CLINICAL REVIEW

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Reviewer Name	Dragos Roman
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Established Name	Anastrozole
(Proposed) Trade Name	Arimidex
Therapeutic Class	Aromatase inhibitor
Applicant	AstraZeneca
Priority Designation	P
Formulation	Tablet
Dosing Regimen	1 mg daily
Indication	Treatment of precocious puberty in McCune-Albright Syndrome Intended Population: Girls with McCune-Albright Syndrome and precocious puberty

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1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

(b) (4) [redacted]

1.2 Recommendation on Postmarketing Actions

None.

1.2.1 Risk Management Activity

None.

1.2.2 Required Phase 4 Commitments

None.

1.2.3 Other Phase 4 Requests

None.

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

Anastrozole is an aromatase inhibitor approved for the treatment of hormone receptor-positive breast cancer in postmenopausal women[1]. On May 9, 2001, the Agency issued a Written Request (WR) for the study of anastrozole in boys with pubertal gynecomastia and girls with McCune-Albright Syndrome (MAS) and progressive precocious puberty. The rationale for using anastrozole in these two conditions is to reduce endogenous conversion of androgens (testosterone and adrenal androgens) to estrogens, and in so doing, to suppress the manifestations of precocious puberty in girls with McCune-Albright syndrome and those of gynecomastia in

[1] Aromatase inhibitors prevent the conversion of testosterone and adrenal androgens to estrogens (estradiol and estrone, respectively). Anastrozole is marketed under the brand name Arimidex. In adults, Arimidex is approved as a 1-mg tablet to be administered orally once a day.

pubertal boys. The WR was amended four times; the last amendment (Amendment # 4) was issued on April 8, 2005. In its final form the WR stipulated the following 4 studies:

- Study 1: a placebo-controlled, randomized, double-blind, multicenter, efficacy and safety study of anastrozole for the treatment of gynecomastia in pubertal boys.
- Study 2: an open-label, single-arm, efficacy and safety study of anastrozole in girls with McCune-Albright syndrome and progressive precocious puberty.
- Study 3: a pharmacokinetic (PK) study of anastrozole in pubertal boys with pubertal gynecomastia.
- Study 4: A population PK analysis conducted in girls enrolled in Study 2.

This review summarizes the efficacy and safety findings of the above-listed studies by indication.

1.3.2 Efficacy

1.3.2.1 McCune-Albright syndrome

(b) (4) the applicant conducted Study 1033IL/0046 (Study 2 of the WR). This was an open-label, single-arm, multicenter, 12-month study conducted in 28 patients with McCune-Albright syndrome who received a daily dose of anastrozole of 1 mg. The main efficacy analyses compared growth velocity, bone age advancement, and vaginal bleeding[2] on treatment relative to baseline. **The results of these efficacy analyses indicate** (b) (4)

These observations were made in the context of biochemical evidence of partial estrogen suppression. Specifically, during anastrozole treatment, the mean estradiol serum concentrations decreased by 32% at Month 6 and by 26.7 % at Month 12[3].

The main efficacy analyses are listed next:

- The mean annualized growth velocity was reduced on anastrozole treatment from 7.9 cm/yr to 6.5 cm/year; although this change was statistically significant (p=0.035), the magnitude of the change is of questionable clinical relevance (1.4 cm reduction over 12 months); in addition, in absence of a control group, it is not clear to what extent this reduction is due to a treatment effect or to variations in endogenous estrogen secretion. When growth velocity was expressed as Z-score, a similar trend was noted.

[2] This included the following endpoints: the frequency of annualized episodes of vaginal bleeding, the proportion of patients with vaginal bleeding at baseline who experienced >50% reduction in the number of vaginal bleeding episodes on treatment, and the proportion of patients with vaginal bleeding at baseline who experienced cessation of vaginal bleeding episodes.

[3] The mean estradiol serum concentrations decreased from 121.85 pmol/L at baseline to 81.95 pmol/L at Month 6 and 89.27 pmol/L at Month 12, respectively (the upper limit of normal was 92 pmol/L); the mean serum testosterone concentration remained virtually unchanged.

- The on-trial change in mean "rate of increase in bone age" (or bone age/chronological age advancement[4]) relative to baseline was small and did not reach statistical significance (p=0.223).
- The mean (annualized) frequency of vaginal bleeding episodes increased on treatment from 13.8 ±9.8 at baseline (median 12; range 0 to 30) to 20.1 ± 24.5 (median 11.4; range 0 to 102); the change was not statistically significant (p = 0.7011)[5].

Overall, there is no disagreement between this reviewer's conclusions and those of the applicant. The applicant states that: "In this heterogeneous population there was no observed benefit in terms of reducing the frequency of vaginal bleeding, decreasing the rate of increase in bone age, or reducing growth rate in the overall group."

1.3.2.2 Pubertal gynecomastia

The efficacy of anastrozole in treating male adolescents with gynecomastia of pubertal onset was evaluated in Study 1033US/0006 (Study 1 of the Written Request). This was a randomized, placebo-controlled, double-blind, multicenter, 6-month efficacy and safety study of a daily anastrozole dose of 1 mg. It was conducted in 80 patients with gynecomastia of a minimum duration of 6 months (approximately 90 % of patients had gynecomastia for more than 1 year). **There were no statistically significant differences between anastrozole and placebo in any of the main efficacy analyses,** (b) (4) [redacted] These observations occurred in the context of a mean serum estradiol reduction of 6.5% at Month 3 and 15.4 % at Month 6 on anastrozole treatment (and minimal changes in the placebo group).

The main efficacy analyses are listed next:

- The percentage of patients who experienced a ≥ 50% reduction in total breast volume following 6 months of treatment was slightly higher in the anastrozole group relative to placebo (38.5 % vs. 31.4 %) but the difference was not statistically significant (p= 0.4687; primary efficacy analysis). Similar results were observed for the ITT and per protocol populations.
- Patients in the placebo group had a higher Month-6 mean reduction in breast volume relative to baseline (216.1 mls) when compared to anastrozole-treated patients (130.3 mls); however, the median percent reduction in breast tissue volume was comparable between treatment groups (-30.6 % anastrozole and -33.3 % placebo).

[4] The "rate of increase in bone age" (or bone age/chronological age advancement) was defined as the ratio between the change in bone age in years and the change in chronological age in years (ΔBA/ΔCA).
[5] Although 7/25 (28%) patients with vaginal bleeding at baseline had a ≥ 50% reduction in the frequency of annualized vaginal bleeding episodes during anastrozole treatment and 10 (40%) experienced cessation in vaginal bleeding on treatment over any 6-month period (with 3 or 12% patients experiencing a cessation in vaginal bleeding for the entire 12 months of treatment), overall, more patients had an increase in the frequency of vaginal bleeding on anastrozole treatment. Specifically, 14 patients had an increase of frequency of vaginal bleeding, 11 patients had a reduction and 3 patients had no change.

- The percentage of patients who had any reduction in breast volume in the anastrozole group (26 patients or 68.4%), was similar to that observed in the placebo-treated group (24 patients or 72.7%). Similar observations were made for the ITT and per protocol populations.
- The percentage of patients with breast pain at baseline who became free of breast pain by Month 6 was similar between the treatment groups (90.9 % in the anastrozole group and 100% in the placebo group).

Additional efficacy assessments were made in the pharmacokinetic study D5394C00001 (Study 3 of the Written Request), which was conducted in a patient population similar to that of Study 1 but with a shorter duration of gynecomastia. (b) (4)

[redacted]

1.3.3 Safety

There were no distinct safety signals identified in any of the three clinical studies conducted in response to the WR. Objective limitations in the interpretation of the safety data come from the absence of a control group for two of the three studies, the relatively limited clinical laboratory assessments, the small size of the datasets, and the lack of vital sign and ECG evaluations. The safety results are presented next by indication and by study.

1.3.3.1 McCune-Albright syndrome

There were no deaths, and no patients discontinued study 1033IL/0046 because of an adverse event (the only patient who discontinued did so because of lack of efficacy). Three patients (10.7%) experienced four serious adverse events: three femoral fractures[6] and an ovarian cyst; none of these events was considered related to the study drug by the investigators. Although 24 (85.7%) patients experienced a treatment-emergent adverse event (TEAE), the vast majority of TEAEs were common childhood illnesses or symptoms; others, either had alternative explanations (e.g. ovarian cyst) or were TEAEs already labeled in adults (i.e. arthralgia[7]). TEAEs judged "treatment-related" by the investigators were few and generally mild in intensity[8]. The clinical laboratory evaluations (other than hormonal assessments) were limited to liver

[6] Fractures in McCune-Albright syndrome patients are not uncommon due to the presence polyostotic fibrosis, a clinical manifestation of the condition. One patient also had a concomitant diagnosis of Cushing's syndrome.
[7] It should be noted that MAS patients have orthopedic problems due to fibrous dysplasia and, at least in some patients, arthralgia may be an associated symptom.
[8] Five (17. 9 %) adverse events were considered by the investigator to be possibly due to study medication. They were nausea, acne, pain in extremity (all mild in intensity and resolved), allergic dermatitis (mild, continuing), increased ALT/AST (moderate in intensity, reportedly resolved).

function tests (ALT and AST); there were no changes of clinical significance in mean values on treatment. One patient had ALT and AST elevations above the normal range but they were < 3X ULN; the ALT elevation was present at baseline and only increased slightly by the end of the treatment. Vital signs and ECGs were not evaluated systematically in the clinical trial.

1.3.3.2 Pubertal gynecomastia indication

1.3.3.2.1 Study 1033US/0006 (Study 1 of the Written Request)

There were no deaths and no SAEs in this study. One patient in the anastrozole group discontinued the study due to an adverse event of enlarged testicular volume; this event was judged as moderate in intensity and "possibly" related to anastrozole by the investigator[9].

A slightly higher percentage of patients in the anastrozole group had treatment - emergent adverse events when compared to the placebo group (76.7% anastrozole vs. 64.9% placebo). In general, the numerical differences in individual adverse events between the two treatment arms were small, and most adverse events were mild or moderate in intensity[10]. Adverse events that occurred with higher frequency in the anastrozole arm (≥ 2 patient difference relative to placebo) were flu syndrome, headache, syncope, and rash.

Almost twice as many patients in the anastrozole group had adverse events that were judged by the investigators to be possibly related to treatment (16.3% anastrozole vs. 8.1% placebo) but the numerical differences between the two groups for individual AEs were, in general, very small. The most frequent were acne (7 % anastrozole group vs. 2.7 % placebo) and headache (7% anastrozole and 0 % placebo)[11]. There were no on-trial clinical laboratory measurements. No ECG and vital signs analyses were provided for this study.

1.3.3.2.2 Study D5394C00001 (Study 3 of the Written Request)

There were no deaths reported in this study. Two patients experienced two serious adverse events (bilateral slipped capital femoral epiphysis in an obese patient, and acute gastroenteritis). Two patients discontinued the trial (one was the above-mentioned patient with slipped capital

[9] An analysis of the change in testicular volume during this trial indicated a slightly higher mean change from baseline in the anastrozole group (6.6 cc ±7.9) than in the placebo group (5.2cc ±8.0). For the patients who had augmentation in testicular volume (21/43 or 49% in the anastrozole group and 19/37 or 51% in the placebo group) there was a slightly larger mean increase in volume for the anastrozole group (13 cc; range 6 cc to 26 cc) than in the placebo group (10.4 cc; range 2 cc to 30 cc). In study D5394C0001 (Study 3 of the WR) the mean change in testicular volume at Month 6 (an increase of 9.4 mls) is slightly higher than that observed in Study 1033US/0006 (6.6 mls) for a similar anastrozole duration exposure and an identical dose. The differences in mean testicular size may be due to increases in serum FSH levels which exceeded those seen in the placebo arm.

[10] The only severe adverse event was in the anastrozole group,diarrhea, which occurred in one patient or 2.3%.

[11] Other "treatment-related" adverse events that were more frequent in the anastrozole group relative to the placebo group were diarrhea, hormone level altered, pharyngitis, speech disorder, urogenital disorder, and vomiting (one patient each in the anastrozole group and none in the placebo group).

femoral epiphysis; the other was a patient with a history of seasonal allergies and urticaria who withdrew consent).

A total of 30 (79.0%) patients experienced at least one adverse event. The most frequently reported adverse events (>10%) were acne (23.7%), acanthosis nigricans (15.8%), vomiting (13.2%) and nasopharyngitis (10.5%). Only one patient (2.6%) reported an AE that was classified as severe in intensity: slipped capital femoral epiphysis (this AE was also categorized as an SAE); all other adverse events were classified as mild or moderate. Most adverse events reported represent common childhood illnesses/conditions; others are adverse events seen in association with obesity (acanthosis nigricans, hypertension, possibly arthralgia)[12].

Eight patients (21.1%) experienced AEs that were considered by the investigators to be possibly due to the study medication. The most frequent of such adverse events was acne (7 patients or 18.4%); all acne AEs were reported as mild to moderate intensity[13].

There were minimal changes in the clinical laboratory tests analyzed (ALT, AST, and alkaline phosphatase) from baseline to Month 6. A few individual ALT and AST values were outside the normal range but none was considered clinically significant (i.e.≥ 3X ULN). Analyses of ECG and vital signs were not submitted for this trial.

When the safety data from the two gynecomastia studies (Studies 1 and 3 of the WR) were pooled and analyzed, the pattern of adverse events was similar to that observed in the analysis of individual studies.

In general, there were no significant disagreements between this reviewer's conclusions and those proposed by the applicant.

1.3.4 Dosing Regimen and Administration

(b) (4)

[redacted]

1.3.5 Drug-Drug Interactions

No drug-drug interaction studies were conducted.

1.3.6 Special Populations

[12] The mean BMI for the patients enrolled in this trial was near the upper limit of normal.
[13] The only other adverse events considered to be possibly associated with the study medication were arthralgia and slipped capital femoral epiphysis; both occurred in the same one patient (2.6%).

There were no studies conducted in patients with renal of liver failure.

2 INTRODUCTION AND BACKGROUND

2.1 Product Information

Anastrozole (brand name Arimidex) is an aromatase inhibitor approved for the treatment of hormone receptor-positive breast cancer in postmenopausal women. Mechanistically, aromatase inhibitors lower the concentration of serum estrogens by inhibiting the conversion of testicular and adrenal androgens to estradiol and estrone, respectively. Arimidex is manufactured as a 1-mg tablet to be administered orally once a day. To date, aromatase inhibitors are not approved in children.

2.2 Currently Available Treatment for Indications

There are no approved drug-products for the treatment of pubertal gynecomastia. Similarly, there are no approved drug products for the treatment of McCune-Albright syndrome[14].

2.3 Availability of Proposed Active Ingredient in the United States

Anastrozole is currently marketed in the US for the treatment of adult women with hormone receptor-positive breast cancer.

2.4 Important Issues With Pharmacologically Related Products

There are no approved aromatase inhibitors for any indication in children.

2.5 Presubmission Regulatory Activity

On May 9, 2001, the Agency issued a Written Request (WR) for the study of anastrozole in boys with pubertal gynecomastia and girls with McCune-Albright syndrome (MAS) and progressive precocious puberty. The WR was amended four times; the last amendment (Amendment # 4) was issued on April 8, 2005. Between 2001 and the date of submission of the current NDA (September 4, 2007) there have been multiple communications between the Division of Metabolism and Endocrinology Products (DMEP) and AstraZeneca in the form of teleconferences and written responses to questions submitted by the sponsor, all addressing various scientific and regulatory aspects related to the WR, that are reflected in the WR's final form (Amendment # 4). In lieu of a pre-NDA meeting, the Division answered the sponsor's questions in correspondence form on November 20, 2006. Some of the clinical issues addressed at that time were as follows:

[14] Nolvadex (tamoxifen citrate) contains information in the Clinical Studies and Adverse Event sections of its label as a result of a study conducted in girls with McCune-Albright syndrome and progressive precocious puberty under a previous WR but no indication was granted.

- the Division waived the requirement for an integrated summary of efficacy due to the heterogeneity of the patient populations studied (adolescent boys with gynecomastia and girls with McCune syndrome and progressive precocious puberty)
- for reasons stated above the Division waived the requirement for an across-indications integrated safety summary; however, the Division asked for a summary of incidence of adverse reports in boys with gynecomastia across both clinical studies conducted in this patient population
- the Division waived the requirement for a 4-month safety update as the clinical trials for male gynecomastia were completed and terminated, and the number of patients with MAS enrolled in extension trials was exceedingly small (such patients will be reported in Annual Reports)
- the Division has accepted that the Clinical Study Report for Study 1033IL/006 submitted early (on August 30, 2003) and archived to NDA 20-541 does not need to be re-submitted and may be cross-referenced.

(b) (4) [redacted]

2.6 Other Relevant Background Information

None.

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC (and Product Microbiology, if Applicable)

Anastrozole is an approved drug product. No new chemistry data were submitted.

3.2 Animal Pharmacology/Toxicology

Anastrozole is an approved drug product. No new animal pharmacology data were submitted.

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

The sources of clinical data are represented exclusively by the clinical trials submitted in response to the WR.

4.2 Tables of Clinical Studies

The clinical studies submitted in this NDA are summarized in Table 1.

Table 1: Summary of clinical studies included in the anastrozole Written Request (WR)

WR study	Description
Study 1 (Study 1033US/0006)	A randomized, placebo-controlled, double-blind, multicenter, 6-month efficacy and safety study of anastrozole conducted in 80 adolescent boys with pubertal gynecomastia of ≥ 6 month duration.
Study 2 (Study 1033IL/0046)	An open-label, single-arm, 12-month efficacy and safety study of anastrozole conducted in 28 girls with McCune-Albright syndrome and progressive precocious puberty.
Study 3 (Study D5394C00001)	A pharmacokinetic (PK) study of anastrozole conducted in 38 pubertal boys with gynecomastia.
Study 4	A population PK analysis conducted in 28 girls enrolled in Study 2.

