Drug product:	Arimidex	**SYNOPSIS**	
Drug substance(s):	Anastrozole		
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An Open-label Pharmacokinetic and Pharmacodynamic Study of Anastrozole (ARIMIDEX™) Used to Treat Pubertal Boys with Gynecomastia of Recent Onset

Study centre(s)

Patients were enrolled from 2 centers in the USA.

Publications

None at the time of writing this report.

Study dates		Phase of development
First patient enrolled	16 June 2005	Therapeutic exploratory (II)
Last patient completed	7 November 2006	

Objectives

The primary objective of this study was to assess anastrozole pharmacokinetics (PK) in boys (aged 11 to 18 years [after his 10th and prior to his 19th birthday]) with pubertal gynecomastia of less than 12 months duration.

The secondary objectives of the study were to evaluate response rate, hormonal changes, tolerability and safety.

Study design

This was a multicenter, single arm, open label PK study in which boys with pubertal gynecomastia of recent onset were given anastrozole 1 mg daily for 6 months (Month 6 = Day 181).

Target patient population and sample size

To enter this study, patients had to satisfy the following inclusion criteria and provide documented, informed consent of parent/legal guardian and patient assent to participate, according to local requirements:

> **Key inclusion criteria:** males aged 11 to 18 years (after his 10th and prior to his 19th birthday); gynecomastia, 1 breast measuring ≥2 cm in diameter (by ultrasound or caliper[1] measurement) that had not decreased during the prior 3-month period by clinical history and had been present for up to or less than 12 months; normal renal, liver, and thyroid function; no evidence of hormone-producing tumor; no evidence of hypogonadism or androgen resistance.
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> **Sample size:** the objective was to have 24 boys complete the study (ie, complete 6 months of study treatment). To allow for approximately 25% of patients failing the inclusion/exclusion criteria or failing to follow through the protocol and receiving 6 months of study treatment, it was planned to enroll (screen) approximately 30 to 35 boys. The planned sample size was thought to be sufficient to provide useful information on the primary objective of PK.

Investigational product and comparator(s): dosage, mode of administration and batch numbers

Anastrozole (ZD1033, ARIMIDEX™) 1 mg tablet, orally once daily. The formulation number was F11292 and batch numbers were 2000077658, 2000083628, 2000085466 and 2000088657.

Duration of treatment

Patients received a 1 mg daily dose of anastrozole for a treatment period of 6 months.

Criteria for evaluation (main variables)

Efficacy and pharmacokinetics

- Primary variable: maximum anastrozole plasma drug concentration ($C_{ss,max}$), minimum anastrozole plasma concentration ($C_{ss,min}$), time to reach the maximum anastrozole concentration (t_{max}), area under the curve at the steady-state (AUC_{ss}), apparent oral clearance (CL/F), and apparent volume of distribution during terminal phase (V_z/F). All primary variables were measured at steady state.

- Secondary variables: response rate, proportion of patients who had complete regression of gynecomastia within the study period, actual change and percent change in calculated volume of gynecomastia from Visit 1 to Visit 8 (Month 6; both

[1] The term "caliper" will be used throughout the synopsis to refer to measurements made by caliper or other method of manual measurement.

breasts combined), change in breast pain/tenderness in symptomatic patients, change in hormone concentration, and change in height.

Breast volume was determined by ultrasound measuring the transverse, sagittal and anteroposterior (AP) diameters of the glandular breast tissue deep beneath the subcutaneous fat to the anterior chest wall. A secondary estimate of breast size was calculated from the transverse, sagittal and AP (from mid axillary point to nipple) measurements by caliper.

Safety

- Incidence and intensity of adverse events (AEs) and serious adverse events (SAEs), study drug discontinuations, study drug exposure, laboratory assessments (including hormone level and liver function tests), physical examination (including change in testicular volume and Tanner Stage).

Statistical methods

The analysis population for the PK and pharmacodynamics (PD) endpoints included treated patients who had evaluable data, and did not have a major protocol violation or deviation as decided at data review prior to database lock.

The primary analysis population for the efficacy endpoints was the intention-to-treat (ITT) population, which included all treated patients with a baseline (Visits 1 and 2) value and at least 1 post baseline value. The secondary analysis population for the efficacy endpoints was the per-protocol (PP) population, which was a subset of the ITT population and included patients who did not have major protocol violations or deviation as decided at data review prior to database lock.

The safety population consisted of all patients who consumed as least 1 dose of the study drug.

The primary endpoints (all PK parameters) were summarized with descriptive statistics. In addition, the effect of baseline characteristics (age and weight) on CL/F and V_z/F respectively, were assessed using Analysis of Variance model, with log transformed CL/F and V_z/F as respective dependent variables. The results were reported as p-values for the covariates, and coefficient of determination, which describe the overall fit of the model.

