DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF BIOSTATISTICS

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/Serial Number:	22-214/N-000
Drug Name:	Arimidex™ (anastrozole) Tablets
Indication(s):	(1) Adolescent boys with gynecomastia
	(2) Pediatric girls with McCune-Albright syndrome with progressive precocious puberty
Applicant:	AstraZeneca Pharmaceuticals LP
Date(s):	Received 09/04/07; user fee (6 months) 03/05/08
Review Priority:	Priority (pediatric exclusivity)
Biometrics Division:	Division of Biometrics II (HFD-715)
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Keywords:	NDA review, clinical study, pediatric exclusivity

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1. EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

Based on the results from 2 submitted clinical efficacy and safety studies, Arimidex™ (b) (4) (b) (4) [redacted]

In the 0006 trial, the observed response rate of a ≥ 50% reduction in total breast volume at Month 6 was 38.5% in the Arimidex group, which was much smaller than the expected rate used in the sample size and power calculation (85%). Similarly, in the 0046 trial, the observed response rate of a ≥ 50% reduction in the frequency of vaginal bleeding days over a 12-month treatment period was 28% in the Arimidex group, which was also much smaller than the expected rate used in the sample size and power calculation (67%). (b) (4) [redacted]

1.2 Brief Overview of Clinical Studies

The sponsor has submitted a Type 6 NDA (No. 22-214) in response to a Pediatric Written Request (Amendment # 4) issued on 04/08/2005 under IND 62,138, (b) (4) [redacted]

[redacted]

There were 2 clinical studies (Nos. 0006 and 0046) and 2 PK studies (No. 0001 and 0046) included in this submission. The 2nd PK study was part of the 0046 study as requested by the Agency. Study 0006 was [redacted] (b) (4) [redacted] and Study 0046 (b) (4) [redacted] (b) (4). This review focused on the clinical aspects of the 0006 and 0046 trials.

Study 0006 (04/12/2000 – 09/19/2001) was a Phase 2, 6-month, randomized, double-blind, placebo-controlled, 2-parallel-group, multicenter, USA trial, conducted in 80 adolescent boys aged between 11 and 18 years with pubertal gynecomastia. The primary efficacy endpoint was the proportion of patients who experienced a ≥ 50% reduction between Visit 1 and end of study in the calculated breast volume (combined) based on ultrasound. Study 0046 (10/23/2002 – 02/06/2006) was a Phase 2, 12-month, open-label, single-group, multicenter, international trial, conducted in 28 pediatric girls aged between 2 and 10 years with MAC due to precocious puberty. There was no primary efficacy endpoint specified in this study. However, change from baseline measurements relating to vaginal bleeding, bone age, and growth velocity were evaluated for efficacy assessment. All subjects who entered the

treatment phase of the study had retrospective data on height, weight, bone age, and vaginal bleeding history for at least 6 months prior to entry.

1.3 Statistical Issues and Findings

There were no serious statistical issues noted by this reviewer. In general, the results based on the PP population were similar to those based on the ITT population in both studies. Also, this reviewer's results summarized below agree with the sponsor's findings.

Study 0006. At the end of the 6-month trial, 38.5% and 31.4% of the Arimidex- and placebo-treated patients, respectively, experienced a 50% or greater reduction in the calculated combined breast volume of gynecomastia based on ultrasound (Text Table 1). Although the response rate was higher in the Arimidex group than in the placebo group, (b) (4) difference was observed between the 2 study groups (odds ratio = 1.364, 95% CI = (0.521, 3.569), p = 0.5275). In addition, the mean and median changes from baseline in total breast volume at Month 6 were also similar between the 2 study groups (Text Table 2). Except for 1 subject in the Arimidex group, all other symptomatic patients (who experienced breast pain at baseline) reported no breast pain (tenderness) at Month 6.

Text Table 1 – Study 0006: Proportion of Patients with Decreased Total Breast Volume at Month 6

ITT population	Arimidex	Placebo
With a reduction in total breast volume of gynecomastia	26/39 (66.7%)	24/35 (68.6%)
With a ≥ 50% reduction in total breast volume of gynecomastia	15/39 (38.5%)	11/35 (31.4%)
With a 100% reduction in total breast volume of gynecomastia	1/39 (2.6%)	0/35 (0%)

Summary statistics for change in hormonal data, height, weight, BMI, and testicular volume from baseline to Month 6 are presented in Text Table 2. According to the sponsor, there were about 50% and 20% of the Arimidex- and placebo-treated patients, respectively, with serum estradiol levels below the limit of detection (LOD, 36.7 pmol/L) at Month 6. Since the LOD value was used in the summary statistics, the mean and median values may have actually been lower than the reported values here. The increases in testicular volume after 6 months of treatment (b) (4) between the 2 study groups.

Text Table 2 – Study 0006: Change from Baseline to Month 6 Measurements

ITT population	Arimidex			Placebo		
	Mean ± SD (n)	Median	Range	Mean ± SD (n)	Median	Range
Total Breast Volume	-130.3 ± 353.5 (38)	-20.1	-1580.9 to 415.2	-216.1 ± 565.8 (33)	-18.7	-2333.4 to 1106.4
E	-18.4 ± 29.1 (36)	-11.1	-77.1 to 36.7	-11.3 ± 28.6 (28)	0	-55.0 to 40.4
T	4.9 ± 5.9 (38)	5.0	-12.5 to 18.5	0.7 ± 3.8 (33)	0.5	-5.5 to 10.4
T/E ratio	170.9 ± 143.2 (36)	168.1	-95.4 to 595.6	35.1 ± 113.6 (27)	24.5	-151.8 to 273.7
FSH	1.3 ± 1.8 (38)	0.9	-3.0 to 6.7	-0.0 ± 0.8 (34)	0.2	-2.9 to 1.3
LH	0.6 ± 1.5 (38)	0.6	-3.2 to 4.3	0.6 ± 1.2 (34)	0.5	-1.9 to 5.7
Height (cm)	2.4 ± 2.1 (38)	2.1	-0.2 to 8.7	2.7 ± 1.6 (35)	2.9	-0.4 to 5.9
Weight (kg)	4.2 ± 4.9 (38)	4.2	-13.5 to 13.3	3.2 ± 3.9 (35)	3.7	-7.7 to 11.0
BMI (kg/m^2)	0.7 ± 1.6 (38)	0.8	-4.2 to 3.7	0.2 ± 1.3 (35)	0.3	-2.7 to 2.7
Testicular Volume (ml)	6.6 ± 7.9 (38)	6.0	-3.0 to 26.0	5.2 ± 8.0 (35)	2.0	-10.0 to 30.0

E = Serum estradiol (pmol/L); T = Testosterone (nmol/L); T/E ratio = Testosterone/estradiol ratio; FSH = Follicle-stimulating hormone (IU/L); LH = Luteinizing hormone (IU/L); SHBG = Sex hormone binding globulin (nmol/L)

Study 0046.

Over the 12 months treatment with Arimidex, the median number of vaginal bleeding days for girls with MAC due to precocious puberty was slightly increased (15 days), (b) (4) (b) (4), when compared to that of the pre-treatment annualized frequency (12 days). Specifically, 28% of the 25 subjects with vaginal bleeding history prior to entry had a ≥ 50% reduction in the frequency of vaginal bleeding days and 12% experienced a cessation over the entire 12-month treatment period.