4.3 Review Strategy

This clinical review has focused on the three clinical studies (studies 1 through 3 of the Written Request), which were reviewed individually.

4.4 Data Quality and Integrity

The applicant states that the quality of study data was assured through monitoring of investigational sites, appropriate training of study personnel, independent audits, investigational site visits, and periodic data source verification.

4.5 Compliance with Good Clinical Practices

The sponsor indicates that the studies were performed "in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with Good Clinical Practice (GCP) and applicable regulatory requirements." Patients had to sign informed consent prior to receiving study drug and the study protocols had to be approved by Institutional Review Boards.

4.6 Financial Disclosures

The applicant submitted a signed Form FDA 3453 indicating that:

- there were no financial agreements with the listed investigators whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a)
- each listed investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b)
- no listed investigator was the recipient of significant payments of other sorts as defined in 21CFR 54.2(f).

A Form FDA 3455 was filed on behalf of Dr. (b) (6) Investigator at site (b) (6) for clinical study (b) (6) where she treated (b) (6) Dr. (b) (6) is listed as having received "significant payments of other sorts". If is worth mentioning that the study (b) (6)

5 CLINICAL PHARMACOLOGY

5.1 Pharmacokinetics

5.1.1 **McCune-Albright syndrome**

Study 4 of the Written Request was a population pharmacokinetic analysis of anastrozole in girls with McCune-Albright syndrome enrolled in Study 1033IL/0046 (Study 2). In this study each girl was treated with 1 mg of orally administrated anastrozole daily for 12 months. Patients had two blood samples collected at the Month 1 visit (the first sample was collected between 0 and 2 h after the first anastrozole dose and the second sample was collected between 3 and 24 h after the first anastrozole dose). Two additional blood samples were collected randomly at anytime after Month 3 (Month 3 and Month 6 of anastrozole therapy). The pharmacokinetic endpoints were as follows: apparent oral clearance (CL/F), apparent volume of distribution at steady state (V_{ss}/F), maximum anastrozole plasma concentration (C_{max}), area under the anastrozole plasma concentration-time curve over the dosing interval (AUC), and terminal elimination half-life ($t_{1/2}$). They are summarized in applicant's Table S 2. For further details and for a critical look at the applicant's pharmacokinetic analysis refer to the clinical pharmacology review.

Table S2 Bayesian estimates of individual model-predicted pharmacokinetic parameters (Final model)

Parameters	Girls			Boys
	3 to 6 y N=19	7 to 10 y N=9	All N=28	All N=36
CL/F, L/h				
Mean (SD)	1.16 (0.327)	1.12 (0.253)	1.14 (0.301)	1.62 (0.660)
Median	1.16	1.17	1.17	1.46
Range	0.565 to 1.64	0.746 to 1.62	0.565 to 1.64	0.753 to 4.24
CL/F/kg, L/h/kg				
Mean (SD)	0.0566 (0.0189)	0.0330 (0.0103)	0.0490 (0.0199)	0.0218 (0.00810)
Median	0.0540	0.0331	0.0463	0.0214
Range	0.0307 to 0.0964	0.0162 to 0.0484	0.0162 to 0.0964	0.0108 to 0.0453
V/F, L				
Mean (SD)	23.8 (7.84)	44.0 (9.65)	30.3 (12.7)	75.1 (23.9)
Median	23.5	43.3	28.4	72.3
Range	12.4 to 40.2	30.1 to 57.3	12.4 to 57.3	38.3 to 131
V_{SS}/F, L				
Mean (SD)	194 (–)[a]	194 (–)[a]	194 (–)[a]	194 (–)[a]
C_{max}, ng/mL				
Mean (SD)	68.2 (17.0)	52.3 (9.23)	63.1 (16.6)	37.2 (11.5)
Median	65.7	51.1	59.6	36.9
Range	43.3 to 108	35.8 to 67.6	35.8 to 108	14.5 to 67.6
AUC, ng·h/mL				
Mean (SD)	943 (312)	938(215)	941 (280)	701 (237)
Median	859	857	858	686
Range	608 to 1770	617 to 1340	608 to 1770	236 to 1330
$t_{1/2}$, h				
Mean (SD)	15.7 (8.57)	28.5 (9.02)	19.8 (10.5)	34.6 (11.9)
Median	12.4	26.8	16.8	29.7
Range	6.92 to 39.8	17.7 to 43.0	6.92 to 43.0	19.3 to 62.3
Q/F, L/h				
Mean (SD)	2.72 (–)[a]	2.72 (–)[a]	2.72 (–)[a]	2.72 (–)[a]
ka, 1/h				
Mean (SD)	2.80 (–)[a]	2.80 (–)[a]	2.80 (–)[a]	2.80 (–)[a]

[a] Steady state total apparent volume of distribution, inter-compartmental clearance, and absorption rate constant were modelled as constant across subject (ie, without random inter-individual error term); therefore, all subjects had a similar estimate for V_{SS}/F, Q/F, and ka.
AUC Area under the plasma concentration-time curve over the dosing interval; CL/F Apparent oral clearance; C_{max} Maximum anastrozole plasma concentration; ka Absorption rate constant; SD Standard deviation of the estimate; $t_{1/2}$ Terminal elimination half life; V/F Apparent central volume of distribution; V_{SS}/F Apparent volume of distribution at steady state; Q/F Apparent inter-compartment clearance.

5.2.2 **Pubertal gynecomastia**

Study 3 of the Written Request (Study D5394C00001) was conducted in adolescents with gynecomastia and had as main objective to evaluate the pharmacokinetics of the 1-mg anastrozole dose. Of the 38 patients who participated to the study, 36 constituted the pharmacokinetic population[15]. Summary statistics for PK parameters following multiple oral

[15] Two patients did not participate in the PK sampling because they withdrew from the study.

administrations of 1 mg of anastrozole (≥ 14 days) are summarized in applicant's Table 23. For further details and for a critical look at this analysis refer to the clinical pharmacology review.

Table 23 **Summary statistics for PK parameter estimates (at Visit 3) for anastrozole following multiple oral administration of anastrozole 1 mg (PK population)**

Parameter	Statistic					
	N	Geometric mean	CV%	Median	Minimum	Maximum
$C_{ss,max}$ (ng/ml)	36	39.3	34.3	41.4	17.2	75.6
t_{max} (hr)	36	-	-	1.00	0.50	3.00
$C_{ss,min}$ (ng/ml)	36	21.5	44.1	22.1	6.05	47.2
$AUC_{ss\,(0\text{-}tau)}$ (ng.hr/ml)	36	648	37.0	682	221	1300
CL/F (L/hr)	36	1.54	37.0	1.47	0.771	4.53
V_z/F (L)	36	98.4	42.6	100	50.7	330

AUC_{ss} Area under the curve at steady state; CL/F Apparent oral clearance; $C_{ss,max}$ Maximum anastrozole plasma concentration at steady-state; $C_{ss,min}$ Minimum anastrozole plasma concentration at steady-state; CV Coefficient of variation (geometric CV presented); t_{max} Time to reach the maximum anastrozole concentration; V_z/F Apparent volume of distribution during terminal phase.
For all PK analyses, pre-dose sample times were assigned a value of '0-hour'.
Data derived from Table 11.2.1.1, Section 11.2.

5.2 Pharmacodynamics

Pharmacodynamic evaluations were conducted in all three clinical studies of theWR (studies 1 through 3) and included measurements of serum hormones (testosterone, estrogen, LH, FSH). Table 2 summarizes these findings for the Month 6 timepoint, which was common to all three studies. A pharmacologic effect of estrogen suppression was observed in all three studies and in both populations. The reduction from baseline in serum estradiol levels ranged from 13-15 % in pubertal gynecomastia males to 32.7% % in girls with McCune –Albright syndrome. Testosterone levels changed minimally in McCune-Albright syndrome patients and increased almost 150-300% in pubertal boys. FSH levels decreased in MAS girls by approximately 74% and increased in boys by 51-125%. Finally, LH levels declined in MAS patients (-87%) and increased in boys with gynecomastia by 82-536%.

Table 2: Pharmcodynamic effects of anastrozole in patients with McCune-Albright syndrome and pubertal gynecomastia

Parameter (units) Mean (SD)	Baseline or screening	Month 6	Change from baseline at Month 6	% change from baseline at Month 6
Study 1033IL/0046 (McCune-Albright patients, Study 2 of the WR)				
Estradiol (pmol/L) Mean (SD)	121.85 (162.98)	81.95 (98.28)	-39.9	-32.7*
Testosterone (nmol/L) Mean (SD)	0.52 (0.21)	0.46 (0.23)	-0.06	-11.5*
LH (IU/L) Mean (SD)	0.94 (1.64)	0.12 (0.06)	-0.82	-87*

FSH (IU/L) Mean (SD)	3.55 (5.77)	0.93 (1.24)	-2.62	-73.8*
Study 1033US/0006 (Pubertal gynecomastia patients, Study 1 of the WR)				
Estradiol (pmol/L) Mean (SD)	65.1 (35.5)	48.0 (21.0)	-18.4 (29.1)	-15.4 (40.0)
Testosterone Mean (SD)	9.2 (7.3)	13.9 (7.1)	4.9 (5.9)	153.2 (204.4)
LH Mean (SD)	2.23 (1.51)	2.83 (1.49)	0.64 (1.49)	82.7 (158.1)
FSH Mean (SD)	3.16 (1.89)	4.53 (2.88)	1.25 (1.80)	50.9 (68.4)
Study D5394C00001 (Pubertal gynecomastia patients, Study 3 of the WR)				
Estradiol (sensitive assay) (pmol/L) Mean (SD)	16.81 (15.39)	11.17 (4.25)	-5.89 (14.30)	-13.17 (29.47)
Testosterone Mean (SD)	5.55 (5.14)	13.29 (7.40)	7.74 (4.92)	285.90 (251.74)
LH Mean (SD)	1.55 (1.42)	3.56 (2.06)	2.01 (1.61)	536.63 (890.40)
FSH Mean (SD)	1.98 (1.09)	3.85 (2.04)	1.87 (1.65)	125.80 (114.24)

Sources: Tables 27, 16, and 25, respectively, of individual study reports.
*Mean percent change was calculated by this reviewer from mean baseline and Month-6 values.

5.3 Exposure-Response Relationships

No analyses of exposure-response were presented (efficacy was not demonstrated in this supplement).

6 INTEGRATED REVIEW OF EFFICACY

6.1 Indication

The two indications studied in this NDA supplement are:

- treatment of "progressive" precocious puberty in girls with McCune-Albright syndrome
- treatment of pubertal gynecomastia

6.1.1 Methods

The clinical trials submitted for the above-listed indications were studies 1 through 3 of the Written Report and they constitute the exclusive focus of this review.

6.1.2 General Discussion of Endpoints

6.1.2.1 **McCune-Albright syndrome indication**

Most efficacy endpoints evaluated in this study are standard for statural studies (e.g growth rate, bone age advancement, Tanner stage). Others (e.g. vaginal bleeding episodes) are somewhat empirical and exploratory but clinically relevant.

6.1.2.2 **Pubertal gynecomastia indication**

The main efficacy endpoint in the pubertal gynecomastia studies (breast volume measured by ultrasound) is an accurate and clinically relevant endpoint.

6.1.3 Study Design

6.1.3.1 **McCune-Albright syndrome indication**

Study 1033IL/0046 was an international[16], multi-center, open-label, single-arm, "exploratory", Phase II study that was conducted in 28 girls with McCune-Albright syndrome and "progressive" precocious puberty. The first patient was enrolled on October 23, 2002 and the last patient completed the study on February 6, 2006. The formal title of the study was "An Open-label Study Evaluating the Safety and Efficacy of Anastrozole (ARIMIDEX™) in the Treatment of Precocious Puberty in Girls with McCune-Albright Syndrome". The stated objective of the study was to "evaluate the safety and efficacy of anastrozole (daily 1 mg dose) for the treatment of MAS in girls up to the age of 10 years, receiving treatment for 1 year". Prior to enrollment patients had to have reliable data on height, bone age, and vaginal bleeding history for at least 6 months. The study's design and flow-chart are summarized in applicant's Figure 2. Anastrozole was supplied as 1-mg oral tablets containing (b) (4) drug[17]. Published pediatric studies indicate that, in male adolescents, doses of 0.5 mg and 1 mg daily for 10 days cause approximately 50% reductions in estradiol concentrations[18].

[16] Patients were enrolled from 14 centers in 7 countries: France (3) Germany (3), Italy (1), Russia (1), Spain (1), United Kingdom (1) and United States (5).

[17] The anastrozole dose of 1 mg daily was selected based on prior experience in adults (although on a per Kg basis, the selected dose is higher than the approved adult dose, doses up to 10 X higher have been reportedly used in adults without apparent additional safety issues (see Jonat W, Howell A, Blomqvist C, Eiermann W, et al. A Randomized trial comparing two doses of the new selective aromatase inhibitor anastrozole with megestrol acetate in Postmenopausal Patients with Advanced Breast Cancer. Eur J Cancer 1996;32A:404-12).

[18] Mauras N et al: Estrogen suppression in males: metabolic effects.J Clin Endocrinol Metab, 2000: 85: 2370-2377.

Figure 2 **Study flow chart - patients with retrospective data**

Study Period	6-Month Retrospective Data	Screening	Enrollment	Study Treatment Period 12 Months			Extension Period
	Visit 0	Visit 1	Visit 2 Month 0	Visit 3 Month 3	Visit 4 Month 6	Visit 5 Month 12	
Anastrozole 1 mg			Anastrozole 1 mg				
	Visit 0	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	
	V0 and V1 could be same day as V0 was not an actual visit (retrospective data collected)		V2 within 6 weeks of V1	3 months	3 months	6 months	Annual follow-up
Key measurements (refer to Table 2)	Bone age (wrist x-ray) - see Table 2. Collection of AEs from time of ICF	Informed consent. GnRH stimulation test; see Table 3	Commencement of study drug should have been within 6 weeks of screening visit, after Informed consent	Refer to Table 2	Refer to Table 2	Patients could enter Extension Period	See Table 4

AE Adverse event.
GnRH Gonadotrophin-releasing hormone.
ICF Informed consent form.
V0 Visit 0.
V1 Visit 1.
V2 Visit 2.

Applicant's Table 2 summarizes the study assessments for patients with retrospectively collected baseline data (all 28 patients enrolled fall into this category; there were no patients for whom the baseline data were collected prospectively). Efficacy evaluations included the following: frequency of vaginal bleeding, changes in growth velocity, predicted adult height, Tanner staging, bone age, uterine and ovarian volume. Safety assessments included physical exams, adverse events, clinical chemistry (ALT and AST)[19], thyroid function tests (TSH, free T4)[20], hormone assays (serum estradiol and estrone, DHEA sulfate, LH, FSH, testosterone)[21], and GnRH stimulation test[22]. In addition, pharmacokinetic measurements and genetic analysis[23] were included.

[19] Measured at screening and Month 12.
[20] Measured at screening only.
[21] Measured at screening, Month 3, Month 6, and Month 12.
[22] GnRH stimulation testing was done at screening to rule out central precocious puberty. Patients previously diagnosed with central precocious puberty who had been on treatment with a GnRH analogue (eg, Lupron) prior to entering the study did not need to undergo a GnRH stimulation test.
[23] For molecular analysis of McCune-Albright syndrome associated Gsα mutations.

Table 2 Patients with retrospective data (6 months)

	6 month Retrospective Data/ Screening		Enrollment	Study Treatment Period		
Visit	6-month retro[a]	Screening[b]	Month 0	Month 3	Month 6	Month 12
Visit number	0	1	2	3	4	5
Informed written consent of parent/legal guardian and patient assent		√				
History		√				
Physical Examination (including height and weight)	√	√	√	√	√	√
Tanner Staging (Breast and Pubic)[c]	√	√	√	√	√	√
Clinical chemistry[d]		√				√
Hormone assays[d]		√		√	√	√
Pelvic ultrasound[e] (uterus and ovaries)		√			√	√
Bone age (wrist x-ray)[f]	√	√[g]			√	√
Vaginal Bleeding Days	√					
Diary Cards[h]			√	√	√	√
Prior/concomitant medication		√	√	√	√	√
Adverse events (serious/non-serious)[i]			√	√	√	√
Pharmacokinetics[j]			√	see footnote[j]		
Dispense study drug			√	√	√	[k]

[a] Visit 0 was not an actual visit, retrospective data of at least 6 months were collected and results obtained at the screening visit.

[b] Screening assessments were performed and results evaluated within 6 weeks before initiation of study treatment, but after informed written consent of parent/legal guardian and patient assent had been signed.

[c] If the stage appeared to be intermediate, the highest stage by any given criteria was recorded.

[d] See Table 3 - Schedule of Laboratory Parameters.

[e] Pelvic ultrasound of ovary included length, width, height, and a description of cystic or solid component, including the number of ovarian cysts and size of the largest cysts; Pelvic ultrasound of the uterus included dimensions (longitudinal, transverse and anterior-posterior diameters at the level of the cornua) and description of the uterine stripe.

[f] Radiographs were required to be available and collected at each visit required and sent to (b) (4) (b)) for an independent evaluation. The determination of retrospective bone age had to be made from a minimum of 6 months of reliable, retrospective data. This could be defined by 2 assessments of bone age, which were at least 6 months apart, but no more than 15 months apart. One of these 2 assessments had to be performed at the screening visit or no more than 3 months prior to the date of first dose (see Figure 1).

[g] For the majority of patients an x-ray performed at screening could be used as one of the 2 x-rays needed for retrospective bone age determination. For patients in whom the retrospective bone age was determined using an x-ray more than 6 weeks from the date of first dose, an additional x-ray within the 6-week screening window was required for a baseline reading (see Figure 1).

[h] Diary cards captured days of vaginal bleeding during the 12 month treatment period.

[i] All adverse events (serious/non-serious) were collected from the time of informed written consent of parent/legal guardian and patient assent until 30 days following the patient's discontinuation of study treatment.

