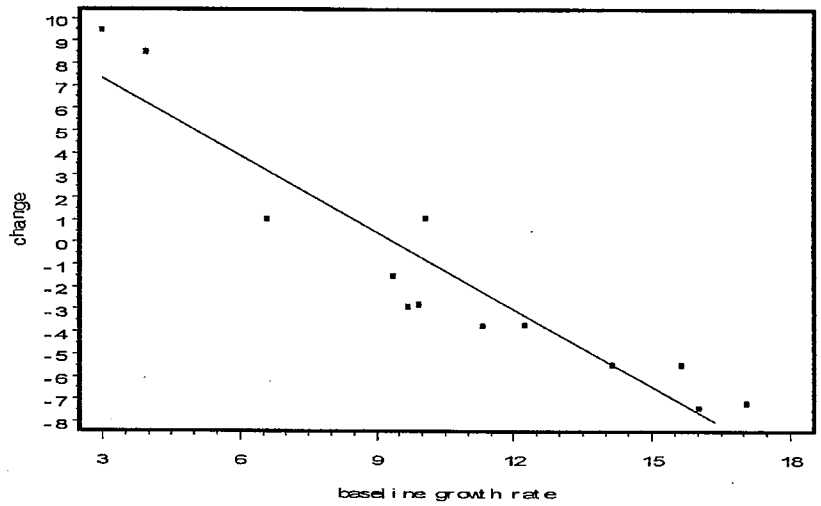
1 Mean change at 12 months from (retrospective) pre-study period
2 Median change at 12 months from (retrospective) pre-study period
3 95% CI and p-value for mean change from pre-study period
4 Median calculated as midpoint of 3rd and 4th ranked observations
5 Reduction from (retrospective) pre-study period

The combination of Casodex and Arimidex failed to significantly reduce growth velocity from pre-study growth rates in the total patient population. The median change in growth velocity after 12 months was -2.8 cm/year from a pre-study growth rate of 10.8 cm/year (mean change = -1.6 cm/yr, 95% CI = (-4.8, 1.7)). The WR specified that statistical testing be confined to naïve patients, that is, patients without previous testotoxicosis treatment (n=7). The mean change in this subgroup was close to nominal significance (-2.8 cm/yr, p=.053). Mean changes were null in previously treated patients. Median changes were similar in the two subgroups.

Figure 2 shows growth change by pre-study growth rate for all patients. There was a strong linear relationship between baseline growth rate and the change from pre-study (Pearson r = -0.94). Patients with higher pre-study rates had greater reductions in growth while on treatment. Prior testotoxicosis treatment status was not a confounding factor. That is, patients with and without prior testotoxicosis treatment had similar pre-study growth rates. Therefore, the observed linear relationship was not artificially induced by potential differences in pre-study rates in these subgroups.

The strong linear relationship shown in Figure 2 could be used to inform clinicians on the appropriate selection of patients and their expected treatment benefit.

Figure 2
Change in growth rate at 12 months by baseline growth rate



4. LABELLING RECOMMENDATIONS

1. The results on the primary endpoint should be described for all patients and for subgroups defined by previous testotoxicosis treatment status. Although growth data were roughly normally distributed, medians should be reported along with means.

2. The strong linear relationship between baseline growth and change from baseline could be used to inform clinicians on the appropriate selection of patients and the expected treatment benefit. A graph similar to Figure 2 in this review could be used to illustrate this relationship.

APPENDIX

Statistical review of Written Request amendment 4

Statistical Review and Evaluation

IND#:	61,238 (serial 0022)
Sponsor:	AstraZeneca
Drug:	Casodex (bicalutamide) tablets
Indication:	Testotoxicosis in boys
Documents reviewed:	Proposed changes to Pediatric Written Request (Amendment #4), submission dated 12/5/05
Medical Reviewer:	Dragos Roman, M.D. (HFD-510)

The current pediatric Written Request (WR) Amendment #4 was issued April 8, 2005. This submission proposes several changes to the WR. This review will focus on the proposed change concerning the number of subjects in Study 3. Given the apparent difficulty in recruiting treatment-naïve subjects (2 patients have been recruited thus far), the sponsor wishes to revise downward the number of evaluable subjects with a full complement of protocol-defined efficacy and safety data at the end of one year of treatment, from 12 to "up to 12".

Study 3 is open-label, non-comparative one-year exposure to bicalutamide and anastrozole in boys aged 2 or older with a confirmed diagnosis of testotoxicosis. Per the current WR, the patient population will consist of 12 patients without prior treatment for testotoxicosis and patients, as available, who have previously been treated. The primary endpoint is change in growth velocity from pre-study to one year of treatment to be analyzed using a paired t test and associated 95% confidence interval.

Sample size calculations in the study protocol (serial 0014) were based on a pre-study mean growth velocity of 16 cm/yr based on a similar study of 10 patients by Leschek et al (Ref. 1). A sample size of n=12 would have > 90% power to detect a 20% decrease (3.2 cm/yr) in growth rate from pre-study assuming a 2-sided significance level of 5%. The actual effect seen in Leschek at al was a decrease of 8 cm/yr. The calculation assumes the SD for the change from pre-study growth rate is 3.2 cm/yr, larger than the SD of 2.2 cm/yr seen in Leschek.

Reviewer's comments

The Table below shows sample sizes for a number of scenarios for effect size, SD and power. The minimum and maximum effect sizes in the Table are based on the protocol (3.2 cm/yr) and Leschek at al (8 cm/yr), respectively. Sample sizes based on the protocol estimates (effect size = 3.2 cm/yr, SD = 3.2 cm/yr) are n=8 for 80% power and n=11 for 90% power. These are the only two scenarios in the Table that require more than half a dozen patients. Sample sizes based on Leschek et al are only n=2 due to the larger effect size. Leschek et al also used a different, and perhaps less potent, combination of drugs, spironolactone and testolactone. Together, these indicate the effect sizes of 4.8 and 8 cm/yr in the Table may be more realistic.

Table. Sample size as a function of effect size, SD and power

Reduction in growth rate (effect size)	SD for change from baseline (cm/yr)	Power	Sample size (n)
20% or 3.2cm/yr (protocol)	2.2	80%	4
		90%	5
	3.2	80%	8
		90%	11
30% or 4.8 cm/yr	2.2	80%	2
		90%	3
	3.2	80%	4
		90%	5
50% or 8 cm/yr (Leschek et al)	2.2	80%	2
		90%	2
	3.2	80%	2
		90%	2

Overall comments

The WR may be amended to request a minimum of five naïve patients.

The statistical analyses for demonstrating an effect on growth rate should be confined to the set of naïve patients. Data for non-naïve patients can be summarized descriptively.

J. Todd Sahlroot, Ph.D.
Team Leader, DB2

Reference

Ellen Werber Leschek, Janet Jones, Kevin M. Barnes, Suvimol C. Hill and Gordon B. Cutler, Jr. **Six-Year Results of Spironolactone and Testolactone Treatment of Familial Male-Limited Precocious Puberty with Addition of Deslorelin after Central Puberty Onset,** ***The Journal of Clinical Endocrinology & Metabolism*****, Vol. 84, No. 1175-1178, 1999**

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

/s/

Todd Sahlroot
12/17/2008 04:22:41 PM
BIOMETRICS