The advancements in bone age were generally similar to the advancements in chronological age during the pre- and post-treatment periods. (b) (4) the mean (and median) rates of increase in bone age and in height of the study girls were decreased during the 1st 6 months of treatment, and then decreased further during the 2nd 6 months of treatment, when compared to the pre-treatment period (Text Table 3). In addition, after treatment with Arimidex, the mean growth rate of study girls with precocious puberty became closer to that of age-matched girls in the National Center for Health Statistics (NCHS) FELS study.

Text Table 3 – Study 0046: Summary Results for Bone Age Advancement and Growth Velocity

Parameter		Anastrozole 1 mg (N=28)				
Visit or interval	n	Mean (SD)	Median	Range	p-value[a]	95% Confidence Intervals
Rate of increase in bone age[b]						
Change from pre-treatment to during treatment	27	-0.25 (1.02)	-0.38	-2.21 to 2.37	0.2213	-0.65 to 0.16
Change from pre-treatment to first 6 months of treatment	27	-0.14 (1.09)	-0.38	-2.08 to 2.64	0.5054	-0.57 to 0.29
Change from pre-treatment to second 6 months of treatment	27	-0.35 (1.24)	-0.67	-2.47 to 2.99	0.1513	-0.84 to 0.14
Growth rate (cm/year)						
Change from pre-treatment to during treatment	26	-1.4 (3.30)	-2.1	-6.6 to 5.3	0.0356	-2.77 to –0.11
Change from pre-treatment to first 6 months of treatment	26	-1.0 (3.75)	-1.3	-8.9 to 7.6	0.1720	-2.55 to 0.48
Change from pre-treatment to second 6 months of treatment	26	-1.8 (3.68)	-2.2	-8.8 to 3.9	0.0186	-3.30 to –0.33

[a] From a 2-sided t-test at the 0.05 significance level.
[b] Defined as the change in bone age (years) divided by the change in chronological age (years).

There were (b) (4) in Tanner staging, uterine volume, ovarian volume, and predicted adult height from baseline to end of the study.

Overall, the statistical results from the 2 studies (b) (4) (b) (4) .

2. INTRODUCTION

2.1 Overview

The sponsor has submitted a Type 6 NDA (No. 22-214) in response to a Pediatric Written Request (Amendment # 4) issued on 04/08/2005 under IND 62,138, (b) (4)

In the Pediatric Written Request (PWR), the Agency asked for 2 clinical studies and 2 PK studies (b) (4) . This submission included results from 3 studies. Studies 0006 and 0046 corresponded to Studies 1 and 2 in the PWR and were the efficacy and safety studies (see the study highlights below). Study 0001 and part of Study 0046 corresponded to Studies 3 and 4 in the PWR and were the PK studies. This review focused on the clinical aspects of the 0006 and 0046 trials.

Type of study	Study identifier	Location of study report	Objectives of the study	Study design and type of control	Test product; dosage regimen; route of administration	Number of patients	Diagnosis of patients	Duration of treatment
Efficacy	0006	Module 5, Section 5.3.5.1[a]	Safety and efficacy	Randomised placebo-controlled	Tablet; 1mg o.d.; oral	80 treated	Pubertal boys with gynecomastia	6 months
PK/PD	0001	Module 5, Section 5.3.3.2	PK, efficacy and safety	Open label	Tablet; 1mg o.d.; oral	38 treated	Pubertal boys with gynecomastia of recent onset	6 months
Efficacy	0046	Module 5, Section 5.3.5.2; Section 5.3.3.5	Safety and efficacy; Population PK analysis	Open label	Tablet; 1mg o.d.; oral	28 treated	Precocious puberty in girls with MAS	12 months

[a] Study report previously submitted to NDA 20-541 on 20 August 2003.

2.2 Data Sources

The Study 0006 clinical report and electronic data files were not included in the current NDA submission. The sponsor stated that they were previously submitted to NDA 20-541 on 08/20/2003 (in the EDR \\Cdsesub1\n20541\N_000\2003-08-20). This submission strategy was agreed to by the medical division, as indicated in the letter dated 11/20/2006. For Study 0046, the clinical study report and electronic data files are located in the EDR \\Cdsesub1\evsprod\NDA022214\0000\m5\53-clin-stud-rep\535-rep-effic-safety-stud\request-for-pediatric-exclusivity-01\5352-stud-rep-uncontr\d5394c00046. In general, the quality and content of the sponsor's clinical study reports and data files are adequate for statistical review.

3. STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

3.1.1 Study Design and Endpoints

Study 0006 (04/12/2000 – 09/19/2001) was a Phase 2, 6-month, randomized, double-blind, placebo-controlled, parallel-group, multicenter (in USA) study, conducted in adolescent boys aged between 11 and 18 years with pubertal gynecomastia. Patients were randomized in a 1:1 ratio to receive either 1 mg of Arimidex or placebo. The study objectives and associated outcome variables are presented in the table below. The primary efficacy endpoint was the proportion of patients who experienced a ≥ 50% reduction between Visit 1 and end of study in the calculated breast volume (combined) based on ultrasound. A total of 24 centers participated in the clinical trial.

Objective	Summary variables for analysis (including timepoint and population)
Primary	Primary variable
To determine whether anastrozole 1 mg is more effective than placebo in the treatment of gynecomastia in pubertal boys as assessed by changes in breast tissue size and symptoms	Response rate, where response is defined as a 50% or greater reduction in the calculated volume of gynecomastia of both breasts combined, between Day 1 (Visit 1) and after 6 months of study treatment (end of study), as measured by ultrasound (intent-to-treat [ITT] population and per protocol [PP] population)
Secondary	Secondary variables
Additional efficacy variables	Proportion of patients who had complete regression of gynecomastia in the trial period
	Actual change and percent change in calculated volume of gynecomastia from Visit 1 to after 6 months of treatment (both breasts combined)
	Pain response in symptomatic patients
	Emotional/psychological effects assessed via questionnaire
	Change in hormone levels (sex steroids and gonadotropins), height

Study 0046 (10/23/2002 – 02/06/2006) was a Phase 2, 12-month, open-label, single-group, multicenter, international study, conducted in girls aged between 2 and 10 years with McCune-Albright syndrome (MAS) with precocious puberty. The efficacy of Arimidex in

this study was mainly assessed based on the change from baseline measurements relating to vaginal bleeding, bone age, and growth velocity (see the outcome variables below). All patients who entered the treatment phase of the study had retrospective data on height, weight, bone age, and vaginal bleeding history for at least 6 months prior to entry. A total of 13 centers from 7 countries participated in the clinical study: France (3), Germany (3), Italy (1), Russia (1), Spain (1), United Kingdom (1), and United States (5).