Inclusion criteria

The main inclusion criteria were as follows:

- age between 2 and 10 years, inclusive
- a diagnosis of McCune-Albright syndrome based on the demonstration of a Gsα mutation associated with peripheral precocious puberty prior to the age of 8 years; alternatively, patients had to meet at least two of the following three criteria: precocious puberty evident before the age of 8 years, café au lait spots, fibrous dysplasia
- evidence of "progressive" precocious puberty at screening, which was defined by the following: 1) physical signs of pubertal development by Tanner Stage assessments, 2) vaginal bleeding and/or 3) advanced bone age (defined as bone age of at least 12 months beyond chronological age)
- retrospective growth data (height and bone age) along with information on the frequency of vaginal bleeding over at least 6 months (if not, patients were to be followed for 6 months to collect such data)
- signed informed consent/assent

Patients who failed other treatments (e.g. tamoxifen, testolactone, antiandrogens, or progestins) were allowed enrollment after a 30-day washout, provided that growth and vaginal bleeding information were available; similarly, MAS patients previously treated for precocious puberty who came off any medication for 6 months and showed evidence of progressive precocious puberty were allowed enrollment. If patients had activation of central puberty due to underlying MAS, they were allowed enrollment only if stable for 6 months on a GnRH agonist.

Exclusion criteria

Patients were excluded from the trial if:

- they failed treatment with a third generation aromatase inhibitor (anastrozole, letrozole, exemestane)
- they received any concomitant treatment of precocious puberty with the exception of LHRH analogues in the case of central precocious puberty (bisphosphonates for fibrous dysplasia were allowed)
- liver function tests at screening (AST, ALT) were ≥ 3 ULN
- they had hypersensitivity to any component of study medication

Patients could discontinue the study for safety reasons, for eligibility criteria violations, if lost for follow-up, at investigator's discretion, or if they chose so.

Treatment compliance

Treatment compliance was assessed by keeping records of the quantity of dispensed medication for each patient and counting unused tablets returned to the investigator. Drug accountability information was recorded on the CRFs.

Efficacy variables

The efficacy variables evaluated in the study were:

- the change in frequency of annualized episodes of vaginal bleeding on treatment compared to baseline[24]
- the proportion of patients who had vaginal bleeding at baseline who experienced >50% reduction in the number of vaginal bleeding episodes on treatment
- the proportion of patients who had vaginal bleeding at baseline who experienced cessation of vaginal bleeding episodes over any 6-month study period and over the whole 12-month study
- the change in bone age advancement on treatment compared to that observed prior to starting anastrozole treatment[25]
- the change in growth velocity on treatment compared to that observed prior to starting anastrozole treatment
- the change in Tanner Stage (as a measure of pubertal progression)
- the change in mean ovarian and uterine volumes by ultrasound, including the number of ovarian cysts and size of the largest cyst
- the predicted adult height[26].

With the exception of Tanner stage, ovarian volume, and predicted adult height, all evaluations were considered ”primary” variables.

Protocol amendments

There was one protocol amendment dated September 16, 2003 (approximately 16 months after the original protocol was issued on May 13, 2002). It harmonized the existing protocol with the amended WR issued on Dec 3, 2002, added a 5-year safety surveillance phase and revised the bone age assessment window. In additions, changes to the statistical plan were made in order to include the inferential analyses requested by the Agency in the WR. This was done, reportedly, prior to unblinding of study data.

Patient disposition

A total of 28 patients were enrolled in the study. One patient (3.6%) discontinued the study after 84 days because the clinical manifestations of MAS worsened while being on treatment.

[24] The term ‘vaginal bleeding episodes’ which appears in the Written Request was interpreted as ‘vaginal bleeding days’, with an episode defined as any day in which vaginal bleeding occurred. The days of vaginal bleeding were captured in diary cards.
[25] The term ‘bone age advancement’ which appears in the Written Request and ‘rate of increase in bone age’ are used interchangeably by the applicant.
[26] This endpoint applies only to children over age 6 years.

Protocol deviations

Only one patient was excluded from the protocol-valid population because she received <180 days of study treatment. This is the same patient mentioned above who discontinued the study.

Datasets analyzed

Efficacy data were analyzed in 2 patient populations:

- the primary analysis population that consisted in all patients exposed to study treatment (28 patients)
- the protocol-valid or secondary analysis population, which included all patients exposed to study treatment minus the one patient who had a major protocol deviation (27 patients).

Safety data were summarized for all patients exposed to study treatment (28).

The applicant states that "the results based on the protocol-valid population confirmed the results obtained from the primary analysis population, and were therefore not presented in detail in this report".

Treatment compliance

The mean compliance to the study drug for patients who completed 12 months of treatment was 98.1 ± 2.7 % (range 87.7% to 100%).

6.1.3.2 **Pubertal gynecomastia indication**

There were two studies conducted for this indication: Study 1033US/0006 (Study 1 of the Written Request) and Study D5394C00001 (Study 3 of the WR). They are presented next.

6.1.3.2.1 Study 1033US/0006

Study objectives and design

Study 1033US/0006, formally titled "A Randomized, Double-blind, Placebo-controlled Trial to Assess the Safety and Efficacy of Anastrozole (ZD1033, RIMIDEX™) versus Placebo for the Treatment of Gynecomastia in Pubertal Boys", was Study 1 of the Written Request and was conducted between April 12, 2000 and September 19, 2001. The stated objective of the study was "to determine whether anastrozole was more effective than placebo in the treatment of gynecomastia in pubertal boys as assessed by changes in breast tissue size and symptoms." Study 1033US/0006 was a randomized, double-blind, placebo-controlled, multicenter study[27]. Eighty-two patients with gynecomastia (aged 11 to 18 years) were randomized 1:1 to receive

[27] 24 centers in the US.

either anastrozole at a daily dose of 1 mg or placebo for 6 months; there were two patients who were later identified as screening failures and were discontinued prior to receiving study drug.

Inclusion and exclusion criteria

The main inclusion criteria were as follows:

- age 11 to 18 years (patients were by definition males)
- presence of gynecomastia defined as one breast measuring at least 3 cm in diameter that had not decreased in diameter by 0.5 cm or more during a 3-month observation period
- normal renal, liver, and thyroid function
- no evidence of hormone-producing tumor
- no evidence of hypogonadism or androgen resistance.

Patients who had been given medications known to cause gynecomastia within the previous 6 months were excluded.

Study assessments

The primary efficacy endpoint was the ≥ 50% reduction of the ultrasound-measured breast volume at Month 6. This was assessed as a response rate (i.e. the number and percentage of patients who had a ≥50% reduction in the volume of both breasts).

Secondary efficacy endpoints were:

- the proportion of patients who had complete regression of gynecomastia at Month 6
- the actual change in the breast volume at Month 6
- the number and percentage of patients with breast pain reduction
- the change in hormone levels (sex steroids and gonadotropins)
- change in height.

Safety assessments included adverse events, and clinical laboratory. There was one amendment to the study; it deleted a restrictive weight inclusion criterion.

The patient populations analyzed were as follows:

- the safety population (defined as all randomized patients who had taken at least one dose of study and had at least one data point after dosing); it included a total of 80 patients (43 patients in the anastrozole arm and 37 patients in the placebo arm).
- the intent-to-treat population (defined as all randomized patients who took the study drug and had a measurement at baseline and at least one post-baseline observation); it included a total of 74 patients (39 patients in the anastrozole arm and 35 patients in the placebo arm).
- the per protocol population (defined as patients who received ≥150 days of treatment, were ≥ 80% compliant, and did not have any significant violations or deviations); it included a total of 56 patients (30 patients in the anastrozole arm and 26 patients in the placebo arm).

The study assessments are summarized in applicant's Table 1.

Table 1 Study plan

	Pretreatment screening	Randomized treatment							Withdrawal	Follow-up
Visit	Screening[a]	1	2	3	4	5	6	7	Withdrawal	Follow-up
Month	-3	0	1	2	3	4	5	6		30 days
Safety assessments										
Adverse events			√[b]	√[b]	√	√[b]	√[b]	√	√[c]	√
Clinical laboratory tests[d]	√	√[b]			√[b]			√[b]		
Physical examination[e]	√	√			√			√	√[c]	

	Pretreatment screening	Randomized treatment							Withdrawal	Follow-up
Visit	Screening[a]	1	2	3	4	5	6	7	Withdrawal	Follow-up
Month	-3	0	1	2	3	4	5	6		30 days
Safety assessments										
Adverse events			√[b]	√[b]	√	√[b]	√[b]	√	√[c]	√
Clinical laboratory tests[d]	√	√[b]			√[b]			√[b]		
Physical examination[e]	√	√			√			√	√[c]	

Treatment compliance

Compliance was defined as the number of tablets consumed divided by the duration of the treatment and is summarized in applicant's Table 10. Compliance was > 90% in both treatment arms.

Table 10 Duration of study treatment and treatment compliance of all patients treated with anastrozole or placebo

Characteristic	Treatment group			
	Anastrozole 1 mg		Placebo	
	N	Mean (SD)	N	Mean (SD)
Duration of study treatment (days)	43	182.0 (37.0)	37	183.5 (34.6)
% compliance[a]	42	90.9 (11.3)	37	92.8 (9.0)

[a] Total compliance was assessed at the Month 6/Final visit.

6.1.3.2.2 Study D5394C00001

Study objectives and design

Study D5394C00001, formally titled "An Open-label Pharmacokinetic and Pharmacodynamic Study of Anastrozole (ARIMIDEX™) Used to Treat Pubertal Boys with Gynecomastia of Recent Onset", is Study 3 of the Written Request. It was conducted between June 16, 2005 and

November 7, 2006. The primary objective of the study was to assess the pharmacokinetics of anastrozole in boys with pubertal gynecomastia of recent onset (i.e. of less than 12 months duration)[28]. The secondary objectives of the study were to evaluate the response rate for resolution of gynecomastia, hormonal changes, tolerability and safety. The study was designed as a two-center, single-arm, open-label, study. Thirty-eight patients were enrolled and received anastrozole for 6 months. Anastrozole was administered as a 1 mg tablet, once, orally.

Inclusion and exclusion criteria

The main inclusion criteria were as follows:

- males with ages between 11 and 18 years
- presence of gynecomastia of less than 12 months duration that did not decrease in size for the immediately preceding 3-month period[29]
- normal renal, liver, and thyroid function[30]
- no evidence of hormone-producing tumor
- no evidence of hypogonadism or androgen resistance.

Except for the gynecomastia inclusion criterion, all others were the same as in Study 1033US/0006. The exclusion criteria were standard.

Study assessments

Efficacy assessments were all secondary endpoints and included

- the proportion of patients who achieved a ≥50% reduction in the calculated volume of gynecomastia of both breasts combined after 6 months of treatment
- the proportion of patients who achieved complete regression of gynecomastia at Month 6
- the actual change in calculated volume of gynecomastia at Month 6 (both breasts combined)
- breast pain/tenderness response rate in symptomatic patients
- change in hormone concentrations (testosterone, estradiol, FSH, LH and SHBG)
- change in height.

[28] This study was conducted after the results of study, 1033US/0006 were analyzed. The applicant (b) (4) Therefore, Study D5394C00001was conducted in patients with gynecomastia of recent onset, (b) (4)

One breast had to measure ≥ 2 cm in diameter by ultrasound or caliper measurement. Patients were eligible if they had a minimum diameter of ≥2 cm in at least one breast.

[30] "Normal renal and thyroid function" was defined as no clinically significant impaired renal or thyroid function in the opinion of the investigator. "Normal liver function" was defined as liver function tests at screening less than or equal to 3x the upper limit of the reference range for age.

Safety assessments included adverse events, clinical laboratory assessments (hormone levels and liver function tests)[31], and physical examination (including change in testicular volume and Tanner Stage).

The patient populations analyzed were as follows:

- the intention-to-treat (ITT) population (36 patients), which included all treated patients who had a baseline and at least one post baseline measurement
- the per-protocol (PP) population (25 patients), a subset of the ITT population defined as all patients who did not have major protocol violations or deviations
- the safety population (38 patients), which included all patients who received at least one dose of study drug
- the pharmacokinetic population (36 patients)
- the pharmacodynamic population (25 patients).

\

The study had one amendment and one administrative change; both clarified some protocol definitions or corrected minor omissions. Most of the protocol deviations were related to poor compliance (defined as drug use < 80%).The study assessments are summarized in applicant's Table 3.

Table 3 Study plan

Visit	1	2	3	4	5	6	7	8	9
Day	0	1	≥14[a]	61	91	121	151	181	211
Visit description	Pre-treatment screening[b]	Screening[c]	Study Visit	Study Visit	Study Visit	Study Visit	Study Visit	Study Visit	30-day follow-up
Informed consent (assent if applicable)	X								
History (including duration and change of gynecomastia)	X								
Physical examination[d]	X				X			X	
Clinical chemistry[e]	X							X[e]	
Pharmacokinetics[f]			X						
Hormone levels[g]	X							X	
Ultrasound measurement of gynecomastia	X[h]							X[i]	
Concomitant medications		X	X	X[j]	X	X[j]	X[j]	X	X[j]
Adverse events		X	X	X[j]	X	X[j]	X[j]	X	X[j]
Dispense study therapy		X			X				

a Visit 3 occurred at least 14 days after Visit 2 (first dose). Patients had to have 7 consecutive days of study drug immediately prior to their PK assessments. Visit 3 could be rescheduled to ensure this dosing requirement was met. The dose of study drug at Visit 3 was taken under fasting conditions (6 to 8 hours prior) and the patient had to fast 2 hours post Visit 3 dose.
b Pre-treatment assessments were performed within 2 weeks prior to screening.
c After patient eligibility was determined, a parent/legal guardian could pick up the patient's study therapy and provide concomitant medication and AE information.
d Included body mass index (height, weight), Tanner Stage, presence of breast pain/tenderness, testicular volume by Prader orchidometer, and caliper measurement of gynecomastia (caliper measurement at Visits 1 and 8 only).
e Pre-treatment labs included complete blood count, sequential multiple analyzer, thyroid function tests (Triiodothyronine [T3], thyroxine test [T4], thyroid-stimulating hormone [TSH]), liver function tests (aspartate transaminase, alanine transaminase, alkaline phosphatase). Only liver function tests were repeated at Visit 8.
f Blood samples (4 ml each) were collected as follows: within 30 minutes of pre-dose (0 hour), 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 16, 20 and 24 hours post dose.
g Hormone tests included testosterone, luteinizing hormone, follicle-stimulating hormone, sex hormone-binding globulin, estradiol (sensitive estradiol assay) and beta-human chorionic gonadotrophin (done at Visit 1 only). Due to the diurnal rhythm of testosterone in adolescence this testing was in the morning.
h Arranged/done at the pre-treatment screening visit and results were obtained prior to the screening visit. Minimum diameter was ≥2 cm (by ultrasound or caliper measurement) in at least 1 dimension in 1 breast, or patient was considered a screen failure.
i If patient discontinued before Visit 8, an ultrasound and caliper measurement were obtained at the time of discontinuation.
j Could be obtained via telephone contact.

[31] Blood samples were analyzed centrally.

Treatment compliance

Treatment compliance was measured as the total number of tablets used divided by the duration of treatment; it is summarized in applicant's Table 14.

Table 14 Treatment compliance (Safety population)

Measure	Anastrozole 1 mg (N=38)
Percent compliance with study treatment [a]	
n	35[b]
Mean (standard deviation)	93.6 (8.4)
Range	72 to 100

a Percent compliance is the total number of tablets used divided by the duration of treatment.
b Percent compliance with study treatment was not calculable for patients E0001006, E0001007 and E0001029 (see Appendix 12.2.5.1).

6.1.4 Efficacy Findings

6.1.4.1 **McCune-Albright syndrome indication**

Demographics and baseline characteristics

Information on the patients' medical history as it relates to the diagnosis of MAS is presented in applicant's Table 12. Twenty-seven out of 28 patients (96.4%) had classical MAS[32] and one patient had atypical MAS[33]. All 28 patients were diagnosed with precocious puberty before age 8 years (range 0.17 to 7 years). Ten out of 28 (35.7%) had a Gsα mutation, 27/28 (96.4%) had café au lait spots, 15/28 (53.6%) had fibrous dysplasia, and 26/28 (92.8%) had at least one day of vaginal bleeding during the 6 months prior to enrollment (two had none and for one patient this information was not known).

[32] i.e, had at least two of a triad of symptoms that included precocious puberty, café au lait spots or fibrous dysplasia.
[33] This patient (E0007003) had precocious puberty with age of onset at 0.33 years, documented Gsα mutation but no café au lait spots and no fibrous dysplasia.

Table 12 McCune-Albright Syndrome history: all patients exposed to study treatment

Patient number	Protocol-valid population	Age (fractional years) when patient first presented with precocious puberty	Fibrous dysplasia	Café au lait spots	Gsα mutation[a]	Number of vaginal bleeding days (last 6 months)
E0001001	Yes	0.33	No	Yes	Yes	14
E0001002	Yes	2.67	No	Yes	No	6
E0001008	Yes	4.25	Yes	Yes	Yes	6
E0002001	Yes	4.00	No	Yes	Yes	3
E0004001	Yes	1.00	Yes	Yes	No	13
E0004003	Yes	0.25	Yes	Yes	No	14
E0004005	Yes	1.00	No	Yes	No	9
E0004006	Yes	5.00	No	Yes	No	14
E0004008	Yes	7.00	No	Yes	No	0
E0005001	Yes	2.50	No	Yes	No	5
E0005002	Yes	2.00	No	Yes	No	4
E0006001	No	0.17	Yes	Yes	No	8
E0007001	Yes	4.83	No	Yes	Yes	8
E0007002	Yes	1.50	Yes	Yes	Yes	1
E0007003	Yes	0.33	No	No	Yes	1
E0007004	Yes	1.17	No	Yes	Yes	3
E0007005	Yes	0.50	Yes	Yes	Yes	U[b]
E0007007	Yes	2.17	No	Yes	No	0
E0008001	Yes	1.67	Yes	Yes	No	13
E0008002	Yes	0.67	Yes	Yes	Yes	2
E0011001	Yes	2.50	Yes	Yes	No	4
E0012001	Yes	2.00	Yes	Yes	No	9
E0012002	Yes	1.50	No	Yes	No	2
E0030001	Yes	5.00	Yes	Yes	No	7
E0034001	Yes	1.75	Yes	Yes	Yes	4
E0035001	Yes	3.00	Yes	Yes	No	14
E0036001	Yes	3.00	Yes	Yes	No	7
E0036002	Yes	0.83	Yes	Yes	No	15

[a] Detected prior to study entry.
[b] Comment field on case report form indicated vaginal bleeding prior to study; however the number of days is unknown.
U Unknown. **Data derived from Listing** 12.2.4.4.

The baseline information for the major efficacy endpoints is summarized in sponsor's Table 14. The mean bone age of 8.57 ±2.62 years was approximately 3 years ahead of the mean chronological age of 5.9 ±2.03 years (range: 3.2 to 11 years) and the rate of increase of bone age was faster than the increase in chronological age (1.25 years). The annualized pre-treatment growth rate was accelerated at 7.87 ±2.94 cm/yr and the growth rate Z-score was above the mean at 1.40 (±3.15). On average, patients experienced approximately 7 days of vaginal bleeding for the 6-months prior to the trial initiation. Twenty-six (92.9%) of patients were Caucasian; one patient (3.6%) was Oriental and one was classified in the "other" category.

Table 14 Baseline information: all patients exposed to study treatment

Parameter	Anastrozole 1 mg (N=28)			
	n	Mean (SD)	Median	Range
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.
Data derived from Summary Table 11.1.3.

The individual patient characteristics related to the main efficacy endpoints showed considerable variability at baseline. This is exemplified in Table 3, which summarizes the rate of bone age increase, the growth rate and the frequency of vaginal bleeding at baseline, as well as the baseline individual estrogen values. Specifically, 12/28 patents had bone age advancement that was lower than the chronological age advancement (i.e. a rate of bone age increase < 1; highlighted in yellow); 13/28 patients had a growth rate that was in the normal range (i.e. < 2; highlighted in yellow)[34]; 2/28 patients did not have evidence of vaginal bleeding and for one of them the data were not available (highlighted in yellow); 20/28 patients has normal (i.e. not elevated) estradiol concentration at baseline (highlighted in yellow), as were 7/28 patients with normal serum estrone concentrations (also highlighted). In fact only 7 patients showed a bone age progression that was higher than the advancement in chronological age, an above normal growth rate, and experienced vaginal bleeding.

Table 3: Individual patient characteristics for major efficacy variables at baseline

Patient ID	Rate of bone age increase	Growth rate Z-score	No. of vaginal bleeding days	Serum estradiol concentration (pmol/L)	Serum estrone concentration (pmol/L)
E0001001	1.59	2.37	14	48.82	259.00
E0001002	1.58	-1.46	6	33.77	222.00
E0001008	1.23	-6.39*	6	117.47	384.80
E0002001	2.65	1.95	3	34.5	92.50
E0004001	1.10	-3.98*	13	261.38	340.40
E0004003	1.86	2.82*	14	216.59	259.00
E0004005	2.45	8.67	9	45.52	218.30
E0004006	-0.03	2.65	14	35.98	70.30
E0004008	1.14	2.50	0	50.66	196.10

[34] It should be recognized that patients with fibrous dysplasia may have significant orthopedic problems that may interfere with the accuracy of height measurements. The potential confounding effect of fibrous dysplasia has not been removed from this analysis of growth rate.

E0005001	3.17	2.61	5	29.37	136.90
E0005002	1.62	3.66	4	57.63	196.10
E0006001	0.49	-0.72*	8	172.90	255.30
E0007001	0.97	2.19	8	60.57	262.70
E0007002	0.87	-1.69*	1	327.82	451.40
E0007003	1.55	1.61	1	669.22	518.00
E0007004	1.60	-1.22	3	<16.89	96.20
E0007005	1.12	6.99*	U	29.00	51.80
E0007007	1.34	4.00	0	<16.89	159.10
E0008001	0.23	-1.18*	13	44.05	170.20
E0008002	0.89	1.42*	2	42.22	129.50
E0011001	0.85	NA*	4	28.27	173.90
E0012001	0.58	2.04*	9	44.05	85.10
E0012002	1.89	4.39	2	40.75	92.50
E0030001	0.73	0.25*	7	363.43	307.10
E0034001	0.26	0.78*	4	38.18	NA
E0035001	0.97	-2.18*	14	503.66	266.40
E0036001	0.23	3.04*	7	38.91	59.20
E0036002	2.18	2.61*	15	43.32	155.40

Siurce: Listings 12.2.4.6, 12.2.6.1.1 and 12.2.8.1.
NA= not available
U=Unknown
*Indicates patients who had manifestations of fibrous dysplasia.
Normal range for serum estradiol: < 92.0 pmol/L
Normal range for serum estrone:" <129.5 pmol/L

Efficacy analyses

Frequency of vaginal bleeding

Applicant's Table 16 summarizes the change in the frequency of episodes of vaginal bleeding (captured as days of bleeding) on treatment relative to baseline. For the 27 (out of 28) patients with baseline information regarding this endpoint, the mean frequency of vaginal bleeding during the 6-month pre-treatment period was 13.8 ±9.8 (median 12, range 0 to 30). During the study, the mean frequency of vaginal bleeding increased to 20.1 ± 24.5 (the median barely changed at 11.4; the range was 0 to 102)[35]. There was a mean increase of 6.7± 25.5 days (median 1.9 days, range -27.1 to 90.6 days) during anastrazole treatment, which was not statistically significant (p = 0.7011). It is worth mentioning that the calculations were made under a "worst case scenario" in which bleeding was assumed to have occurred on days with missing data.

[35] Two patients had large increases in the frequency of vaginal bleeding days. Patient E0001008 had an increase in number of annualized vaginal bleeding days from 12 to 103 and, under a worst case scenario, 106 days (a 754% increase). Patient E0008002 had an increase in annualized vaginal bleeding days from 4 days at baseline to 85 days on trial (a 1940% increase)

Table 16 Frequency of vaginal bleeding days: all patients exposed to study treatment

		Anastrozole 1 mg (N=28)				
Parameter assessed	N	Mean (SD)	Median	Range	p-value	2-sided 95% CI
Frequency pre-treatment (number of bleeding days in prior 6 months, annualized)	27[a]	13.8 (9.82)	12.0	0.0 to 30.0		
Frequency during treatment (number of bleeding days during 12 months, annualized)	28	20.1 (24.54)	11.4	0.0 to 102.6		
Change in frequency of vaginal bleeding from pre-treatment to during-treatment (annualized)	27[a]	6.7 (25.49)	1.9	-27.1 to 90.6	0.7011	-6.00 to 14.26

[a] Patient E0007005 was excluded as although the comment field on case report form indicated vaginal bleeding prior to study, the number of days is unknown.
CI Confidence interval.
N Number of patients.
SD Standard deviation.
Data derived from Summary Table 11.2.1.1

Proportion of patients with baseline vaginal bleeding who experienced ≥ 50% reduction in the number of vaginal bleeding episodes on treatment

Twenty-six out of 28 patients had vaginal bleeding at baseline (this includes one patient for whom the number of episodes of vaginal bleeding was not specified). Of the remaining 25 patients, similar proportions had increases or reductions in the number of vaginal bleeding days (11 patients had a reduction of frequency of vaginal bleeding, 14 patients had an increase of such frequency, and 3 patients had no change during anastrozole treatment). Seven (28%) patients had a reduction ≥ 50% 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

The number of patients who experienced vaginal bleeding within the 6 month pretreatment period and who had cessation of vaginal bleeding on treatment is presented in applicant's Table 18. Ten (40%) patients experienced cessation in vaginal bleeding on treatment over a 6-month period (i.e. over any ≥180 of the 360 days of the trial) and three (12%) patients experienced a cessation in vaginal bleeding on treatment over the whole 12-month period.

Table 18 Patients with cessation of vaginal bleeding days: all patients exposed to study treatment

	Anastrozole 1 mg (N=28)	
	n	95% Confidence Intervals
Number of patients with baseline vaginal bleeding	25	
Number (%)[a] of patients with baseline vaginal bleeding and a cessation for ≥180 days	10 (40.0)	21.1% to 61.3%
Number (%)[a] of patients with baseline vaginal bleeding and cessation from Day 1 to Day 360	3 (12.0)	2.5% to 31.2%

[a] Percentages are based on the number of patients with baseline vaginal bleeding.
N Number of patients.

Change in bone age advancement on treatment relative to baseline

The on-trial change in the rate of bone age advancement[36] is illustrated in applicant's Table 20. During the pre-treatment period, the mean rate of bone age advancement was 1.25, indicating a faster change in bone age relative to chronological age. During anastrozole treatment the mean bone age advancement slowed somewhat (1.04) but the change was not statistically significant (p=0.223). Descriptively, the change in rate was smaller during the first 6 months (1.14) than the last 6 months (0.93). The changes relative to baseline were not statistically significant for any of the 6-month periods analyzed (first six months or the last six months).

Table 20 Bone age and rate of increase in bone age: all patients exposed to study treatment

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).
N Number of patients.
SD Standard deviation.

Change in growth velocity on treatment relative to baseline

The change in growth velocity on anastrozole treatment relative to baseline is summarized in applicant's Table 21. The mean baseline growth rate of 7.9 cm/yr slowed down during anastrozole treatment to 6.5 cm/year; although this change was statistically significant (p=0.035) its magnitude was of small clinical relevance (1.4 cm/yr). The annualized growth velocity during the first 6 months (6.9 cm/yr) was comparable to that of the last 6-months of the study (6.1 cm/yr)[37]. When growth velocity was expressed as Z-score, similar observations were

[36] Defined as the ratio between the change in bone age in years and the change in chronological age in years (ΔBA/ΔCA).
[37] The change in growth rate during the first 6 months (-1 cm/yr) did not reach statistical significance (p=0.172); the change for the last 6 months was statistically significant (p=0.018).

made; although the changes did not reach statistical significance, there was a positive trend, particularly for the last 6 months of treatment (p =0.0564). The mean pretreatment Z-score decreased on treatment from 1.4 at baseline (indicating a high normal mean growth rate) to 0.26 (a value closer to the mean). The change for the last 6 months was higher than that observed during the first 6-months. To what extent this is due to a treatment effect or to variations in estrogen secretion is not clear.

Table 21 Growth rate (measured data and Z-score): all patients exposed to study treatment

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

[a] From sign test for the median at the 0.05 significance level.
[b] The growth rate from the previous visit to the current visit, minus the mean growth rate, divided by the SD, where the mean and SD are the age- and gender-specific statistics from the National Center for Health Statistics (NCHS) Fels study, and age is the age at the current visit. See Listing 12.2.6.3.1 for the reference table of age-dependent means and SDs of growth rate.
N Number of patients.
SD Standard deviation.

Changes in Tanner stage

Overall, there were small mean increases in both breast and pubic hair Tanner stages on anastrozole treatment.

At baseline, the mean ± SD Tanner stage for breast was 2.7± 0.81 (range 1 to 4); at Month 12 it was 2.9 ± 0.89 (range 1 to 4). The change from baseline to Month 12 was 0.1 ± 0.71 (range -1 to 2). The mean ± SD Tanner stage for pubic hair was 2.1± 0.86 (range 1 to 3) at baseline; at Month 12 it was 2.5 ± 1.00 (range 1 to 4). The change from baseline to Month 12 was 0.4 ± 0.63 (range -1 to 2).

Applicant's Table 23 illustrates the change from baseline in Tanner stage to Month 12. With respect to breast development, one Tanner 1 patient advanced to Tanner 2; two Tanner 2 patients regressed to Tanner 1, four remained Tanner 2, four advanced to Tanner 3, and one advanced to Tanner 4. All 5 patients who were Tanner stage 4 remained so during the trial.

With respect to Tanner pubic stage, of the patients who were Tanner 1 at baseline, six remained so on trial, two advanced to Tanner 2 and one to Tanner 3; of the Tanner 2 patients one regressed to Tanner 1, two remained the same, and five advanced to Tanner 3. Of the Tanner 3 patients 8 did not change Tanner stage and three advanced to Tanner 4.

Table 23 Frequency in transition of Tanner Staging: all patients exposed to study treatment

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

N Number of patients.

Change in mean uterine and ovarian volumes

The change in mean uterine volume is presented in applicant's Table 25. There was a mean increase of 1.16 cc in uterine volume by Month 12 (approximately 10% increase); the median change was minimal (-0.33) and the range of changes was broad (-12.67 to 14.13) as marked individual variations were observed.

Table 25 Uterine volume[a]: all patients exposed to study treatment

	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.
N Number of patients.

The mean change in ovarian volume is presented in applicant's Table 11.3.8.1.3. There was a small decline in mean ovarian volume at Month 12 (-0.41) with a wide range of individual changes (-10.78 to 9.30).

Table 11.3.8.1.3 Average Ovarian Volume

Population: All Patients Exposed to Study Treatment

	Arimidex 1 MG (N=28)					
	N	Mean	Median	SD	Min	Max
Average Ovarian Volume (cc) at Screening Visit	19	4.51	4.37	3.412	0.68	11.64
Average Ovarian Volume (cc) at Month 6	15	3.46	1.58	4.540	0.62	15.85
Average Ovarian Volume (cc) at Month 12/Final Visit	18	2.99	1.78	3.029	0.28	10.35
Change in Average Ovarian Volume (cc), Screening to Month 6*	9	0.34	-0.20	2.516	-3.33	4.50
Change in Average Ovarian Volume (cc), Month 6 to Month 12/Final Visit*	12	-0.65	0.49	5.916	-14.99	9.22
Change in Average Ovarian Volume (cc), Screening to Month 12/Final Visit*	13	-0.41	-0.65	4.887	-10.78	9.30

Predicted adult height

Information on the predicted adult height for children over 6 years of age (for whom the prediction method of Bayley and Pinneau applies) is provided in applicant's Table 26. The mean change in predicted adult height was minimal (around 1 cm).

Table 26 Predicted adult height[a] – method of Bayley and Pinneau: all patients exposed to study treatment

	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

[a] Equals the current height divided by a factor (the fraction of final adult height) based on current bone age and current bone age relative to chronological age, classified as retarded, average or advanced. Retarded is defined as current bone age (years) < chronological age (years) minus 1; advanced is defined as current bone age (years) > chronological age (years) plus 1; otherwise, bone age is classified as average. See Listing 12.2.6.5.2 in Appendix 12.2 for the reference table of values for the calculation of predicted adult (mature) height attained at each bone age – method of Bayley and Pinneau.

[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.

N Number of patients.

SD Standard deviation.

Hormone levels

Hormone levels that were measured during this clinical trial included serum estradiol, serum estrone, dehydroepiandrosterone (DHEA) sulfate, testosterone, follicle-stimulating hormone, and luteinizing hormone. The mean serum concentrations for estradiol decreased during the trial from 121.85 pmol/L at screening to 89.27 pmol/L at Month 12; serum estrone concentrations also declined (from 207.75 pmol/L at baseline to 114.47 pmol/L at Month 12). This corresponds to estradiol reductions of 32% at Month 6 and 26.7% at Month 12, respectively. Mean serum levels of testosterone and DHEA sulfate levels remained relatively constant, while levels of LH and FSH both decreased. No formal statistical analyses are presented.

Table 27 Hormone levels: all patients exposed to study treatment

Parameter (units)		Anastrozole 1 mg (N=28) N	Mean (SD)	Median	Range
Serum estradiol (pmol/L)	Screening	28	121.85 (162.98)	44.05	16.89 to 669.22
	Month 6	27	81.95 (98.28)	34.51	16.89 to 335.16
	Month 12/ Final visit	27	89.27 (138.83)	37.44	16.89 to 708.14
Serum estrone (pmol/L)	Screening	27	207.75 (118.83)	196.10	51.80 to 518.00
	Month 6	27	106.07 (95.61)	81.40	18.50 to 462.50
	Month 12/ Final visit	27	114.70 (113.83)	81.40	18.50 to 399.60
DHEA sulfate (µmol/L)	Screening	28	0.82 (0.90)	0.36	0.27 to 3.89
	Month 6	27	0.93 (1.06)	0.41	0.27 to 3.79
	Month 12/ Final visit	27	1.03 (1.11)	0.55	0.27 to 4.57
Testosterone (nmol/L)	Screening	28	0.52 (0.21)	0.47	0.35 to 1.08
	Month 6	27	0.46 (0.23)	0.35	0.35 to 1.21
	Month 12/ Final visit	27	0.53 (0.34)	0.35	0.35 to 1.60
FSH (ultrasensitive) (IU/L)	Screening	28	3.55 (5.77)	0.65	0.30 to 20.80
	Month 6	27	0.93 (1.24)	0.40	0.30 to 5.40
	Month 12/ Final visit	27	1.23 (1.40)	0.60	0.30 to 5.90
LH (ultrasensitive) (IU/L)	Screening	28	0.94 (1.64)	0.40	0.10 to 8.40
	Month 6	27	0.12 (0.06)	0.10	0.10 to 0.30
	Month 12/ Final visit	27	0.26 (0.44)	0.10	0.10 to 1.60

DHEA Dehydroepiandrosterone.
FSH Follicle-stimulating hormone.
LH Luteinizing hormone.
IU International units.
N Number of patients.
SD Standard deviation.

6.1.4.2 **Pubertal gynecomastia indication**

6.1.4.2.1 Study 1033US/0006 (Study 1 of the Written Request)

Demographics and baseline characteristics

The main baseline characteristics and demographics are summarized in Table 4. The mean baseline age was 14.6 years (range 10 to18 years). Patients had gynecomastia that lasted from > 6 months to > 3 years. The mean duration of gynecomastia was comparable between the two treatment groups. Baseline breast volume was higher in the placebo group (574.5 mls) relative to the anastrozole group (439.5 mls). Breast pain was present in 28.2 % of anastrozole-treated patients and 25.7% of the placebo-treated patients. The BMI Z-score was similar in both groups (1.4).