Objective	Outcome variables
Primary	**Primary outcome variable**
To evaluate the safety and efficacy of anastrozole (daily 1 mg dose) for the treatment of MAS in girls less than or equal to 10 years of age, receiving treatment for 1 year	Tolerability and safety (including adverse events, withdrawals and laboratory data) Change in frequency of annualized episodes of vaginal bleeding on treatment compared to baseline Proportion of patients with baseline vaginal bleeding who experienced >50% reduction in the number of vaginal bleeding episodes on treatment Proportion of patients with baseline vaginal bleeding who experienced cessation of vaginal bleeding episodes over a 6-month study period and over the whole 12-month study Change in bone age advancement on treatment compared to change during baseline Change in growth velocity on treatment compared to change during baseline
Secondary	**Secondary outcome variables**
To evaluate pubertal progression by assessment of change in Tanner Stage	Change in Tanner Stage (measure of pubertal progression)
To evaluate effects on ovarian and uterine volume as assessed by ultrasound	Change in mean ovarian and uterine volumes by ultrasound, including the number of ovarian cysts and size of the largest cyst
To evaluate bone growth by assessment of predicted adult height for children aged over 6 years	Predicted adult height for children over age 6 years

MAS McCune-Albright Syndrome.

3.1.2 Statistical Methods

Study 0006. The primary analysis population for the efficacy variables was the ITT population consisting of all randomized subjects who had a baseline observation, took at least 1 dose of study medication, and had at least 1 on-treatment observation. A logistic regression, adjusted for total breast volume, Tanner staging, testosterone, testosterone/estradiol (T/E) ratio, BMI, duration of gynecomastia, and FSH at baseline, was used by the sponsor for the analysis of primary efficacy variable (response rate). Since those prognostic factors (b) (4) at baseline, this reviewer did not include them in her own logistic regression model. Depending on distribution of data, an analysis of

covariance model with treatment as the main factor and baseline as the covariate (parametric test) or a Wilcoxon-Mann-Whitney test (non-parametric test) was used to analyze change from baseline measurements.

Study 0046. The primary analysis population for the efficacy variables consisted of all patients exposed to study treatment. Depending on distribution of data, a 2-sided paired t-test (parametric test) or a sign test (non-parametric test) was used to analyze change from baseline measurements.

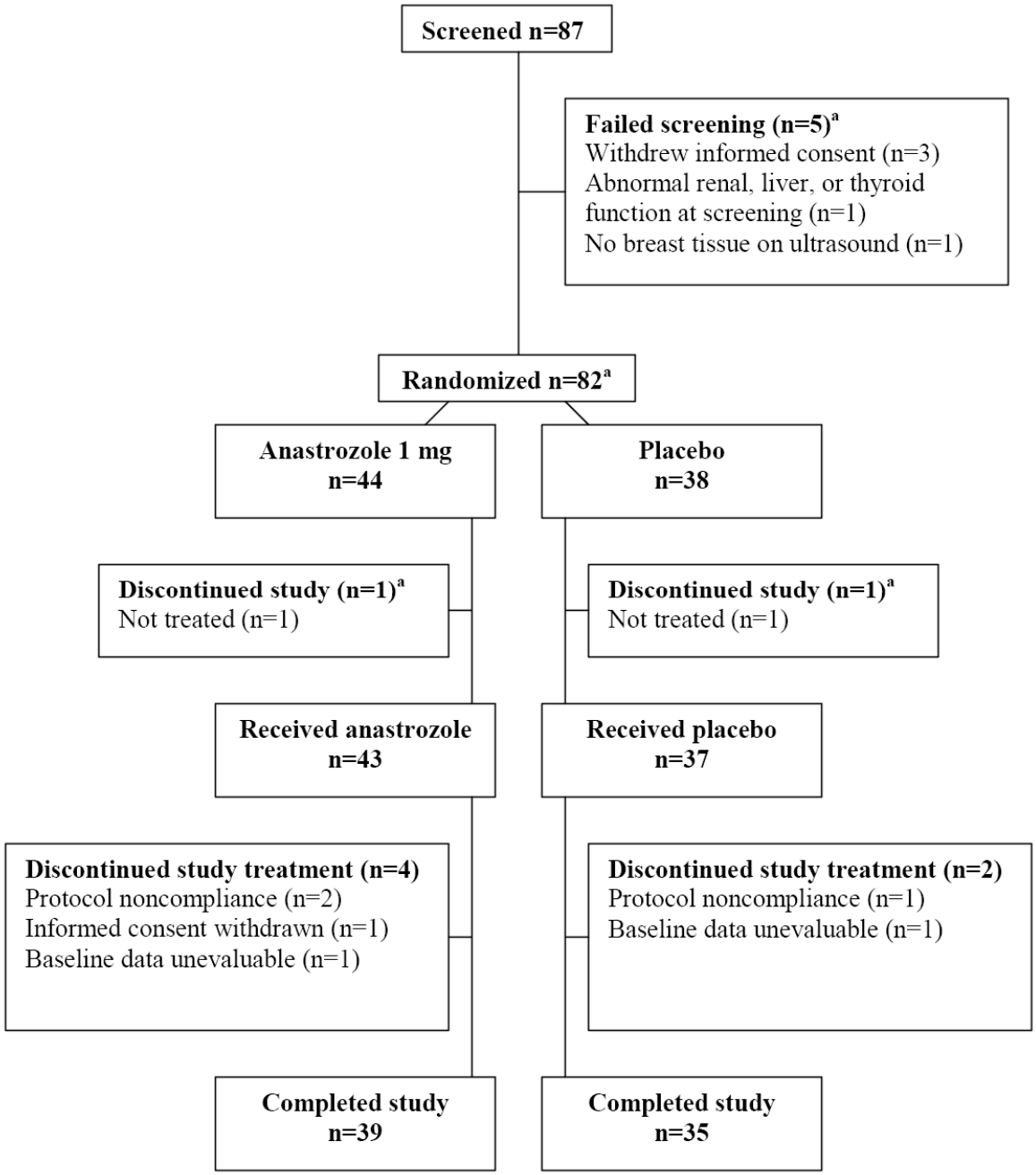
All p-values reported in this review and the sponsor's clinical study reports were nominal. In other words, no p-value adjustments were made for multiple comparisons.

3.1.3 Subject Disposition

Study 0006. A total of 82 subjects were enrolled and randomized in this study: 44 in the Arimidex group and 38 in the placebo group. However, 2 subjects (one in each group) did not receive any study medication. Among the 80 treated subjects, 39 in the Arimidex group and 35 in the placebo group completed the trial. The reasons for withdrawal were similar between the 2 study groups (Figure 1, copied from the sponsor's clinical study report).

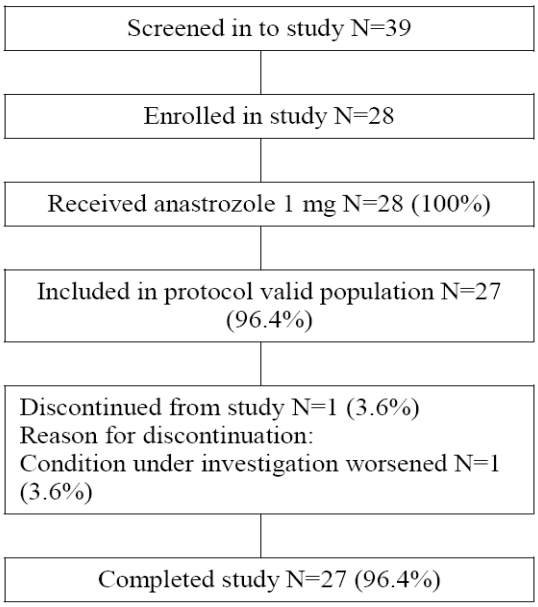
According to the sponsor, there were 4 subjects in the Arimidex group and 2 subjects in the placebo group with no baseline and/or Month 6/Final visit data available. Therefore, they were excluded from the ITT (primary analysis) population.