Table 4: Baseline demographics and characteristics (ITT Population)

Demographics or baseline characteristic	Treatment arm	
	Anastrozole 1 mg (N=39)	Placebo (N=35)
Age (years)		
Mean (SD)	14.6 (1.8)	14.7 (1.8)
Range	10.8 to 18.1	11 to 18.6
Duration of gynecomastia (>6		

months to 12 months) N (%)	4 (10.3)	3 (8.6)
Duration of gynecomastia (>1 year to 2 years) N (%)	16 (41.0)	13 (37.1)
Duration of gynecomastia (>2 years to 3 years) N (%)	10 (25.6)	11 (31.4)
Duration of gynecomastia (>3 years) N (%)	9 (23.1)	8 (22.9)
BMI (z-score) Mean (SD)	1.43 (0.98)	1.41 (0.90)
Breast volume (ml) by ultrasound n Mean (SD) Range	38 439.5 (596.2) 3.8 to 2065.7	33 574.5 (722.4) 1.5 to 2686.6

Source: Table 9 Clinical Study report

Efficacy results

Applicant's Table 12 summarizes the results for the primary efficacy analysis conducted in the ITT population. The primary efficacy endpoint was the number and percentage of patients who had a 50% or greater reduction in total breast volume at Month 6. A slightly higher percentage of patients on anastrozole had a ≥50% reduction in breast volume at Month 6 relative to placebo (38.5 % vs. 31.4 %); however, this difference was not statistically significant (p= 0.4687). Similar results were observed in the per protocol population (36.7% in the anastrozole group and 30.8% in the placebo group had ≥50% reduction in breast volume; p=0.326). Only one patient[38] experienced a complete reduction of gynecomastia at Month 6.

Table 12 Percentage of patients with 50% or greater reduction in total breast volume (ITT population)

	Randomized treatment	
	Anastrozole 1 mg (N=39)	Placebo (N=35)
n	15	11
Percentage of patients (%)	38.5	31.4
Upper and lower 95% confidence limits	23.4 to 55.4	16.9 to 49.3

The actual change in the volume of breast tissue is presented in applicant's Table 14. Patients in the placebo group had a slightly higher Month-6 absolute mean reduction in breast volume relative to baseline (216.1 mls) when compared to anastrozole-treated patients (130.3 mls). The percentage of patients who had a reduction in breast volume in the anastrozole group (26 patients or 68.4%), was similar to that observed in the placebo-treated group (24 patients or 72.7%);

[38] Patient 0001/0021 in the anastrozole group.

similar observations were made for the per protocol populations. The median percent changes in breast tissue volume were reported as -30.6 % in the Arimidex group and -33.3 % in the placebo group, respectively.

Table 14 Change in calculated volume of gynecomastia from Visit 1 to Month 6/Final visit (ITT population)

		Randomized treatment	
		Anastrozole 1 mg (N=39)	**Placebo (N=35)**
Baseline	n	38	33
	Mean (SD)	439.5 (596.2)	574.5 (722.4)
	Range	4 to 2066	2 to 2687
Month 6/Final visit	n	38	34
	Mean (SD)	309.2 (540.5)	369.0 (450.3)
	Range	0 to 2376	1 to 1932
Change from baseline to Month 6/Final visit	n	38	33
	Mean (SD)	-130.3 (353.5)	-216.1 (565.8)
	Range	-1581 to 415	-2333 to 1106
Percent change from baseline to Month 6/Final visit	n	38	33
	Mean (SD)	-23.5 (66.1)	-5.9 (118.3)
	Range	-100 to 266	-96 to 593

SD standard deviation

Applicant's Table 15 summarizes the number and percentage of patients who reported breast pain reduction (ITT population). By Month 6, 90-100% of the patients enrolled became pain-free and there were no statistically significant differences between treatment groups. Similar results are reported for the per protocol population.

Table 15 Percentage of patients with breast pain (tenderness) – ITT population

		Number (%) of randomized patients			
		Anastrozole 1 mg		Placebo	
All patients		39		35	
Baseline (n and % of patients)	Asymptomatic patients	28	(71.8)	26	(74.3)
	Symptomatic patients	11	(28.2)	9	(25.7)
Patients symptomatic at baseline		11		9	
Month 3[a] (n and % of patients)	Symptomatic patients reporting no pain at visit	8	(72.7)	6	(66.7)
	Symptomatic patients reporting pain at visit	3	(27.3)	3	(33.3)
Month 6/Final visit[a] (n and % of patients)	Symptomatic patients reporting no pain at visit	10	(90.9)	9	(100.0)
	Symptomatic patients reporting pain at visit	1	(9.1)	0	

[a] Percentages are based on the number of symptomatic patients at baseline.

The changes in serum estradiol and testosterone levels are presented in applicant's Table 16. In the anastrozole treatment group there was a 6.5% mean reduction in the serum estradiol levels at Month 3 and a 15.4 % reduction at Month 6, respectively; the estradiol % changes in the placebo group were minimal (both treatment arms had similar estradiol levels at baseline). The mean testosterone serum levels increased by 169% at Month 3 and 153% at Month 6, respectively, in the anastrozole arm; in the placebo group they increased by 23 % at Month 3 and 53 % at Month 6, respectively (both treatment arms had similar baseline values).

Table 16 Hormone levels and change from baseline – ITT population

	Randomized treatment					
	Anastrozole 1 mg (N=39)			Placebo (N=35)		
	n	Mean (SD)	Range	n	Mean (SD)	Range
Serum estradiol (pmol/L)						
Baseline	38	65.1 (35.5)	18.4 to 165.2	34	68.3 (32.8)	36.7 to 146.8
Month 3	38	54.0 (29.3)	36.7 to 161.5	34	64.4 (33.8)	36.7 to 139.5
Change from baseline to Month 3	37	-9.7 (24.4)	-62.5 to 33.0	33	-4.3 (30.4)	-102.7 to 51.4
Percent change from baseline to Month 3 (%)	37	-6.5 (35.7)	-63.0 to 99.5	33	0.9 (42.1)	-70.0 to 140.1
Month 6/Final visit	37	48.0 (21.0)	18.4 to 102.8	29	57.7 (21.8)	36.7 to 102.8
Change from baseline to Month 6/ Final visit	36	-18.4 (29.1)	-77.1 to 36.7	28	-11.3 (28.6)	-55.0 to 40.4
Percent change from baseline to Month 6/ Final visit (%)	36	-15.4 (40.0)	-70.5 to 100.0	28	-4.5 (41.4)	-56.5 to 100.0
Testosterone (nmol/L)						
Baseline	38	9.2 (7.3)	1.0 to 32.1	34	9.3 (6.2)	0.5 to 30.7
Month 3	37	15.6 (7.1)	0.7 to 28.5	34	9.7 (5.9)	0.8 to 24.8
Change from baseline to Month 3	36	6.2 (5.3)	-5.8 to 15.7	33	0.3 (5.5)	-12.2 to 14.3
Percent change from baseline to Month 3 (%)	36	169.2 (226.4)	-85.8 to 819.8	33	23.2 (86.0)	-64.5 to 365.0
Month 6/Final visit	39	13.9 (7.1)	3.4 to 28.6	34	10.1 (5.9)	1.6 to 27.1
Change from baseline to Month 6/ Final visit	38	4.9 (5.9)	-12.5 to 18.5	33	0.8 (3.8)	-5.5 to 10.4
Percent change from baseline to Month 6/ Final visit (%)	38	153.2 (204.4)	-69.2 to 830.7	33	52.9 (129.9)	-47.3 to 537.5

The changes in serum FSH and LH levels are presented in a continuation of applicant's Table 16 (below). The mean FSH levels increased by 61.3 % at Month 3 and 50.9 % at Month 6 in the anastrozole group. In contrast, the changes in the placebo group were small (0.3 % at Month 3 and 3.3 % at Month 6, respectively). The mean percent LH changes were two-fold higher in the placebo group at both Month 3 and Month 6, when compared to the anastrozole group.

Follicle-stimulating hormone (FSH) (IU/L)						
Baseline	38	3.16 (1.89)	0.66 to 9.52	35	3.29 (1.50)	0.95 to 7.26
Month 3	38	4.72 (2.57)	1.14 to 11.55	34	3.22 (1.50)	0.86 to 7.21
Change from baseline to Month 3	37	1.35 (2.15)	-8.30 to 5.41	34	-0.06 (0.65)	-2.47 to 1.39
Percent change from baseline to Month 3 (%)	37	61.3 (61.9)	-87.2 to 221.8	34	0.3 (17.7)	-51.2 to 47.4
Month 6/Final visit	39	4.53 (2.88)	1.08 to 13.74	34	3.35 (1.49)	0.88 to 7.99
Change from baseline to Month 6/ Final visit	38	1.25 (1.80)	-3.01 to 6.67	34	-0.01 (0.84)	-2.91 to 1.33
Percent change from baseline to Month 6/ Final visit (%)	38	50.9 (68.4)	-57.9 to 296.9	34	3.3 (24.2)	-60.4 to 68.1
Luteinizing hormone (LH) (IU/L)						
Baseline	38	2.23 (1.51)	0.33 to 8.13	35	1.77 (1.23)	0.06 to 4.53
Month 3	38	2.74 (1.32)	0.60 to 6.18	34	2.36 (1.03)	0.91 to 4.40
Change from baseline to Month 3	37	0.46 (1.44)	-3.79 to 3.78	34	0.54 (1.13)	-2.40 to 3.10
Percent change from baseline to Month 3 (%)	37	70.0 (163.2)	-67.4 to 879.1	34	140.2 (466.1)	-53.0 to 2718.2
Month 6/Final visit	39	2.83 (1.49)	0.45 to 7.23	34	2.42 (1.33)	0.45 to 5.81
Change from baseline to Month 6/ Final visit	38	0.64 (1.49)	-3.16 to 4.30	34	0.62 (1.23)	-1.92 to 5.70
Percent change from baseline to Month 6/ Final visit (%)	38	82.7 (158.1)	-70.2 to 651.2	34	218.0 (885.7)	-57.8 to 5181.8

Changes in height and weight

Descriptively there were no differences in the mean change in height measurements between the two treatment groups as illustrated in applicant's Table 17 (2.4 cm in the anastrozole group and 2.7 cm in the placebo group). Similar results were observed for weight parameters. Specifically, the mean BMI-Z score remained relatively constant throughout the trial in the anastrozole group (1.43 at baseline, 1.47 at Month 3 and 1.48 at Month 6) and in the placebo group (1.41 at baseline, 1.45 at Month 3, and 1.41 at month 6).

Table 17 Change in height, weight, and BMI – ITT population

	Randomized treatment					
	Anastrozole 1 mg (N=39)			Placebo (N=35)		
	n	Mean (SD)	Range	n	Mean (SD)	Range
Height (cm)						
Baseline	39	167.6 (8.0)	149.0 to 183.0	35	171.2 (9.9)	150.0 to 191.2
Month 3	37	169.7 (7.0)	155.6 to 185.2	34	173.4 (9.0)	153.1 to 191.0
Month 6/Final visit	38	170.1 (7.4)	152.1 to 183.4	35	173.8 (9.4)	151.8 to 191.4
Change from baseline to Month 6/ Final visit	38	2.4 (2.1)	-0.2 to 8.7	35	2.7 (1.6)	-0.4 to 5.9

6.1.4.2.2 Study D5394C00001

Demographics and baseline characteristics

The main baseline characteristics and demographics are summarized in Table 5. The patients' mean age was 13 years (range 10 to 17 years). Most patients enrolled were Caucasian (65.5%); 23% were Native-Americans, 18.4% were African-American, 13.2% were Hispanic, and 2.6% were Asian. The mean duration of gynecomastia was 7 months (and less than 12 months in all patients). At study entry, 13.2% of patients reported breast pain. The mean breast volume (both breasts combined) by ultrasound was 224.8 ml ± 174.1 (range 15.7 to 781 ml).

Table 5: Baseline demographics and characteristics

Age (years)	
Mean (SD)	13 (1.8)
Range	10 to 17
Height (z-score)	
Mean (SD)	0.7 (1.3)
Range	-2.8 to 3.4
Weight (z-score)	
Mean (SD)	2.0 (0.9)
Range	-0.7 to 3.6
BMI (z-score)	
Mean (SD)	1.8 (0.7)
Range	-0.2 to 2.9
Duration of gynecomastia (months)	
Mean (SD)	7 (2.5)
Range	3 to 11
Breast volume (ml) - ultrasound	
Mean (SD)	224.8 (174.1)
Range	15.7 to 781
Breast size (ml) - caliper	
Mean (SD)	2522.5 (2159.6)

Range	172 to 8295.8

Source: Tables 12 and 13 of study report.

Efficacy results

For a summary of the primary endpoint analyses (all pharmacokinetic) refer to section 5.1. All other efficacy assessments are summarized next.

Applicant's Table 16 summarizes the number and percentage of patients who had ≥50% reduction in ultrasound-measured breast volume at Month 6 for the ITT and the per-protocol populations. A little over half of patients showed improvement during the trial. In the absence of a control group and taking into consideration that spontaneous reduction in breast size occurs in a significant number of patients with pubertal gynecomastia, it is difficult to make definitive statements of efficacy. There were no patients who experienced a 100% reduction in total breast volume.

Table 16 Patients with a ≥50% reduction in total breast volume, measured by ultrasound

Analysis population (N)	Number (%) of patients with response[a]	95% CI
Intention-to-treat (36)	20 (55.6)	38.1 to 72.1
Per-protocol (25)	15 (60.0)	38.7 to 78.9

a Response defined as ≥50% reduction in total breast volume.
CI Confidence interval.
All patients received anastrozole.
Data derived from Tables 11.2.3.1.1.1 and 11.2.3.1.1.2, Section 11.2.

The total change in breast volume (both breasts) at Month 6 is summarized for the ITT population in applicant's Table 18. The mean percent reduction in breast volume was 44.8 ± 66 % (range -99.3% to 264.8%). Similar results were obtained for the per protocol population (51.5% mean percent reduction).

Table 18 Change in total breast volume by ultrasound (ITT population)

	Anastrozole 1 mg (N=36)
Baseline (Visit 1)	
n	36
Mean (standard deviation)	226.1 (178.8)
Range	15.7 to 781.0
Month 6 (Visit 8)	
n	32
Mean (standard deviation)	97.2 (117.4)
Range	1.5 to 560.3
Change from baseline to Month 6	
n	32
Mean (standard deviation)	-126.6 (132.5)
Range	-416.4 to 103.1
Percent change from baseline to Month 6	
n	32
Mean (standard deviation)	-44.8 (66.4)
Range	-99.3 to 264.8

Data derived from Table 11.2.3.2.1, Section 11.2.

Five patients in the ITT population reported breast pain at baseline; four of them completed the 6-Month study and none had pain at their final visit. As breast pain may improve spontaneously, in absence of a control group, this cannot be seen as demonstration of efficacy.

Changes in Tanner staging

Changes in Tanner stage are summarized in applicant's Table 37. At Month 6 testicular and scrotum Tanner stage advanced on average by approximately one stage (0.8; range -1 to 3). The advance in pubic hair staging was slightly less (0.6 on average).

Table 37 Change in Tanner Stage (Safety population)

Tanner Stage criteria	Anastrozole 1 mg (N=38)			
	n	Mean (SD)	Median	Range
Testes and Scrotum				
Baseline	38	3.4 (1.24)	3	2 to 5
Month 6	32	4.2 (1.00)	4.5	2 to 5
Change from baseline to Month 6	32	0.8 (0.88)	1	-1 to 3
Pubic hair				
Baseline	38	3.4 (1.31)	4	1 to 5
Month 6	32	4.0 (1.05)	4	1 to 5
Change from baseline to Month 6	32	0.6 (0.80)	0	-1 to 3

SD Standard deviation.

Hormonal changes

On-treatment changes for serum testosterone, estradiol, LH, and FSH and are summarized in applicant's Table 25. After 6 months of treatment the mean serum estradiol concentrations decreased by approximately 13%, while mean testosterone levels increased by 285%. FSH and LH concentrations also increased.

Table 25 Hormone levels and change from baseline (PD population)

		Anastrozole 1 mg (N=25)		
	n	Mean (SD)	95% CI	Range
Testosterone (nmol/L)				
Baseline	25	5.55 (5.14)	3.43, 7.67	0.76 to 16.02
Month 6	25	13.29 (7.40)	10.24, 16.35	1.38 to 24.70
Change from baseline to Month 6	25	7.74 (4.92)	5.71, 9.77	-0.45 to 17.27
Percent change, baseline to Month 6	25	285.90 (251.74)	181.99, 389.82	-4.00 to 847.40
Estradiol (sensitive assay) (pmol/L)				
Baseline	24	16.81 (15.39)	10.31, 23.31	9.18 to 72.30
Month 6	24	11.17 (4.25)	9.37, 12.96	9.18 to 23.86
Change from baseline to Month 6	23	-5.89 (14.30)	-12.07, 0.30	-63.12 to 5.87
Percent change, baseline to Month 6	23	-13.17 (29.47)	-25.91, -0.43	-87.30 to 48.50
Testosterone/estradiol ratio				
Baseline	24	377.79 (323.82)	241.05, 514.53	50.20 to 1266.90
Month 6	24	1227.84 (720.94)	923.41, 1532.27	150.30 to 2690.60
Change from baseline to Month 6	23	932.43 (599.59)	673.15, 1191.71	-329.20 to 1881.20
Percent change, baseline to Month 6	23	465.69 (644.50)	186.99, 744.39	-35.30 to 3241.80
FSH (IU/L)				
Baseline	25	1.98 (1.09)	1.53, 2.43	0.60 to 4.50
Month 6	25	3.85 (2.04)	3.01, 4.69	1.40 to 10.50
Change from baseline to Month 6	25	1.87 (1.65)	1.19, 2.55	-0.40 to 7.10
Percent change, baseline to Month 6	25	125.80 (114.24)	78.65, 172.96	-12.50 to 400.00
LH (IU/L)				
Baseline	25	1.55 (1.42)	0.96, 2.14	0.10 to 4.50
Month 6	25	3.56 (2.06)	2.71, 4.41	0.70 to 7.80
Change from baseline to Month 6	25	2.01 (1.61)	1.34, 2.67	-0.90 to 5.70
Percent change, baseline to Month 6	25	536.63 (890.40)	169.09, 904.17	-28.10 to 4000.00
SHBG (nmol/L)				
Baseline	25	21.64 (7.31)	18.62, 24.66	5.00 to 34.00
Month 6	25	18.08 (7.29)	15.07, 21.09	7.00 to 34.00
Change from baseline to Month 6	25	-3.56 (6.67)	-6.31, -0.81	-15.00 to 18.00
Percent change, baseline to Month 6	25	-11.87 (34.65)	-26.18, 2.43	-60.00 to 112.50

CI Confidence interval; FSH Follicle-stimulating hormone; LH Luteinizing hormone; SD Standard deviation; SHBG Sex-hormone binding globulin.

6.1.5 Clinical Microbiology

Not applicable.

6.1.6 Efficacy Conclusions

6.1.6.1 **McCune-Albright syndrome indication**

(b) (4) [redacted]

(b) (4)

6.1.6.2 **Pubertal gynecomastia indication**

(b) (4)

7 INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

7.1.1 Deaths

7.1.1.1 **McCune-Albright syndrome indication**

No deaths were reported in this study.

7.1.1.2 **Pubertal gynecomastia indication**

7.1.1.2 Study 1033US/0006

There were no deaths reported in this study.

7.1.1.2 Study D5394C00001

There were no deaths reported in this study.

7.1.2 Other Serious Adverse Events

7.1.2.1 **McCune-Albright syndrome indication**

Three patients (10.7%) experienced four serious adverse events, summarized in applicant's Table 33. Two patients experienced femoral fractures (one patient had two such events) and one had a right ovarian cyst. None of these SAEs was judged related to the study treatment[39].

Table 33 Listing of all patients who had a serious adverse event (SAE) other than death: all patients exposed to study treatment

Patient	Time to event (days)*	Start date	Stop date	Serious adverse event (preferred term)	Serious adverse event (investigator text)	Severity	Study treatment related	Outcome
E0004003	-11	(b) (6)	04 May 2003	Femur fracture	Fracture of femur bone left femur	Severe	No	Resolved
	108		16 Jul 2003	Femur fracture	Fracture right femur	Severe	No	Resolved
E0007002	312		15 Mar 2004	Femoral neck fracture	Basi cervical left femoral fracture	Severe	No	Resolved
E0011001	74		10 Jul 2003	Ovarian cyst	Right ovarian cyst	Moderate	No	Resolved

* Number of days from start of study medication to start date of adverse event.

7.1.2.2 **Pubertal gynecomastia indication**

7.1.2.2.1 Study 1033US/0006

There were no SAEs reported in this study.

7.1.2.2.2 Study D5394C00001

There were two serious adverse events reported in this study: 1) bilateral slipped capital femoral epiphysis, which was diagnosed 4 months after the beginning of treatment in a 12-year-old obese patient (BMI of 36.3 and BMI Z-score of 2.56) and was judged by the investigator to be related to the study medication[40], and 2) a self-limited acute gastroenteritis in a 15-year old male.

7.1.3 Dropouts and Other Significant Adverse Events

7.1.3.1 Overall profile of dropouts

7.1.3.1.1 **McCune-Albright syndrome indication**

[39] Patient E0004003, a 4-year-old with a history of polyostotic fibrous bone dysplasia and corrective bone surgeries had a bone fracture following minor trauma eleven days prior to starting the study medication. Fifteen weeks after the start of anastrozole therapy the same patient had a second fall that resulted in a right femoral fracture that required surgical intervention. This same patient experienced later in the trial a tibial fracture that was not considered an SAE.
Patient E0007002, a 6 year old female with a history of Cushing's syndrome and fibrous dysplasia, experienced a left femoral neck fracture that required hospitalization.
Patient E0011001, a 7 year-old girl, was hospitalized for vaginal bleeding. She was found to have a 4 cm right ovarian cyst. She underwent a transabdominal puncture that showed "evolution of disease that was not controlled by study medication" (the patient continued the treatment).

[40] Slipped capital femoral epiphysis is a condition known to be associated with obesity in children.

No patients discontinued due to adverse events.

7.1.3.1.2 **Pubertal gynecomastia indication**

7.1.3.1.2.1 Study 1033US/0006

One patient in the anastrozole group discontinued the study due to an adverse event of enlarged testicular volume; this event was judged by the investigator as moderate in intensity and "possibly" related to anastrozole[41].

7.1.3.1.2.2 Study D5394C00001

Two patients discontinued the trial. One patient developed bilateral slipped capital femoral epiphysis (already described as an SAE). The other was an 11-year old male with a history of seasonal allergies and urticaria who withdrew informed consent 62 days within the trial.

7.1.3.2 Adverse events associated with dropouts

7.1.3.2.1 **McCune-Albright syndrome indication**

No patients withdrew due to an adverse event (one patient withdrew for to lack of efficacy).

7.1.3.2.2 **Pubertal gynecomastia indication**

7.1.3.2.2.1 Study 1033US/0006

Refer to Section 7.1.5.6.2.1 for an analysis of changes in testicular volume in the clinical trial.

7.1.3.2.2.2 Study D5394C00001

None of the adverse events that resulted in patient discontinuation in this clinical trial can be ascribed with a reasonable degree of certainty to the study drug.

7.1.3.3 Other significant adverse events

7.1.3.3.1 **McCune-Albright syndrome indication**

[41] Patient 0043/0001 was a 15.6-year-old male going through normal puberty who was noticed after 3 months of anastrozole therapy to have an increase in testicular volumes from 10 cc and 12 cc, respectively, to 20 cc bilaterally. There were no other associated abnormalities: the testicle felt normal to palpation, the increase in testosterone level was not considered clinically significant (the testosterone level was 246 ng/dL with a laboratory normal range of 194 to 833 ng/dL).and the bone age revealed, reportedly, a normal rate of skeletal maturation. The patient was unblinded and withdrawn at investigator's request. Reported initially as an SAE, this adverse event was subsequently downgraded to an AE after the rate of skeletal maturation was found to be normal.

No other significant adverse events were reported[42].

7.1.3.3.2 **Pubertal gynecomastia indication**

7.1.3.3.2.1 Study 1033US/0006

No other significant adverse events were reported.

7.1.3.3.2.2 Study D5394C00001

No other significant adverse events were reported.

7.1.4 Other Search Strategies

7.1.4.1 **McCune-Albright syndrome indication**

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

7.1.4.2 **Pubertal gynecomastia indication**

7.1.4.2.1 Study 1033US/0006

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

7.1.4.2.2 Study D5394C00001

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

7.1.5 Common Adverse Events

7.1.5.1 Eliciting adverse events data in the development program

7.1.5.1.1 **McCune-Albright syndrome indication**

Adverse events were assessed using standard clinical trial methodology at baseline, Month 3, Month 6, and Month 12.

7.1.5.1.2 **Pubertal gynecomastia indication**

[42] The applicant defined "other significant adverse events" as "adverse events of particular clinical importance, other than SAEs and those AEs leading to discontinuation of the patient from study treatment"; included in this category were "hematological and other laboratory abnormalities, and certain events that lead to intervention (other than those already classified as serious), dose reduction or significant additional treatment".

7.1.5.1.2.1 Study 1033US/0006

Adverse events were assessed using standard clinical trial methodology at baseline, Week 2, Months 2, 3, 4, 5, and 6.

7.1.5.1.2.2 Study D5394C00001

Adverse events were assessed using standard clinical trial methodology at baseline, Months 1, 2, 3, 4, 5, and 6.

7.1.5.2 Appropriateness of adverse event categorization and preferred terms

7.1.5.2.1 McCune-Albright syndrome indication

Visual inspection of Listing 12.2.7.1 titled "List of Adverse Events" finds appropriate correspondence of preferred and higher level terms in the MeDRA coding system.

7.1.5.2.2 Pubertal gynecomastia indication

Study 1033US/0006

Visual inspection of Listing G12.1 titled "List of Adverse Events" finds, in general, appropriate adverse event designation using COSTART.

Study D5394C00001

Visual inspection of Listing 12.2.7.1 titled "List of Adverse Events" finds appropriate MeDRA adverse event designation of adverse events.

7.1.5.3 Incidence of common adverse events

7.1.5.3.1 **McCune-Albright syndrome indication**

A total of 24 (85.7%) patients experienced at least one adverse event (Table 6). Adverse events that occurred with a frequency >10% (i.e. in ≥3 patients) were upper respiratory tract infection (21.4%), cough (17.9%), pharyngitis (14.3%), pyrexia (14.3%), arthralgia (10.7%), ear infection (10.7%), gastroenteritis (10.7%) and nasopharyngitis (10.7%). With the possible exception of arthralgia, all the above-listed AEs represent commonly encountered childhood illnesses and symptoms[43]. Two (7.1%) patients reported adverse events that were classified as severe in intensity: femoral neck fracture (in a patient who also had Cushing's syndrome) and 2 events of

[43] Arthralgia is a labeled adverse event for anastrozole in adults; in addition, due to the presence of fibrous dysplasia, McCune-Albright syndrome patients may have arthralgia as a manifestation of the underlying condition or its corrective surgeries.

femoral fracture (all were also listed as SAEs; refer to Section 7.1.2). All other adverse events reported were classified as mild or moderate in intensity. Of the adverse events that occurred in 2 patients (7.1%), with the exception of ovarian cyst (a relatively frequent occurrence in McCune-Albright syndrome) all were common childhood symptoms or conditions.

Table 6: Adverse events reported in two patients or more (≥ 7.1 %)

Adverse event (preferred term)	Number	%
Upper respiratory tract infection	6	21.4
Cough	5	17.9
Pyrexia	4	14.3
Pharyngitis	4	14.3
Arthralgia	3	10.7
Ear infection	3	10.7
Gastroenteritis	3	10.7
Nasopharyngitis	3	10.7
Ear pain	2	7.1
Diarrhoea	2	7.1
Vomiting	2	7.1
Bronchitis	2	7.1
Otitis media	2	7.1
Pharyngitis streptococcal	2	7.1
Tibia fracture	2	7.1
Ovarian cyst	2	7.1
Epistaxis	2	7.1

Source: Table 32

Five (17. 9 %) adverse events were considered by the investigator to be possibly due to study medication. They were nausea, acne, pain in extremity (all mild in intensity and resolved), allergic dermatitis (mild, continuing), increased ALT/AST (moderate in intensity, reportedly resolved).

7.1.5.3.2 **Pubertal gynecomastia indication**

7.1.5.3.2.1 Study 1033US/0006

As illustrated in applicant's Table 23, a slightly higher percentage of patients in the anastrozole group had treatment - emergent adverse events when compared to the placebo group (76.7% anastrozole vs. 64.9% placebo). Almost twice as many patients in the anastrozole group had adverse events that were judged by the investigators to be possibly treatment related (16.3% anastrozole vs. 8.1% placebo).

Table 23 **Number (%) of patients who had at least 1 adverse event in any category, and total numbers of adverse events (safety population)**

Category of adverse event	Number (%) of patients who had an adverse event in each category[a]			
	Anastrozole 1 mg (N=43)		Placebo (N=37)	
Any adverse events	33	(76.7)	24	(64.9)
Possibly treatment-related events	7	(16.3)	3	(8.1)
Serious adverse events	0		0	
Discontinuations of study treatment due to adverse events	1	(2.3)	0	
Discontinuations of study treatment due to possibly treatment-related events	1	(2.3)	0	
Other significant adverse events	0		0	
	Total number of adverse events[b]			
Any adverse events	77		63	

[a] Patients with multiple events in the same category are counted only once in that category. Patients with events in more than 1 category are counted once in each of those categories.
[b] Total number of adverse events by term. Events are counted by preferred term, ie, for patients with multiple events falling under the same preferred term, only 1 occurrence of the event is counted.

Table 7 summarizes the number and percentage of patients with adverse events that were higher in the anastrozole group relative to the placebo arm. The numerical differences between adverse events in the two treatment arms are mostly small. Adverse events that occurred with higher frequency in the anastrozole arm (by ≥ 2 patients difference) are flu syndrome, headache, syncope, and rash. The only adverse event that was judged severe in intensity in the anastrozole group was diarrhea (one patient or 2.3%); all other adverse events were mild or moderate in intensity.

Table 7: Treatment-emergent adverse events that occurred with higher frequency in the anastrozole group relative to placebo

Preferred term	Anastrozole 1 mg (N=43) N (%)	Placebo (N=37) N (%)
Abdominal pain	2 (4.7)	1 (2.7)
Accidental injury	4 (9.3)	3 (8.1)
Chest pain	1 (2.3)	0 (0)
Fever	2 (4.7)	1 (2.7)
Flu syndrome	3 (7)	0 (0)
Headache	11 (25.6)	8 (21.6)
Hormone level altered	1 (2.3)	0 (0)
Pain	3 (7)	2 (5.4)
Syncope	2 (4.7)	0 (0)
Varicose vein	1 (2.3)	0 (0)
Constipation	1 (2.3)	0 (0)
Diarrhea	2 (4.7)	1 (2.7)
Gastritis	1 (2.3)	0 (0)
Nausea	1 (2.3)	0 (0)

Echymosis	1 (2.3)	0 (0)
Weight gain	1 (2.3)	0 (0)
Depression	2 (4.7)	1 (2.7)
Insomnia	1 (2.3)	0 (0)
Speech disorder	1 (2.3)	0 (0)
Pneumonia	1 (2.3)	0 (0)
Rhinitis	6 (14)	5 (13.5)
Acne	5 (11.5)	4 (10.8)
Rash	4 (9.3)	0 (0)
Skin disorder	1 (2.3)	0 (0)
Conjunctivitis	1 (2.3)	0 (0)
Breast enlargement	1 (2.3)	0 (0)
Hematuria	1 (2.3)	0 (0)
Prostatic disorder*	1 (2.3)	0 (0)
Urogenital disorder**	1 (2.3)	0 (0)

Source: Table T12.2
*Prostatitis (patient 0035/0009).
** Enlarged testicular volume (patient 0043/0001)

Applicant's Table 26 lists the adverse events that were judged by the investigators to be treatment-related. Acne and headache were the most frequent ones (7% in the anastrozole group each vs. 2.7% and 0%, respectively in the placebo arm). Other "treatment-related" adverse events that were more frequent in the anastrozole group were diarrhea, hormone level altered, pharyngitis, speech disorder, urogenital disorder, and vomiting. It should be mentioned that with the exception of acne and headache all had very small numerical differences relative to placebo.

Table 26 **Number (%) of patients with treatment-related adverse events[a] as judged by the investigator, sorted by decreasing order of frequency as summarized over all treatment groups (safety population)**

Preferred term[b]	Anastrozole 1 mg (N=43)		Placebo (N=37)	
	n	(%)	n	(%)
Acne	3	(7.0)	1	(2.7)
Headache	3	(7.0)	0	
Diarrhea	1	(2.3)	0	
Hormone level altered	1	(2.3)	0	
Pharyngitis	1	(2.3)	0	
Speech disorder	1	(2.3)	0	
Urogenital disorder	1	(2.3)	0	
Vomiting	1	(2.3)	0	
Dry mouth	0		1	(2.7)
Hirsutism	0		1	(2.7)
Thirst	0		1	(2.7)

[a] Adverse events are included in this table if they started during study treatment or within 30 days of the last day of study treatment.
[b] Patients may appear more than once in the table (once per preferred term).

7.1.5.3.2.2 Study D5394C00001

A total of 30 (79.0%) patients experienced at least one adverse event. The most frequently reported adverse events (>10%) were acne (23.7%), acanthosis nigricans (15.8%), vomiting (13.2%) and nasopharyngitis (10.5%). One patient (2.6%) reported an AE that was classified as severe in intensity, slipped capital femoral epiphysys (this AE was also categorized as an SAE); all other adverse events were classified as mild or moderate in intensity. Adverse events reported in ≥ 2 (5.3%) patients are summarized in Table 8. Most adverse events are common childhood ilnesses/conditions. Others are adverse events seen in association with obesity (e.g. acanthosis nigricans, hypertension, possibly arthralgia); it is noteworthy that the mean BMI for the patients enrolled in this trial was near the upper limit of normal.

Table 8: Adverse events reported in two patients or more (≥ 5.3 %)

Adverse event (preferred term)	Number	%
Acne	9	23.7
Acanthosis nigricans	6	15.8
Vomiting	5	13.2
Nasopharyngitis	4	10.5
Arthralgia	3	7.9
Headache	3	7.9
Gastroenteritis viral	2	5.3
Sinusitis	2	5.3
Upper respiratory tract infection	2	5.3

Cough	2	5.3
Pharyngolaryngeal pain	2	5.3
Pyrexia	2	5.3
Hypertension	2	5.3

Source: Table 30 in Clinical Study Report

Eight patients (21.1%) experienced AEs that were considered by the investigator to be possibly due to study medication (applicant's Table 32). The most frequently reported treatment-related adverse event was acne (7 patients or 18.4%; all acne AEs were reported mild to moderate intensity). One patient (2.6%) reported as treatment-related AEs arthralgia and epiphysiolysis, of moderate and severe intensity, respectively.