Figure 1 – Study 0006: Subject Disposition



Study 0046. A total of 28 subjects were enrolled in this study. Among them, 1 subject withdrew from the study after 3 months of treatment due to the worsening condition under investigation (Figure 2, copied from the sponsor's clinical study report). All the 28 subjects were included in the "all patients exposed to study treatment" (primary analysis) population.

Figure 2 – Study 0046: Subject Disposition



3.1.4 Demographic and Baseline Characteristics

Study 0006. All patients were males in this study and 64% (= 47/74) of the ITT subjects were Caucasian. Although the Written Request calls for recruiting pediatric patients ≥ 11 years of age, there were 2 subjects enrolled at 10.84 and 10.98 years old. The mean chronological age at entry was about 15 years. The mean body mass index (BMI) at baseline was about 27 kg/m^2. Approximately 90% of the subjects had more than 1 year of gynecomastia prior to enrollment. The total breast volume data were highly variable across patients at baseline (minimum = 1.5 ml and maximum = 2686.6 ml, see the stem-and-leaf plots below for data distributions). The mean and median total breast volume at baseline were both greater in the placebo group than in the Arimidex group (574.5 ± 722.4 ml vs. 439.5 ± 596.2 ml for the means and 203.5 ml vs. 139.7 ml for the medians).

Total Breast Volume at Baseline – Arimidex

```
Stem Leaf                     #  Boxplot
  20 7                        1     *
  18 6                        1     *
  16 2                        1     0
  14 07                       2     0
  12 3                        1     0
  10 6                        1     0
   8 4                        1     |
   6                                |
   4 13                       2  +--+--+
   2 3442257                  7  |     |
   0 011234566778890112445   21  *-----*
     ----+----+----+----+-
 Multiply Stem.Leaf by 10**+2
```

*** See Note in next page ***

Total Breast Volume at Baseline – Placebo

```
Stem Leaf                     #  Boxplot
  26 9                        1     0
  24 4                        1     |
  22                                |
  20                                |
  18                                |
  16 0                        1     |
  14 18                       2     |
  12 6                        1     |
  10 358                      3  +-----+
   8                             |     |
   6 33                       2  |     |
   4 38                       2  |  +  |
   2 0347                     4  *-----*
   0 0112333556826899        16  +-----+
     ----+----+----+----+
 Multiply Stem.Leaf by 10**+2
```

Note: In the stem-and-leaf plot, (Stem.Leaf)*100 shows the response of each subject. In the box plot, the horizontal line inside the box shows median and + sign shows the mean. Any value more than 1.5 interquartile range (= 75th – 25th percentiles0 is marked with a 0 or a *.

Table 1 – Study 0006: Demographic and Baseline Characteristics – ITT Population

Demographic or baseline characteristic		**Treatment group**			
		Anastrozole 1 mg (N=39)		**Placebo (N=35)**	
Demographic characteristics					
Sex (n and % of patients)	Male	39	(100)	35	(100)
Age (years)	Mean (SD)	14.6	(1.8)	14.7	(1.8)
	Range	10.8 to 18.1		11 to 18.6	
Race (n and % of patients)	Caucasian	27	(69.2)	20	(57.1)
	Black	10	(25.6)	11	(31.4)
	Oriental	0		0	
	Hispanic	2	(5.1)	4	(11.4)
	Other	0		0	
Baseline characteristics					
Height (cm)	Mean (SD)	167.6	(8.0)	171.2	(9.9)
Weight (kg)	Mean (SD)	76.6	(20.6)	78.9	(20.4)
Body mass index (BMI) (kg/m^2)	Mean (SD)	27.1	(6.2)	26.7	(5.4)
Body mass index (z-score)	Mean (SD)	1.43	(0.98)	1.41	(0.90)
Duration of gynecomastia (n and % of patients)	>6 months to 12 months	4	(10.3)	3	(8.6)
	>1 year to 2 years	16	(41.0)	13	(37.1)
	>2 years to 3 years	10	(25.6)	11	(31.4)
	>3 years	9	(23.1)	8	(22.9)
Family history of gynecomastia (n and % of patients)	No	32	(82.1)	30	(85.7)
	Yes	7	(17.9)	5	(14.3)
Breast volume (mL)	n	38		33	
	Mean (SD)	439.5	(596.2)	574.5	(722.4)
Breast pain (n and % of patients)	No	28	(71.8)	26	(74.3)
	Yes	11	(28.2)	9	(25.7)

The mean testosterone and FSH levels at baseline were 9.2 nmol/L and 3.2 IU/L in the Arimidex group, respectively, and 9.3 nmol/L and 3.3 IU/L in the placebo group, respectively. The mean testosterone/estradiol (T/E) ratios were 144.2 and 142.3 for the Arimidex and placebo groups, respectively. Overall, the demographic and baseline characteristics were similar between the 2 study groups (all $p > 0.10$).

Study 0046. All patients were females in this study and 93% (= 26/28) of them were Caucasian. Although the Written Request calls for recruiting pediatric patients ≤ 10 years of age, there was 1 patient enrolled at 11.0 years old. The mean chronological and bone ages at entry were 5.9 and 8.6 years, respectively. The mean ratio of change in bone age to change in chronological age over the 6-month period prior to the start of treatment (i.e., bone age advancement during the pre-treatment period) was 1.25, where 16 of the 28 subjects had a ratio > 1 and 12 had a ratio < 1. Note that there was 1 subject with a negative change in bone age during the pre-treatment period (ratio = -0.03), which may be due to an error/variability in measurement according to the sponsor. The median Tanner stages for breast and pubic hair at baseline were 3 (further enlargement of breast mound; increased palpable glandular tissue) and 2 (sparse growth of long, slightly pigmented, downy hair or only slightly curled hair, appearing along labia), respectively. The mean and median growth rates during the pre-treatment period were both around 8 cm/year and most of the subjects had a higher growth rate than the mean rate of the age-matched girls in the National Center for Health Statistics (NCHS) FELS study.

Table 2 – Study 0046: Demographic and Baseline Characteristics

Parameter	Anastrozole 1 mg (N=28)			
	n	Mean (SD)	Median	Range
Age at informed consent (fractional year)	28	5.88 (2.03)	5.60	3.20 to 11.00
Weight (kg) at Month 0 visit	26	25.33 (8.59)	24.25	14.80 to 53.00
Breast Tanner Staging	28	2.71 (0.81)	3	1 to 4
Pubic Tanner Staging	28	2.07 (0.86)	2	1 to 3
Bone age at baseline (screening visit) (years)	28	8.57 (2.62)	8.38	3.95 to 14.86
Rate of increase in bone age during pre-treatment period[a]	28	1.25 (0.77)	1.13	-0.03 to 3.17
Height at baseline for growth rate (month 0) (cm)	27	121.23 (14.86)	119.70	99.50 to 150.60
Growth rate during pre-treatment period (cm/year)	27	7.87 (2.94)	8.30	1.05 to 13.17
Growth rate during pre-treatment period (Z-score)	27	1.40 (3.15)	2.04	-6.39 to 8.67
Number of vaginal bleeding days during pre-treatment period	27	6.89 (4.91)	6.00	0.00 to 15.00

[a] Defined as change in bone age (years) divided by the change in chronological age (years).
N Number of patients.
SD Standard deviation.