Table 32 Treatment-related adverse events summarized by system organ class and preferred term, categorized by intensity (Safety population)

System organ class[a] / Preferred term	Total number (%) of patients with adverse event[b] Anastrozole 1 mg (N=38)			
	Total	Mild	Moderate	Severe
Skin and subcutaneous tissue disorders				
Acne	7 (18.4)	4 (10.5)	3 (7.9)	0
Musculoskeletal and connective tissue disorders				
Arthralgia[c]	1 (2.6)	0	1 (2.6)	0
Epiphysiolysis[c]	1 (2.6)	0	0	1 (2.6)

a Adverse events are ordered by MedDRA system organ class and then by preferred term in decreasing frequency.
b Adverse events are included if they started during study treatment or within 30 days of the last day of study treatment. A patient may have had more than 1 adverse event. If patients experienced the same event on more than 1 occasion, the most severe intensity is summarized.
c Both events were reported by Patient E0005003.

7.1.5.4 Common adverse event tables

7.1.5.4.1 **McCune-Albright syndrome indication**

Refer to Section 7.1.5.3.1

7.1.5.4.2 **Pubertal gynecomastia indication**

7.1.5.4.2.1 Study 1033US/0006

See Section 7.1.5.3.2.1.

7.1.5.4.2.2 Study D5394C00001

See Section 7.1.5.3.2.2.

7.1.5.5 Identifying common and drug-related adverse events

7.1.5.5.1 **McCune-Albright syndrome indication**

The vast majority of adverse events observed in this clinical trial are conditions commonly encountered in children. Others (e.g. ovarian cyst, fractures due to underlying fibrous dysplasia) represent known complications of McCune-Albright syndrome. The small size of the dataset and the absence of a control group make causality assignment difficult.

7.1.5.5.2 **Pubertal gynecomastia indication**

7.1.5.5.2.1 Study 1033US/0006

Most adverse events recorded in this clinical trial were due to childhood illnesses and symptoms. Of the AEs that occurred with higher frequency in the anastrozole group, acne and headache were the only adverse events that showed a somewhat distinct numerical difference relative to placebo. Acne is an anticipated adverse event due to the pharmacodynamic effect of anastrozole, which elevates testosterone serum concentration.

7.1.5.5.2.2 Study D5394C00001

In this clinical trial, acne was the only adverse event likely to be associated with the study medication. Most other adverse events were common childhood illnesses or manifestations of childhood obesity. The small size of the dataset and the absence of a control group make causality assignment difficult.

7.1.5.6 Additional analyses and explorations

7.1.5.6.1 **McCune-Albright syndrome indication**

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

7.1.5.6.2 **Pubertal gynecomastia indication**

7.1.5.6.2.1 Study 1033US/0006

Changes in the total testicular volume

The changes in the total testicular volume at Month 6 relative to baseline are presented in applicant's Table 28. At baseline, the mean testicular volume was similar in both treatment groups: 31.6 ±13.6 in the anastrozole group and 30.9 ±11.8 in the placebo group. The mean change from baseline was slightly higher in the anastrozole group (6.6 ±7.9) than in the placebo group (5.2 ±8.0). Similar percentages of patients (42% in the anastrozole group and 40% in the placebo group) had no changes in total testicular volume over the 6-month trial treatment period.

Two patients in each group had reductions in testicular volume (range -3 to -10). For the patients who had augmentation in testicular volume (21/43 or 49 % in the anastrozole group and 19/37 or 51 % in the placebo group) there was a slightly larger mean increase in volume for the anastrozole group (13 cc; range 6 cc to 26 cc) than in the placebo group (10.4 cc; range 2 cc to 30 cc).

Table 28 Total testicular volume and change from baseline (ITT population)

Total testicular volume (cc)		**Anastrozole 1 mg (N=39)**	**Placebo (N=35)**
Baseline	n	39	35
	Mean (SD)	31.6 (13.6)	30.9 (11.8)
	Range	2 to 60	8 to 58
Month 3	n	38	34
	Mean (SD)	34.9 (13.8)	33.9 (11.5)
	Range	6 to 60	8 to 60
Month 6/Final visit	n	38	35
	Mean (SD)	37.7 (10.9)	36.1 (11.6)
	Range	10 to 60	10 to 60
Change from baseline to Month 6/Final visit (cc)	n	38	35
	Mean (SD)	6.6 (7.9)	5.2 (8.0)
	Range	-3 to 26	-10 to 30

Data derived from Section 11.1, Table T11.1.

7.1.5.6.2.2 Study D5394C00001

Change in total testicular volume

The changes in testicular volume at Month 3 and Month 6 are summarized in applicant's Table 36. There was a mean increase of 21 % at Month 3 and 57 % at Month 6. The baseline-subtracted Month 6 mean increase of 9.4 mls is slightly higher than that observed in Study 1033US/0006 (6.6 mls) for a similar duration of anastrozole exposure and dose. As patients were progressing through puberty, changes in total testicular volume are to be expected. The absence of a control group limits the ability to assess whether these changes were excessive.

Table 36 Change in total testicular volume (Safety population)

	Anastrozole 1 mg (N=38)		
	n	Mean (SD)	Range
Total testicular volume (ml)			
Baseline	38	25.1 (14.8)	4.0 to 50.0
Month 3	33	29.8 (15.2)	8.0 to 50.0
Change from baseline to Month 3 (ml)	33	4.1 (7.3)	-10 to 30.0
Percent change from baseline (%)	33	21.2 (33.7)	-25.0 to 150.0
Month 6	32	34.8 (14.5)	6.0 to 50.0
Change from baseline to Month 6 (ml)	32	9.4 (8.8)	0 to 30.0
Percent change from baseline (%)	32	57.0 (57.7)	0 to 233.3

SD Standard deviation.

7.1.6 Less Common Adverse Events

7.1.6.1 **McCune-Albright syndrome indication**

Adverse events that occurred in only one patient (3.6%) were conjunctivitis, eye swelling, abdominal pain, abdominal pain upper, nausea, asthenia, drug hypersensitivity, acute tonsillitis, gastroenteritis viral, impetigo, pertussis, respiratory tract infection, rhinitis, scarlet fever, sinusitis, tonsillitis, urinary tract infection, varicella, femoral neck fracture, femur fracture, joint sprain, limb injury, alanine aminotransferase increased, aspartate aminotransferase increased, increased appetite, back pain, bone formation increased, bone pain, pain in extremity, headache, depressed mood, breast tenderness, hypertrophy breast, polymenorrhoea, pharyngolaryngeal pain, rhinorrhoea, tonsillar disorder, acne, dermatitis allergic, eczema, and urticaria.

7.1.6.2 **Pubertal gynecomastia indication**

7.1.6.2.1 Study 1033US/0006

Refer to section 7.1.5.3.2.1 for a comparison of adverse event incidence relative to placebo.

7.1.6.2.2 Study D5394C00001

Adverse events that occurred in only one patient (2.6%) were: in-growing nail, oily skin, post inflammatory pigment change, rash, urticaria, bronchitis, gastroenteritis, onychomycosis, otitis media acute, tonsilitis, diarrhea, stomach discomfort, toothache, epiphysiolysis, musculoskeletal pain, pain in extremity, rotator cuff syndrome, tendonitis, asthma, rhinitis allergic, tonsillar hypertrophy, wheezing, hyperphagia, increased appetite, polydipsia, migraine, nephrolithiasis, nocturia, polyuria, vision blurred, contusion, weight increased, hypersensitivity, and mood swings.

7.1.7 Laboratory Findings

7.1.7.1 Overview of laboratory testing in the development program

7.1.7.1 **McCune-Albright syndrome indication**

Laboratory assessments included primarily hormone measurements (estrogens, testosterone, LH, and FSH), which were evaluated as secondary efficacy endpoints (refer to the efficacy section). Clinical chemistries were limited to liver function testing (ALT and AST).

7.1.7.2 **Pubertal gynecomastia indication**

7.1.7.2.1 Study 1033US/0006

Clinical laboratory testing, which included CBC and SMA, was done only at baseline. Hormonal evaluations were conducted during the trial as secondary endpoints (refer to the efficacy section).

7.1.7.2.2 Study D5394C00001

Pre-treatment laboratory tests included CBC, thyroid function tests, and liver function tests (aspartate transaminase, alanine transaminase and alkaline phosphatase). Thyroid function tests were performed at the screening visit only and no follow-up measurements were collected. Hormone assessments included testosterone, estradiol, LH, and FSH and are presented in the efficacy section.

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

7.1.7.2.1 **McCune-Albright syndrome indication**

Study 1033IL/0046 was a single arm study and did not have a control group.

7.1.7.2.2 **Pubertal gynecomastia indication**

7.1.7.2.2.1 Study 1033US/0006

There were no on-trial clinical laboratory measurements (refer to Section 7.1.7.2.1).

7.1.7.2.2.2 Study D5394C00001

Study D5394C00001 was a single arm study and did not have a control group.

7.1.7.3 Standard analyses and explorations of laboratory data

7.1.7.3.1 Analyses focused on measures of central tendency

7.1.7.3.1.1 **McCune-Albright syndrome indication**

The mean values for liver function tests (ALT/AST) at baseline and Month 12 (final visit) are presented in applicant's Table 14. There were no clinically significant changes in mean values from baseline to endpoint.

Table 34 Liver function tests: all patients exposed to study treatment

		Anastrozole 1 mg (N=28)				
Parameter (units)		**N**	**Mean (SD)**		**Median**	**Range**
ALT (SGPT) (U/L)	Screening	28	23.32	(20.01)	18.00	10.00 to 94.00
	Month 12/ Final visit	27	22.07	(24.45)	15.00	7.00 to 131.00
AST (SGOT) (U/L)	Screening	28	31.11	(11.11)	29.00	18.00 to 71.00
	Month 12/ Final visit	27	29.48	(10.53)	26.00	21.00 to 73.00

ALT (SGPT) Alanine transaminase (serum glutamate pyruvate transaminase).
AST (SGOT) Aspartate transaminase (serum glutamic oxaloacetic transaminase).
N Number of patients.
SD Standard deviation.

7.1.7.3.1.2 **Pubertal gynecomastia indication**

7.1.7.3.1.2.1 Study 1033US/0006

There were no on-trial clinical laboratory measurements (refer to Section 7.1.7.2).

7.1.7.3.1.2.2 Study D5394C00001

Clinical laboratory evaluation

Changes in ALT, AST, and alkaline phosphatase are summarized in applicant's Table 35. The mean change from baseline to Month 6 was minimal for all three analytes.

Table 35 Liver function tests (Safety population)

Parameter (units)		n	Anastrozole 1 mg (N=38) Mean (SD)	Median	Range
ALT (IU/L)	Baseline	38	26.5 (14.4)	21.0	14.0 to 83.0
Reference range 5 to 45 IU/L	Month 6	31	25.0 (12.7)	22.0	9.0 to 66.0
	Change from baseline to Month 6	31	0.13 (7.7)	-1.0	-17.0 to 21.0
	% Change from baseline	31	3.61 (33.91)	-5.30	-43.80 to 100
AST (IU/L)	Baseline	38	27.1 (8.4)	25.5	15.0 to 65.0
Reference range 15 to 45 IU/L	Month 6	31	24.9 (7.0)	25.0	14.0 to 54.0
Extended: 20 to 60 IU/L	Change from baseline to Month 6	31	-0.9 (6.3)	-1.0	-10.0 to 23.0
	% Change from baseline	31	-2.00 (22.87)	-3.70	-33.30 to 74.20
Alkaline phosphatase (IU/L)	Baseline	38	266.8 (118.8)	246.5	83.0 to 641.0[a]
Reference range 45 to 145 IU/L	Month 6	31	259.9 (128.9)	240.0	74.0 to 693.0[a]
Extended: 110 to 510 IU/L	Change from baseline to Month 6	31	-11.9 (52.0)	-11.0	-132 to 108.0
	% Change from baseline	31	-4.04 (17.51)	-7.60	-31.40 to 43.90

ALT Alanine transaminase; AST Aspartate transaminase; SD Standard deviation.
a Alkaline phosphatase values were high in 1 patient (E0001033) at baseline (641.0 IU/L) and increased slightly at Month 6 (693.0 IU/L). Alkaline phosphatase levels are known to increase in times of rapid growth.

7.1.7.3.2 Analyses focused on outliers or shifts from normal to abnormal

7.1.7.3.2.1 **McCune-Albright syndrome indication**

One patient exhibited ALT and AST elevations above the normal range during the trial[44]. This patient had an elevated ALT level at screening (89 IU/L) which increased slightly at Month 12 (131 IU). The Month 12 measurement was > 2X ULN but < 3X UNL[45]. The AST values for the same patient were 57 IU/L at screening and 73 IU/L at Month 12[46]. No follow-up information is presented. The elevated ALT value at baseline suggests an on-going liver condition but no additional investigations are reported.

7.1.7.3.2.2 **Pubertal gynecomastia indication**

7.1.7.3.2.2.1 Study 1033US/0006

There were no on-trial clinical laboratory measurements (refer to Section 7.1.7.2).

7.1.7.3.2.2.2 Study D5394C00001

[44] Patient E0008002.
[45] ALT reference range: 5 to 45 IU/L.
[46] AST reference range: 20 to 60 IU/L.

Several individual ALT and AST evaluations were outside the normal range but none was considered clinically significant (i.e.≥ 3 ULN). Some of the observations were made at baseline only. There were only two ALT/AST elevations at Month 6 and both were minimal (one was accompanied by a similar elevation at baseline). They are summarized in applicant's table titled "List of Clinically Significant Abnormalities - ALT (SGPT) and AST (SGOT)", below.

Study 1033IL D5394C00001 Pubertal Boys with Gynecomastia of Recent Onset

LISTING 12.2.8.3 List of Clinically Significant Abnormalities - ALT (SGPT) and AST (SGOT)

(Patients Included: Safety Population)
TREATMENT RECEIVED=ANASTROZOLE (1 MG)

CENTER/ PATIENT	PP	VISIT	DATE OF SAMPLE	LAB TEST	RESULT#	CLIN. SIG. >=3 ULN
0001/E0001021	YES	DAY 181/FINAL	2006-07-11	ALANINE AMINOTRANSFERASE	57 H	NO
			2006-07-11	ASPARTATE AMINOTRANSFERASE	54 H	NO
0001/E0001022	NO	BASELINE	2006-01-17	ALANINE AMINOTRANSFERASE	83 H	NO
			2006-01-17	ASPARTATE AMINOTRANSFERASE	65 H	NO
0001/E0001024	YES	BASELINE	2006-01-16	ALANINE AMINOTRANSFERASE	67 H	NO
		DAY 181/FINAL	2006-07-25	ALANINE AMINOTRANSFERASE	66 H	NO
0001/E0001036	YES	DAY 181/FINAL	2006-09-26	ASPARTATE AMINOTRANSFERASE	14 L	NO

7.1.3.3.3 Marked outliers and dropouts for laboratory abnormalities

7.1.3.3.3.1 **McCune-Albright syndrome indication**

There were no marked outliers in AST/ALT values.

7.1.3.3.3.2 **Pubertal gynecomastia indication**

7.1.3.3.3.2.1 Study 1033US/0006

There were no on-trial clinical laboratory measurements (refer to Section 7.1.7.2).

7.1.3.3.3.2.2 Study D5394C00001

There were no marked outliers in AST/ALT values.

7.1.7.4 Additional analyses and explorations

7.1.7.4.1 **McCune-Albright syndrome indication**

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

7.1.7.4.2 **Pubertal gynecomastia indication**

7.1.7.4.2.1 Study 1033US/0006

There were no on-trial clinical laboratory measurements (refer to Section 7.1.7.2).

7.1.7.4.2.2 Study D5394C00001

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

7.1.7.5 Special assessments

7.1.7.5.1 **McCune-Albright syndrome indication**

No specials assessments were collected.

7.1.7.5.2 **Pubertal gynecomastia indication**

7.1.7.5.2.1 Study 1033US/0006

No specials assessments were collected.

7.1.7.5.2.2 Study D5394C00001

No specials assessments were collected.

7.1.8 Vital Signs

7.1.8.1 Overview of vital signs testing in the development program

7.1.8.1.1 **McCune-Albright syndrome indication**

Vital signs data were not collected systematically and routinely in this study.

7.1.8.1.2 **Pubertal gynecomastia indication**

7.1.8.1.2.1 Study 1033US/0006

Vital signs data were not collected systematically and routinely in this study.

7.1.8.1.2.2 Study D5394C00001

Vital signs data were not collected systematically and routinely in this study.

7.1.8.2 Selection of studies and analyses for overall drug-control comparisons

7.1.8.2.1 **McCune-Albright syndrome indication**

Study1033IL/0046 was a single arm study and did not have a control group.

7.1.8.2.2 **Pubertal gynecomastia indication**

7.1.8.2.2.1 Study 1033US/0006

Refer to Section 7.1.8.1.2.

7.1.8.2.2.2 Study D5394C00001

Study D5394C00001 was a single arm study and did not have a control group.

7.1.8.3 Standard analyses and explorations of vital signs data

7.1.8.3.1 **McCune-Albright syndrome indication**

Refer to Section 7.1.8.1.1.

7.1.8.3.2 **Pubertal gynecomastia indication**

7.1.8.3.2.1 Study 1033US/0006

Refer to Section 7.1.8.1.2.1.

7.1.8.3.2.2 Study D5394C00001

Refer to Section 7.1.8.1.2.2.

7.1.8.3.1 Analyses focused on measures of central tendencies

7.1.8.3.1.1 **McCune-Albright syndrome indication**

Refer to Section 7.1.8.1.1.

7.1.8.3.1.2 **Pubertal gynecomastia indication**

7.1.8.3.1.2.1 Study 1033US/0006

Refer to Section 7.1.8.1.2.1.

7.1.8.3.1.2.2 Study D5394C00001

Refer to Section 7.1.8.1.2.2.

7.1.8.3.2 Analyses focused on outliers or shifts from normal to abnormal

7.1.8.3.2.1 **McCune-Albright syndrome indication**

Refer to Section 7.1.8.1.1.

7.1.8.3.2.2 **Pubertal gynecomastia indication**

7.1.8.3.2.2.1 Study 1033US/0006

Refer to Section 7.1.8.1.2.1.

7.1.8.3.2.2.2 Study D5394C00001

Refer to Section 7.1.8.1.2.2.