Among the 28 enrolled subjects, 26 of them had at least 1 vaginal bleeding day over the last 6 months prior to entry (including 1 subject whose prior bleeding history was confirmed, but the number of bleeding days was unknown). The median vaginal bleeding days during the pre-treatment period was 6 days.

3.1.5 Efficacy Results and Discussion

Study 0006.

Total Breast Volume of Gynecomastia. In the ITT population, there were 3 subjects with no baseline and/or Month 6 total breast volume recorded. Therefore, they were excluded from the numerator (but not the denominator) in the calculation of percentage of patients achieving a response, which was defined as a ≥ 50% (primary efficacy variable) or 100% (secondary efficacy variable) reduction between Day 1 and end of study in the calculated total breast volume of gynecomastia based on ultrasound.

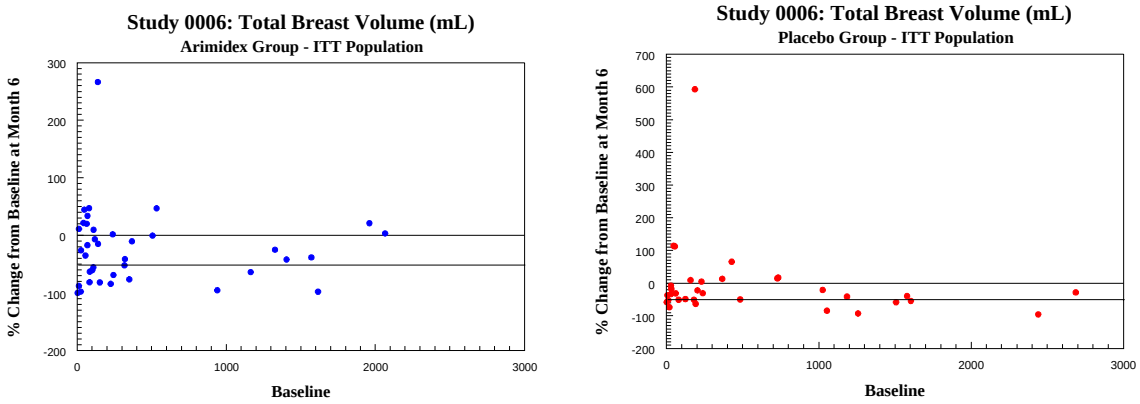
There were 38.5% (= 15/39) and 31.4% (=11/35) of the ITT patients in the Arimidex and placebo groups, respectively, with a 50% or greater reduction in total breast volume after 6 months of treatment. Although the response rate was higher in the Arimidex group than in the placebo group, (b) (4) difference was observed between the 2 study groups (odds ratio = 1.364, 95% CI = (0.521, 3.569), p = 0.5275). In addition, among all the ITT subjects, only 1 patient, who was in the Arimidex group, experienced a 100% reduction in total breast volume (complete regression of gynecomastia) at the end of the trial.

There was also (b) (4) (p > 0.1) in mean or median % change from baseline in total breast volume of gynecomastia at Month 6, as shown in Table 3 below.

Table 3 – Study 0006: Absolute and % Change from Baseline in Total Breast Volume

Treatment		N	Mean	SD	Median	Minimum	Maximum
Arimidex	Baseline	38	439.5	596.2	139.7	3.8	2065.7
	Month 6	38	309.2	540.5	79.6	0	2376.1
	Change from baseline	38	-130.3	353.5	-20.1	-1580.9	415.2
	% Change from baseline	38	-23.5	66.1	-30.5	-100.0	266.4
Placebo	Baseline	33	574.5	722.4	203.5	1.5	2686.6
	Month 6	33	358.4	452.9	158.9	0.6	1932.2
	Change from baseline	33	-216.1	565.8	-18.7	-2333.4	1106.4
	% Change from baseline	33	-5.9	118.3	-33.3	-95.6	593.1

The following 2 figures show that there were no correlations between the total breast volume at baseline and % change from baseline at Month 6.



Breast Pain Response in Symptomatic Patients. There were 20 subjects reporting breast pain (tenderness) at baseline: 11 in the Arimidex group and 9 in the placebo group (called symptomatic patients). By Month 3, 8 of the 11 Arimidex-treated patients (72.7%) and 6 of the 9 placebo-treated patients (66.7%) reported no breast pain. By Month 6, breast pain was resolved in 10 of the 11 Arimidex-treated patients and all the 9 placebo-treated patients.

Hormone Levels. Hormonal data were collected for serum estradiol (E), testosterone (T), T/E ratio, FSH, LH, and SHBG. Summary statistics for change from baseline to Month 6 data are presented in Table 4. (b) (4) differences between the 2 study groups were observed in testosterone, T/E ratio, FSH, and SHGB (all $p < 0.05$).

Table 4 – Study 0006: Change in Hormone Levels from Baseline to Month 6

	Arimidex			Placebo		
	Mean ± SD (n)	Median	Range	Mean ± SD (n)	Median	Range
E	-18.4 ± 29.1 (36)	-11.1	-77.1 to 36.7	-11.3 ± 28.6 (28)	0	-55.0 to 40.4
T	4.9 ± 5.9 (38)	5.0	-12.5 to 18.5	0.7 ± 3.8 (33)	0.5	-5.5 to 10.4
T/E ratio	170.9 ± 143.2 (36)	168.1	-95.4 to 595.6	35.1 ± 113.6 (27)	24.5	-151.8 to 273.7
FSH	1.3 ± 1.8 (38)	0.9	-3.0 to 6.7	-0.0 ± 0.8 (34)	0.2	-2.9 to 1.3
LH	0.6 ± 1.5 (38)	0.6	-3.2 to 4.3	0.6 ± 1.2 (34)	0.5	-1.9 to 5.7
SHBG	-0.2 ± 5.6 (37)	-1.0	-9.0 to 23.0	3.7 ± 10.1 (34)	3.0	-15.0 to 35.0

E = Serum estradiol (pmol/L); T = Testosterone (nmol/L); T/E ratio = Testosterone/estradiol ratio; FSH = Follicle-stimulating hormone (IU/L); LH = Luteinizing hormone (IU/L); SHBG = Sex hormone binding globulin (nmol/L)

Height, Weight, BMI, and Testicular Volume. Summary statistics for change in height, weight, BMI, and testicular volume from baseline to Month 6 are presented in Table 5.

There (b) (4) differences between the 2 study groups in these variables (all $p > 0.1$).

Table 5 – Study 0006: Change in Height, Weight, BMI, and Testicular Volume from Baseline to Month 6

	Arimidex			Placebo		
	Mean ± SD (n)	Median	Range	Mean ± SD (n)	Median	Range
Height (cm)	2.4 ± 2.1 (38)	2.1	-0.2 to 8.7	2.7 ± 1.6 (35)	2.9	-0.4 to 5.9
Weight (kg)	4.2 ± 4.9 (38)	4.2	-13.5 to 13.3	3.2 ± 3.9 (35)	3.7	-7.7 to 11.0
BMI (kg/m^2)	0.7 ± 1.6 (38)	0.8	-4.2 to 3.7	0.2 ± 1.3 (35)	0.3	-2.7 to 2.7
BMI z-score	0.1 ± 0.2 (38)	0.1	-0.6 to 0.5	0.0 ± 0.2 (35)	-0.0	-0.4 to 0.6
Testicular Volume (ml)	6.6 ± 7.9 (38)	6.0	-3.0 to 26.0	5.2 ± 8.0 (35)	2.0	-10.0 to 30.0

Study 0046.