7.1.8.3.3 Marked outliers and dropouts for vital sign abnormalities

7.1.8.3.3.1 **McCune-Albright syndrome indication**

Refer to Section 7.1.8.1.1.

7.1.8.3.3.2 **Pubertal gynecomastia indication**

7.1.8.3.3.2.1 Study 1033US/0006

Refer to Section 7.1.8.1.2.1.

7.1.8.3.2.2 Study D5394C00001

Refer to Section 7.1.8.1.2.2.

7.1.8.4 Additional analyses and explorations

7.1.8.4.1 **McCune-Albright syndrome indication**

Refer to Section 7.1.8.1.1.

7.1.8.4.2 **Pubertal gynecomastia indication**

7.1.8.4.2.1 Study 1033US/0006

Refer to Section 7.1.8.1.2.1.

7.1.8.4.2.2 Study D5394C00001

Refer to Section 7.1.8.1.2.2.

7.1.9 Electrocardiograms (ECGs)

7.1.9.1 Overview of ECG testing in the development program, including brief review of preclinical results

7.1.9.1.1 **McCune-Albright syndrome indication**

ECG data were not collected systematically and routinely in this study.

7.1.9.1.2 **Pubertal gynecomastia indication**

7.1.9.1.2.1 Study 1033US/0006

ECG data were not collected systematically and routinely in this study.

7.1.9.1.2.2 Study D5394C00001

ECG data were not collected systematically and routinely in this study.

7.1.9.2 Selection of studies and analyses for overall drug-control comparisons

7.1.9.2.1 **McCune-Albright syndrome indication**

Refer to Section 7.1.9.1.1.

7.1.9.2.2 **Pubertal gynecomastia indication**

7.1.9.2.2.2 Study 1033US/0006

Refer to Section 7.1.9.1.2.1.

7.1.9.2.2.2 Study D5394C00001

Refer to Section 7.1.9.1.2.2.

7.1.9.3 Standard analyses and explorations of ECG data

7.1.9.3.1 Analyses focused on measures of central tendency

7.1.9.1.1 **McCune-Albright syndrome indication**

Refer to Section 7.1.9.1.1.

7.1.9.1.2 **Pubertal gynecomastia indication**

7.1.9.1.2.1 Study 1033US/0006

Refer to Section 7.1.9.1.2.1.

7.1.9.1.2.1 Study D5394C00001

Refer to Section 7.1.9.1.2.2.

7.1.9.3.2 Analyses focused on outliers or shifts from normal to abnormal

7.1.9.3.2.1 **McCune-Albright syndrome indication**

Refer to Section 7.1.9.1.1.

7.1.9.3.2.1 **Pubertal gynecomastia indication**

7.1.9.3.2.1. 1 Study 1033US/0006

Refer to Section 7.1.9.1.2.1.

7.1.9.3.2.1.2 Study D5394C00001

Refer to Section 7.1.9.1.2.2.

7.1.9.3.3 Marked outliers and dropouts for ECG abnormalities

7.1.9.3.3.1 **McCune-Albright syndrome indication**

Refer to Section 7.1.9.1.1.

7.1.9.3.3.2 **Pubertal gynecomastia indication**

7.1.9.3.3.2.1 Study 1033US/0006

Refer to Section 7.1.9.1.2.1.

7.1.9.3.3.2.2 Study D5394C00001

Refer to Section 7.1.9.1.2.2.

7.1.9.4 Additional analyses and explorations

7.1.9.4.1 **McCune-Albright syndrome indication**

Refer to Section 7.1.9.1.1.

7.1.9.4.2 **Pubertal gynecomastia indication**

7.1.9.4.2.1 Study 1033US/0006

Refer to Section 7.1.9.1.2.1.

7.1.9.4.2.2 Study D5394C00001

Refer to Section 7.1.9.1.2.2.

7.1.10 Immunogenicity

Not applicable (anastrozole is not a therapeutic protein).

7.1.11 Human Carcinogenicity

Refer to the Arimidex label. No additional carcinogenicity studies were conducted for this supplement.

7.1.12 Special Safety Studies

No special safety studies were conducted.

7.1.13 Withdrawal Phenomena and/or Abuse Potential

To date, there are no data to suggest withdrawal phenomena and abuse potential for anastrozole.

7.1.14 Human Reproduction and Pregnancy Data

Refer to the Arimidex label. No additional reproduction and pregnancy data were submitted with this supplement.

7.1.15 Assessment of Effect on Growth

7.1.15.1 **McCune-Albright syndrome indication**

The effects of anastrozole on growth were a secondary efficacy endpoint. Refer to section 6.1.4.1 for details.

7.1.15.2 **Pubertal gynecomastia indication**

7.1.15.2.1 Study 1033US/0006

The effects of anastrozole on growth (linear growth and weight) were evaluated as secondary efficacy analyses. Refer to section 6.1.4.2.1 for details. There were no adverse effects on growth after 6 months of treatment.

7.1.15.2.2 Study D5394C00001

The effects of anastrozole on growth (linear growth and weight) were evaluated as secondary efficacy analyses. There were no changes in height Z score and weight Z-score at Month 6[47].

7.1.16 Overdose Experience

There were no adverse events of accidental overdose reported any of the three clinical studies.

7.1.17 Postmarketing Experience

Currently, anastrozole is not approved for any pediatric indication.

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

7.2.1.1.1 **McCune-Albright syndrome indication**

[47] The height Z-score was 0.9 ± 1.1 at baseline and 0.9 ± 1.2 at Month 6. The weight Z-score was 2.0 ± 0.8 at baseline and 2.0 ± 0.9 at Month 6. The BMI Z-score changed minimally (1.9 ± 0.7 at baseline and 1.7 ± 0.8 at Month 6).

Refer to Section 6.1.3.1.

7.2.1.1.2 **Pubertal gynecomastia indication**

7.2.1.1.2.1 Study 1033US/0006

Refer to Section 6.1.3.2.1.

7.2.1.1.2.2 Study D5394C00001

Refer to Section 6.1.3.2.2.

7.2.1.2 Demographics

7.2.1.2.1 **McCune-Albright syndrome indication**

Refer to Section 6.1.3.1.

7.2.1.2.2 **Pubertal gynecomastia indication**

7.2.1.2.2.1 Study 1033US/0006

Refer to Section 6.1.3.2.1.

7.2.1.2.2.2 Study D5394C00001

Refer to Section 6.1.3.2.2.

7.2.1.3 Extent of exposure (dose/duration)

7.1.1.3.1 **McCune-Albright syndrome indication**

The mean ± SD duration of exposure to anastrozole in this study was 362.43 ± 55.13 days (median: 371 days; range 88 to 388 days); the total patient exposure was over 27 patient-years. Seventeen (61%) of the patients enrolled continued in a study extension period (currently 12 patients are still enrolled in this extension study).

7.1.1.3.2 **Pubertal gynecomastia indication**

7.1.1.3.2.1 Study 1033US/0006

The mean exposure to the study drug for the 43 patients in the anastrozole group was 182 days (range: 13 to 233 days). This is equivalent to approximately 20 patient-years[48].

7.1.1.3.2.2 Study D5394C00001

The mean duration of anastrozole treatment for the 38 patients enrolled in this study was 166 ± 47.1 days (range 17 to 230 days). This amounts to approximately 19 patient-years.

7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

No secondary data sources were used in this review.

7.2.2.1 Other studies

No other studies were submitted and reviewed in this NDA supplement.

7.2.2.2 Postmarketing experience

Anastrozole is not approved for treatment in children.

7.2.2.3 Literature

Published anastrozole data in children is limited to one clinical trial, which is study 1033US/0006[49]. References to other pediatric information, where applicable, are made in the body of the review.

7.2.3 Adequacy of Overall Clinical Experience

Not applicable (b) (4) [redacted]

7.2.4 Adequacy of Special Animal and/or In Vitro Testing

See Arimidex label and refer also to section 7.2.3.

7.2.5 Adequacy of Routine Clinical Testing

The routine clinical testing was adequate. The clinical laboratory assessments were limited mostly to liver enzyme measurements and hormonal assessments. Vital signs and ECGs were not evaluated systematically.

[48] 39 patients completed the 6 month study.
[49] Plourde PV et al. Safety and efficacy of anastrozole for the treatment of pubertal gynecomastia: a randomized, double-blind, placebo-controlled trial. J Clin Endocrinol Metab. 2004 Sep;89(9):4428-33.

7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup

See Arimidex label and refer also to section 7.2.3.

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

Refer also to section 7.2.3.

7.2.8 Assessment of Quality and Completeness of Data

The quality of the data was adequate.

7.2.9 Additional Submissions, Including Safety Update

The requirement for a safety update was waived in the pre-NDA meeting (all studies were completed).

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

There were very few adverse events that could be assigned with a reasonable degree of certainty to the study drug. The most likely one is acne, which was seen with some consistency across the gynecomastia clinical trials and is an anticipated adverse event in the light of the fact that anastrozole increases testosterone serum concentrations. Other adverse events that were judged drug-related were headache (seen in excess in the anastrozole group relative to the placebo group in Study 1033US/0006) and arthralgia (encountered in both uncontrolled studies but not seen in excess in the anastrozole arm in the placebo-controlled study). Slipped capital femoral epiphysis, an SAE considered drug-related by the investigator, was seen only in an uncontrolled setting in a patient with obesity (a risk factor for this condition); therefore, assignment of this adverse event to anastrozole is doubtful. Some degree of testicular enlargement appears to be associated with anastrozole when compared to placebo (this may be due to FSH elevations, which were seen in association with anastrozole use during the gynecomastia clinical trials). The absence of control groups in two of the three clinical studies and the small size of the datasets limit the ability to draw additional conclusions.

7.4 General Methodology

7.4.1 Pooling Data Across Studies to Estimate and Compare Incidence

7.4.1.1 **McCune-Albright syndrome indication**

Not applicable (there was a single McCune-Albright study).

7.4.1.2 **Pubertal gynecomastia indication**

At the request of the Division, the applicant has provided an analysis of common adverse events in the combined datasets of the two pubertal gynecomastia studies. The applicant has pooled AE data from Study 1033US/0006 (Study 1), Study D5394C0001 (Study 3), and added data from an extension phase of Study 1033US/0006 ("Study 0016"). It should be mentioned that different coding dictionaries were used in these studies[50] and adverse events were re-coded in MedDRA, where applicable. Across all three studies, 71 (78%) patients had adverse events in the anastrozole group and fewer (32 patients or 61.5%) in the placebo group. As noted in the analysis of individual studies, most adverse events reported are common pediatric conditions or symptoms. Applicant's Table 7 summarizes the most common adverse events (i.e. ≥ 5%) across all gynecomastia studies. The adverse events that occurred more frequently in the anastrozole group relative to placebo were vomiting, pyrexia, arthralgia, and acne. Of these, acne is to be expected since anastrozole tends to increase testosterone levels; arthralgia (a labeled adverse event in adults) was also observed in Study 2 conducted in girls with McCune-Albright syndrome but was not seen in excess in the anastrozole arm of the placebo-controlled gynecomastia study. Vomiting and pyrexia are a very common symptoms in pediatric patients and therefore drug causality is difficult to assign.

Table 7 Most commonly reported[a] adverse events in pubertal boys with gynecomastia in Studies 0006, 0016 and 0001: safety population

System organ class	MedDRA preferred term	Number (%) of patients[b] who had an adverse event	
		Anastrozole 1 mg (N=91)[c]	Placebo (N=52)[d]
Gastrointestinal disorders	Vomiting	7 (7.7)	2 (3.9)
General disorders and administration site conditions	Pyrexia	6 (6.6)	1 (1.9)
Infections and infestations	Nasopharyngitis	5 (5.5)	3 (5.8)
	Sinusitis	7 (7.7)	4 (7.7)
	Upper respiratory tract infection	10 (11.0)	9 (17.3)
Musculoskeletal and connective tissue disorders	Arthralgia	5 (5.5)	2 (3.9)
Nervous system disorders	Headache	15 (16.5)	12 (23.1)
Respiratory, thoracic and mediastinal disorders	Pharyngolaryngeal pain	5 (5.5)	3 (5.8)
	Sinus congestion	0	3 (5.8)
Skin and subcutaneous tissue disorders	Acne	14 (15.4)	5 (9.6)

[a] Defined as >5% for either treatment group.
[b] Patients may appear more than once in the table (once per preferred term).
[c] Ten patients who received placebo in Study 0006 received anastrozole in Study 0016. Data are presented according to actual treatment received in Study 0016.
[d] Fifteen patients who received anastrozole in Study 0006 received placebo in Study 0016. Data are presented according to actual treatment received in Study 0016.
MedDRA Medical dictionary for regulatory activities.
N Number of patients.

[50] COSTART in studies1033US/0006 and 0016 and MedDRA in study D5394C0001.

Treatment-related adverse events are summarized in applicant's Table 8. Fifteen (16.5%) patients who received anastrozole and 3 (5.8%) patients who received placebo, reported at least one AE that was considered by the investigator to be possibly due to study medication. Several adverse events occurred with higher frequency in the anastrozole group but the numerical differences were too small to be able to draw forceful conclusions. Acne was the only adverse event seen clearly in excess in the anastrozole group (11% relative to 1.9% in the placebo group); headache showed a similar pattern albeit less clearly.

Table 8 Treatment-related adverse events, as judged by the investigator, in pubertal boys with gynecomastia in Studies 0006, 0016 and 0001: safety population

System organ class	MedDRA preferred term	Number (%) of patients[a] who had a treatment-related adverse event	
		Anastrozole 1 mg (N=91)[b]	Placebo (N=52)[c]
Gastrointestinal disorders	Diarrhea	1 (1.1)	0
	Dry mouth	0	1 (1.9)
	Vomiting	1 (1.1)	0
General disorders and administration site conditions	Thirst	0	1 (1.9)
Infections and infestations	Upper respiratory tract infection	1 (1.1)	0
Investigations	Blood testosterone increased	1 (1.1)	0
Musculoskeletal and connective tissue disorders	Arthralgia	1 (1.1)	0
	Epiphysiolysis	1 (1.1)	0
Nervous system disorders	Headache	3 (3.3)	0
Reproductive system and breast disorders	Testicular swelling	1 (1.1)	0
Respiratory, thoracic and mediastinal disorders	Dysphonia	1 (1.1)	0
Skin and subcutaneous tissue disorders	Acne	10 (11.0)	1 (1.9)
	Hair growth abnormal	0	1 (1.9)

[a] Patients may appear more than once in the table (once per preferred term).
[b] Ten patients who received placebo in Study 0006 received anastrozole in Study 0016. Data are presented according to actual treatment received in Study 0016.
[c] Fifteen patients who received anastrozole in Study 0006 received placebo in Study 0016. Data are presented according to actual treatment received in Study 0016.
MedDRA Medical dictionary for regulatory activities.
N Number of patients.

7.4.1.1 Pooled data vs. individual study data

7.4.1.1.**1 McCune-Albright syndrome indication**

Not applicable.

7.4.1.1.1 **Pubertal gynecomastia indication**

The pooled data did not lead to different conclusions or observations.

7.4.1.2 Combining data

See Section 7.4.1.1.

7.4.2 Explorations for Predictive Factors

None conducted.

7.4.2.1 Explorations for dose dependency for adverse findings

Not applicable (only one dose was evaluated in the clinical program).

7.4.2.2 Explorations for time dependency for adverse findings

None conducted due to the small size of the datasets and the nature of adverse events encountered.

7.4.2.3 Explorations for drug-demographic interactions

None conducted.

7.4.2.4 Explorations for drug-disease interactions

None conducted.

7.4.2.5 Explorations for drug-drug interactions

None conducted.

7.4.3 Causality Determination

Refer to Section 7.3.

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

(b) (4)

[redacted]

8.2 Drug-Drug Interactions

No drug-drug interaction studies were conducted.

8.3 Special Populations

There were no studies conducted in patients with renal or liver failure.

8.4 Pediatrics

All clinical studies and analyses submitted in this supplement were conducted in pediatric patients. Under PREA a waiver should be issued for the gynecomastia indication in boys of prepubertal ages (0 to 11 years, inclusive). Similarly, a waiver should be granted for the McCune-Albright syndrome indication for ages <3 years (patients <3 years of age were not studied) and 11-18 years (patients > 10 years were not studied; in addition, once patients reach pubertal age treatment is no longer indicated).

8.5 Advisory Committee Meeting

There were no advisory committee meetings related to this application.

8.6 Literature Review

There is very limited published information regarding anastrozole use in pediatric patients. The only controlled clinical trial published to date is Study 1 of the Written Request[51].

8.7 Postmarketing Risk Management Plan

None.

[51]Plourde PV et al. Safety and efficacy of anastrozole for the treatment of pubertal gynecomastia: a randomized, double-blind, placebo-controlled trial. J Clin Endocrinol Metab. 2004 Sep;89(9):4428-33.

8.8 Other Relevant Materials

None.

9 OVERALL ASSESSMENT

9.1 Conclusions

(b) (4)

9.2 Recommendation on Regulatory Action

(b) (4)

9.3 Recommendation on Postmarketing Actions

9.3.1 Risk Management Activity

None.

9.3.2 Required Phase 4 Commitments

None.

9.3.3 Other Phase 4 Requests

None.

9.4 Labeling Review

Significant modifications to applicant's proposed labeling have been made (refer to Section 10.2. for specific, line-by-line labeling recommendations in track changes).

9.5 Comments to Applicant

See recommendation section. No additional comments.

10 APPENDICES

10.1 Review of Individual Study Reports

Individual studies were reviewed in the body of the clinical review.

10.2 Line-by-Line Labeling Review

(b) (4)

(b) (4)

(b) (4)

[redacted]

[redacted]

REFERENCES

References are included as footnotes in the clinical review.

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/s/

Dragos Roman
2/19/2008 02:28:25 PM
MEDICAL OFFICER

Mary Parks
2/20/2008 09:20:15 AM
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I concur with Dr. Roman that (b) (4) [redacted]