Annualized Frequency of Vaginal Bleeding Days. As shown in Table 6, the mean number of vaginal bleeding days during the 12-month treatment period was increased over that of the pre-treatment period (annualized), regardless of actual frequency or worst case scenario frequency (assuming bleeding occurred on the days with missing data) used. (b) (4)

However, although the median change in vaginal bleeding episodes from the pre-treatment period was +1.6 days (worst case scenario), the increase (b) (4) based on the Sign test ($p = 0.4421$).

Table 6 – Study 0046: Results for Number (Frequency) of Vaginal Bleeding Days

	Mean ± SD (n)	95% C.I	Median	Min – Max
6-month pre-treatment period (annualized)	13.8 ± 9.8 (27)	(10.1, 17.5)	12	0 – 30
12-month on-treatment period (annualized): Actual	19.2 ± 24.8 (27)	(9.8, 28.6)	11.0	0 – 99.7
12-month on-treatment period (annualized): Worst	21.6 ± 24.4 (27)	(12.4, 30.8)	15.0	0 – 102.6
Change in annualized frequency: Actual Sign test p-value = 1.0000	5.4 ± 25.4 (27)	(-4.2, 15.0)	0	-28.0 – 87.7
Change in annualized frequency: Worst Sign test p-value = 0.4421	7.9 ± 24.7 (27)	(-1.4, 17.2)	1.6	-21.2 – 90.6

Actual: Assuming no bleeding occurred on missing diary days.
Worst: Assuming bleeding occurred on missing diary days (worst case scenario).

Seven (28%) of the 25 subjects with vaginal bleeding history prior to entry had a ≥ 50% reduction in the frequency of vaginal bleeding days over the 12-month treatment period when compared to the annualized pre-treatment frequency for the worst case scenario. In addition,

five (20%) of the 25 subjects with vaginal bleeding history prior to entry had a cessation in vaginal bleeding over the 1st 6-month treatment period, and three (12%) experienced a cessation over the entire 12-month treatment period.

Bone Age and Advancement (Rate of Increase). Bone age advancement (rate of increase in bone age) was calculated as the ratio of change in bone age (in years) to change in chronological age (in years) over a time interval. As shown in Table 7 (copied from the sponsor's clinical study report), the mean and median rates of increase in bone age during the pre-treatment period (Month -6 to Screening), the 12-month treatment period (Months 0 – 12), the first 6-month treatment period (Months 0 – 6), and the second 6-month treatment period (Months 6 – 12) were all around 1, indicating that the advancements in bone age during these intervals were all close to the advancements in chronological age in general. In fact, the mean rates of increase in bone age during the treatment periods were all slightly smaller (b) (4)) than that of the pre-treatment period according to the paired t-test.

Table 7 – Study 0046: Results for Bone Age and Advancement (Rate of Increase)

Parameter	Anastrozole 1 mg (N=28)					
Visit or interval	n	Mean (SD)	Median	Range	p-value[a]	95% Confidence Intervals
Bone age (years)						
6 months prior to treatment	28	7.70 (2.77)	7.10	2.94 to 14.17		
Screening	28	8.57 (2.62)	8.38	3.95 to 14.86		
Month 6	27	9.29 (2.47)	9.04	4.28 to 14.81		
Month 12/ Final visit	27	9.76 (2.43)	9.98	4.87 to 14.85		
Rate of increase in bone age[b]						
Pre-treatment	28	1.25 (0.77)	1.13	-0.03 to 3.17		
During treatment	27	1.04 (0.66)	1.01	-0.01 to 2.63		
During first 6 months of treatment (Month 0 to Month 6)	27	1.14 (0.89)	1.09	-0.27 to 3.00		
During second 6 months of treatment (Month 6 to Month 12)	27	0.93 (0.83)	0.84	-0.12 to 3.22		
Change from pre-treatment to during treatment	27	-0.25 (1.02)	-0.38	-2.21 to 2.37	0.2213	-0.65 to 0.16
Change from pre-treatment to first 6 months of treatment	27	-0.14 (1.09)	-0.38	-2.08 to 2.64	0.5054	-0.57 to 0.29
Change from pre-treatment to second 6 months of treatment	27	-0.35 (1.24)	-0.67	-2.47 to 2.99	0.1513	-0.84 to 0.14

[a] From a 2-sided t-test at the 0.05 significance level.
[b] Defined as the change in bone age (years) divided by the change in chronological age (years).

Growth Velocity. As shown in Table 8 (copied from the sponsor's clinical study report), the mean and median growth rates during the 12-month treatment period (Months 0 – 12), the first 6-month treatment period (Months 0 – 6), and the second 6-month treatment period (Months 6 – 12) were all smaller than that of the pre-treatment period (Month -6 to Screening). The decrease in growth rate from the pre-treatment period to the first 6-month treatment period was (b) (4) (p = 0.1720), (b) (4) for the second 6-month treatment period (p = 0.0186) according to the paired t-test. Similar findings were also observed for the standardized growth velocity data (Z-score) using the age-

matched information from the National Center for Health Statistics (NCHS) FELS study. Note that after treatment with Arimidex, the mean growth rate of study girls with precocious puberty became closer to that of age-matched girls in the FELS study.

Table 8 – Study 0046: Results for Growth Velocity (in cm/year and in Z-score)

Parameter	Anastrozole 1 mg (N=28)					
Interval	n	Mean (SD)	Median	Range	p-value[a]	95% Confidence Intervals
Growth rate (cm/year)						
Pre-treatment	27	7.9 (2.94)	8.3	1.1 to 13.2		
During treatment (Month 0 to Month 12)	26	6.5 (2.59)	6.6	1.0 to 11.7		
During first 6 months of treatment (Month 0 to Month 6)	26	6.9 (2.77)	6.3	2.9 to 13.7		
During second 6 months of treatment (Month 6 to Month 12)	27	6.1 (3.33)	7.0	-1.9 to 11.2		
Change from pre-treatment to during treatment	26	-1.4 (3.30)	-2.1	-6.6 to 5.3	0.0356	-2.77 to –0.11
Change from pre-treatment to first 6 months of treatment	26	-1.0 (3.75)	-1.3	-8.9 to 7.6	0.1720	-2.55 to 0.48
Change from pre-treatment to second 6 months of treatment	26	-1.8 (3.68)	-2.2	-8.8 to 3.9	0.0186	-3.30 to –0.33
Growth rate (Z-score[b])						
Pre-treatment	27	1.40 (3.15)	2.04	-6.39 to 8.67		
During treatment (Month 0 to Month 12)	26	0.26 (2.71)	0.45	-5.80 to 5.23		
During first 6 months of treatment (Month 0 to Month 6)	26	0.48 (2.54)	0.05	-3.42 to 5.43		
During second 6 months of treatment (Month 6 to Month 12)	27	-0.06 (3.62)	0.75	-9.21 to 5.48		
Change from pre-treatment to during treatment	26	-1.22 (3.62)	-1.76	-7.39 to 5.33	0.0981	-2.68 to 0.24
Change from pre-treatment to first 6 months of treatment	26	-1.00 (3.85)	-1.07	-10.40 to 6.65	0.1970	-2.56 to 0.55
Change from pre-treatment to second 6 months of treatment	26	-1.57 (4.01)	-1.84	-8.49 to 4.85	0.0564	-3.19 to 0.05

Tanner Staging for Breast and Pubic Hair. As shown in Table 9, there were no marked changes in breast or pubic hair Tanner stages from Month 0 to Month 12. Although 7 (25%) and 11 (39%) of the enrolled subjects had a progressed breast and pubic hair Tanner staging, respectively, after 12 months of treatment, more than 50% of the enrolled subjects did not have their breast or pubic hair Tanner stages changed while on treatment (Table 10).

Table 9 – Study 0046: Results for Tanner Staging for Breast and Pubic Hair (copied from the sponsor's report)

Parameter	Anastrozole 1 mg (N=28)			
	n	Mean (SD)	Median	Range
Tanner Staging (Breast)				
Month 0	28	2.7 (0.81)	3	1 to 4
Month 12/ Final visit	28	2.9 (0.89)	3	1 to 4
Change from Month 0 to Month 12/ Final visit	28	0.1 (0.71)	0	-1 to 2
Tanner Staging (Pubic)				
Month 0	28	2.1 (0.86)	2	1 to 3
Month 12/ Final visit	28	2.5 (1.00)	3	1 to 4
Change from Month 0 to Month 12/ Final visit	28	0.4 (0.63)	0	-1 to 2

Table 10 – Study 0046: Frequency in Transition of Tanner Staging (copied from the sponsor's report)

Tanner Stage	Anastrozole 1 mg (N=28)				
	Month 12/ Final visit				
Baseline	Stage 1	Stage 2	Stage 3	Stage 4	Stage 5
Breast					
Stage 1	0	1	0	0	0
Stage 2	2	4	4	1	0
Stage 3	0	2	8	1	0
Stage 4	0	0	0	5	0
Stage 5	0	0	0	0	0
Pubic					
Stage 1	6	2	1	0	0
Stage 2	1	2	5	0	0
Stage 3	0	0	8	3	0
Stage 4	0	0	0	0	0
Stage 5	0	0	0	0	0

Uterine Volume. There were (b) (4) in uterine volume from Screening to Month 6, Screening to Month 12, and Months 6 to 12 according to the paired t-test (p = 0.8873, 0.5073, and 0.7904, respectively).

Table 11 – Study 0046: Results for Uterine Volume (copied from the sponsor's report)

	Anastrozole 1 mg (N=28)			
	n	Mean (SD)	Median	Range
Uterine volume (cc) at screening visit	27	10.39 (8.27)	7.01	1.32 to 31.84
Uterine volume (cc) at Month 6	21	10.62 (9.72)	6.63	1.84 to 37.85
Uterine volume (cc) at Month 12/ Final visit	20	10.78 (7.80)	9.85	0.65 to 26.25
Change[b] in uterine volume (cc) from screening to Month 6	20	-0.28 (8.73)	0.42	-18.37 to 12.29
Change[b] in uterine volume (cc) from Month 6 to Month 12/ Final visit	17	0.62 (9.42)	1.77	-18.45 to 14.63
Change[b] in uterine volume (cc) from screening to Month 12/ Final visit	19	1.16 (7.49)	-0.33	-12.67 to 14.13

[a] Volume was calculated as 0.5 multiplied by (longitudinal multiplied by anteroposterior multiplied by transverse), if all 3 linear dimensions were recorded; otherwise volume is missing.
[b] Calculated only for those patients with data at both time-points.
cc Cubic centimetre.

Ovarian Volume. There were (b) (4) in ovarian volume from Screening to Month 6, Screening to Month 12, and Months 6 to 12 according to the paired t-test (p = 0.6921, 0.7653, and 0.7118, respectively).

Table 12 – Study 0046: Results for Ovarian Volume (copied from the sponsor's report)

	Anastrozole 1 mg (N=28)			
	n	**Mean (SD)**	**Median**	**Range**
Average ovarian volume (cc) at screening visit	19	4.51 (3.41)	4.37	0.68 to 11.64
Average ovarian volume (cc) at Month 6	15	3.46 (4.54)	1.58	0.62 to 15.85
Average ovarian volume (cc) at Month 12/ Final visit	18	2.99 (3.03)	1.78	0.28 to 10.35
Change[b] in average ovarian volume (cc) from screening to Month 6	9	0.34 (2.52)	-0.20	-3.33 to 4.50
Change[b] in average ovarian volume (cc) from Month 6 to Month 12/ Final visit	12	-0.65 (5.92)	0.49	-14.99 to 9.22
Change[b] in average ovarian volume (cc) from screening to Month 12/ Final visit	13	-0.41 (4.89)	-0.65	-10.78 to 9.30

[a] Volume was calculated as 0.5 multiplied by (longitudinal multiplied by anteroposterior multiplied by transverse), if all 3 linear dimensions were recorded; otherwise volume is missing. Average volume was calculated as 0.5 multiplied by (volume of left ovary plus volume of right ovary) if both volumes were calculated; otherwise average ovarian volume is missing.
[b] Calculated only for those patients with data at both time-points.
cc Cubic centimetre.

Predicted Adult Height. Predicted adult height was calculated based on the method of Bayley and Pinneau. There was (b) (4) in predicted adult height from Screening to Month 12 according to the paired t-test (p = 0.2912 for change and p = 0.2834 for % change).

Table 13 – Study 0046: Results for Predicted Adult Height (copied from the sponsor's report)

	Anastrozole 1 mg (N=28)			
	n[b]	**Mean (SD)**	**Median**	**Range**
Predicted adult height (cm) at screening visit	19	153.9 (11.56)	153.2	131.8 to 178.6
Predicted adult height (cm) at Month 12/ Final visit	24	156.5 (11.3)	156.0	132.9 to 180.8
Change in predicted adult height (cm) from screening to Month 12/ Final visit	18	0.9 (3.68)	1.7	-6.3 to 6.9
Percent change in predicted adult height from screening to Month 12/ Final visit	18	0.6 (2.36)	1.1	-4.2 to 4.1

[b] According to the method of Bayley and Pinneau, predicted adult height is not calculated at any timepoint when the patient's then current age is either <6 years, or between 6 and 7 years and categorized as advanced.

3.2 Evaluation of Safety

In consultation with the reviewing medical officer, except for bone maturation age advancement parameter, there were no other aspects of safety that required review by a statistician. See Dr. Dragos Roman's report for the complete safety evaluation.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race, and Age

No subgroup analyses for gender and age were performed for either study since they were conducted in a gender-specific pediatric population. Also, no subgroup analysis for race was performed for Study 0046 since 93% of the patients were Caucasian. The primary response rate of a ≥ 50% reduction between Day 1 and end of study in the calculated total breast volume of gynecomastia based on ultrasound was similar among Caucasian, Black, and Hispanic patients in the 0006 trial.

4.2 Other Special/Subgroup Populations

No special/subgroup population analysis was requested by the reviewing medical officer and performed by this reviewer for either study.

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

There were no serious statistical issues noted by this reviewer. In general, the results based on the PP population were similar to those based on the ITT population in both studies. Also, this reviewer's results summarized below agree with the sponsor's findings.

Study 0006. At the end of the 6-month trial, 38.5% and 31.4% of the Arimidex- and placebo-treated patients, respectively, experienced a 50% or greater reduction in the calculated combined breast volume of gynecomastia based on ultrasound (Table 14). Although the response rate was higher in the Arimidex group than in the placebo group, (b) (4) difference was observed between the 2 study groups (odds ratio = 1.364, 95% CI = (0.521, 3.569), p = 0.5275). In addition, the mean and median changes from baseline in total breast volume at Month 6 were also similar between the 2 study groups (Table 15). Except for 1 subject in the Arimidex group, all other symptomatic patients (who experienced breast pain at baseline) reported no breast pain (tenderness) at Month 6.

Table 14 – Study 0006: Proportion of Patients with Decreased Total Breast Volume at Month 6

	Arimidex	Placebo
With a reduction in total breast volume of gynecomastia	26/39 (66.7%)	24/35 (68.6%)
With a ≥ 50% reduction in total breast volume of gynecomastia	15/39 (38.5%)	11/35 (31.4%)
With a 100% reduction in total breast volume of gynecomastia	1/39 (2.6%)	0/35 (0%)

Summary statistics for change in hormonal data, height, weight, BMI, and testicular volume from baseline to Month 6 are presented in Table 15. According to the sponsor, there were about 50% and 20% of the Arimidex- and placebo-treated patients, respectively, with serum estradiol levels below the limit of detection (LOD, 36.7 pmol/L) at Month 6. Since the LOD

value was used in the summary statistics, the mean and median values may have actually been lower than the reported values here. The increases in testicular volume after 6 months of treatment were (b) (4) between the 2 study groups.

Table 15 – Study 0006: Change from Baseline to Month 6 Measurements

	Arimidex			Placebo		
	Mean ± SD (n)	Median	Range	Mean ± SD (n)	Median	Range
Total Breast Volume	-130.3 ± 353.5 (38)	-20.1	-1580.9 to 415.2	-216.1 ± 565.8 (33)	-18.7	-2333.4 to 1106.4
E	-18.4 ± 29.1 (36)	-11.1	-77.1 to 36.7	-11.3 ± 28.6 (28)	0	-55.0 to 40.4
T	4.9 ± 5.9 (38)	5.0	-12.5 to 18.5	0.7 ± 3.8 (33)	0.5	-5.5 to 10.4
T/E ratio	170.9 ± 143.2 (36)	168.1	-95.4 to 595.6	35.1 ± 113.6 (27)	24.5	-151.8 to 273.7
FSH	1.3 ± 1.8 (38)	0.9	-3.0 to 6.7	-0.0 ± 0.8 (34)	0.2	-2.9 to 1.3
LH	0.6 ± 1.5 (38)	0.6	-3.2 to 4.3	0.6 ± 1.2 (34)	0.5	-1.9 to 5.7
Height (cm)	2.4 ± 2.1 (38)	2.1	-0.2 to 8.7	2.7 ± 1.6 (35)	2.9	-0.4 to 5.9
Weight (kg)	4.2 ± 4.9 (38)	4.2	-13.5 to 13.3	3.2 ± 3.9 (35)	3.7	-7.7 to 11.0
BMI (kg/m^2)	0.7 ± 1.6 (38)	0.8	-4.2 to 3.7	0.2 ± 1.3 (35)	0.3	-2.7 to 2.7
Testicular Volume (ml)	6.6 ± 7.9 (38)	6.0	-3.0 to 26.0	5.2 ± 8.0 (35)	2.0	-10.0 to 30.0

E = Serum estradiol (pmol/L); T = Testosterone (nmol/L); T/E ratio = Testosterone/estradiol ratio; FSH = Follicle-stimulating hormone (IU/L); LH = Luteinizing hormone (IU/L); SHBG = Sex hormone binding globulin (nmol/L)

Study 0046.

Over the 12 months treatment with Arimidex, the median number of vaginal bleeding days for girls with MAC due to precocious puberty was slightly increased (15 days), (b) (4) (b) (4), when compared to that of the pre-treatment annualized frequency (12 days). Specifically, 28% of the 25 subjects with vaginal bleeding history prior to entry had a ≥ 50% reduction in the frequency of vaginal bleeding days and 12% experienced a cessation over the entire 12-month treatment period.

The advancements in bone age were generally similar to the advancements in chronological age during the pre- and post-treatment periods. (b) (4) the mean (and median) rates of increase in bone age and in height of the study girls were decreased during the 1st 6 months of treatment, and then decreased further during the 2nd 6 months of treatment, when compared to the pre-treatment period (Table 16). In addition, after treatment with Arimidex, the mean growth rate of study girls with precocious puberty became closer to that of age-matched girls in the National Center for Health Statistics (NCHS) FELS study.

Table 16 – Study 0046: Summary Results for Bone Age Advancement and Growth Velocity

Parameter		Anastrozole 1 mg (N=28)				
Visit or interval	n	Mean (SD)	Median	Range	p-value[a]	95% Confidence Intervals
Rate of increase in bone age[b]						
Change from pre-treatment to during treatment	27	-0.25 (1.02)	-0.38	-2.21 to 2.37	0.2213	-0.65 to 0.16
Change from pre-treatment to first 6 months of treatment	27	-0.14 (1.09)	-0.38	-2.08 to 2.64	0.5054	-0.57 to 0.29
Change from pre-treatment to second 6 months of treatment	27	-0.35 (1.24)	-0.67	-2.47 to 2.99	0.1513	-0.84 to 0.14
Growth rate (cm/year)						
Change from pre-treatment to during treatment	26	-1.4 (3.30)	-2.1	-6.6 to 5.3	0.0356	-2.77 to –0.11
Change from pre-treatment to first 6 months of treatment	26	-1.0 (3.75)	-1.3	-8.9 to 7.6	0.1720	-2.55 to 0.48
Change from pre-treatment to second 6 months of treatment	26	-1.8 (3.68)	-2.2	-8.8 to 3.9	0.0186	-3.30 to –0.33

[a] From a 2-sided t-test at the 0.05 significance level.
[b] Defined as the change in bone age (years) divided by the change in chronological age (years).

There were (b) (4) in Tanner staging, uterine volume, ovarian volume, and predicted adult height from baseline to end of the study.

Overall, the statistical results from the 2 studies (b) (4) (b) (4).

5.2 Conclusions and Recommendations

Based on the results from 2 submitted clinical efficacy and safety studies, (b) (4)

In the 0006 trial, the observed response rate of a ≥ 50% reduction in total breast volume at Month 6 was 38.5% in the Arimidex group, which was much smaller than the expected rate used in the sample size and power calculation (85%). Similarly, in the 0046 trial, the observed response rate of a ≥ 50% reduction in the frequency of vaginal bleeding days over a 12-month treatment period was 28% in the Arimidex group, which was also much smaller than the expected rate used in the sample size and power calculation (67%). (b) (4)

Primary Statistical Reviewer: Cynthia Liu, MA

Concurring Reviewer: Todd Sahlroot, Ph.D.
Statistical Team Leader and Deputy Director of Biometrics II

CC: HFD-510/JJohnson, MParks, DRoman
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/s/

Cynthia Liu
3/4/2008 11:07:40 AM
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3/5/2008 04:37:42 PM
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