All secondary endpoints including PD, efficacy and safety were summarized with descriptive statistics.

Patient population

In total, 42 patients were screened, and 42 patients were enrolled into this study from 2 centers in the USA. The first patient was enrolled in the study on 16 June 2005, and the last patient completed the study on 7 November 2006. Of the 42 patients who were screened, 2 failed to meet study entry criteria and were not dosed and 2 were not willing to continue in the study and withdrew prior to dosing; therefore 38 patients were dosed.

Table S1 summarizes the patient disposition, analysis sets, demographic and baseline characteristics for patients in the safety population.

Table S1 Summary of patient disposition, analysis sets, demographic and baseline characteristics

		Anastrozole 1 mg
Disposition		
Patients screened		42
Patients enrolled		42
Patients exposed to treatment		38
Analysis populations		
Safety population		38
Intention-to-treat population		36
Pharmacokinetic population		36
Pharmacodynamic population		25
Per-protocol population (for efficacy)		25
Demographic characteristics (Safety population)		
Age (years)[a]	Mean (SD)	13 (1.8)
	Median	13
	Range	10 to 17
Race, n (%):	Caucasian	25 (65.8)
	Black	9 (23.7)
	Other	4 (10.5)
Ethnicity, n (%):	Native-American	9 (23.7)
	African-American	7 (18.4)
	Hispanic	5 (13.2)
	African-Caribbean	2 (5.3)
	Asian	1 (2.6)
	Not applicable	9 (23.7)
	Other	5 (13.2)
Baseline characteristics (Safety population)		
Duration of gynecomastia (months)	Mean (SD)	7 (2.5)
	Range	3 to 11
Breast volume (ml) - ultrasound[b]	Mean (SD)	224.8 (174.1)
	Range	15.7 to 781
Height (cm)	Mean (SD)	162.9 (10.1)
Height (z-score)[c]	Mean (SD)	0.7 (1.3)
Weight (kg)	Mean (SD)	75.6 (18.8)
Weight (z-score)[c]	Mean (SD)	2.0 (0.9)
BMI (kg/m^2)	Mean (SD)	28.3 (5.9)
BMI (z-score)[c]	Mean (SD)	1.8 (0.7)

a Age at date of informed consent.
b Volume of both breasts combined.
c z-score is a dimensionless quantity derived by subtracting the population mean from an individual (raw) score and then dividing the difference by the population standard deviation.
BMI Body Mass Index; SD Standard deviation.

The study population was predominantly Caucasian and Black, 65.8% and 23.7%, respectively, with a mean (standard deviation [SD]) age of 13 (1.8) years (range 10 to 17). The mean (SD) duration of gynecomastia was 7 (2.5) months (range 3 to 11) and the mean (SD) breast volume (both breasts combined) by ultrasound was 224.8 (174.1) ml (range 15.7 to 781). Body mass index (BMI), mean (SD) for the population was 28.3 (5.9) kg/m^2 (range 17.8 to 46.6) with a corresponding mean (SD) z-score of 1.8 (0.7). The concomitant medication administered was representative of those commonly taken by pubertal patients. Compliance with study treatment was good with a mean (SD) percent compliance of 93.6% (8.4), (range 72 to 100%).

Efficacy, pharmacokinetic and pharmacodynamic results

Analysis of the PK and PD data indicate that:

- The disposition of anastrozole after multiple oral doses of 1 mg follows a multi-exponential decay, a rapid absorption (median t_{max} of 1 hour) and a rapid distribution phase followed by a slow elimination phase.

- The estimated systemic exposure as described by AUC_{ss} and $C_{ss,max}$ were 648 ng.hr/ml (37.0%) and 39.3 ng/ml (34.3%), respectively and $C_{ss,\,min}$ 21.5 ng/ml (44.1%); geometric mean and geometric coefficient of variation (CV) presented. Median $C_{ss,max}$ was 41.4 ng/ml (range 17.2 to 75.6).

- Elimination characteristics indicate that anastrozole was slowly cleared with an CL/F of 1.54 (CV 37.0%) L/h, and a terminal elimination half-life of 46.8 h. Further, anastrozole was extensively distributed with an V_z/F of 98.4 (CV 42.6%) L.

- There was no statistically significant evidence of effect of age and weight on anastrozole apparent oral clearance, and no effect of age on volume of distribution. However, there was evidence of effect of weight on apparent volume of distribution (p=0.0319).

- After 6 months of treatment with anastrozole the following change from baseline in PD effects (mean ± SD [95% confidence interval]) were noted:

  – plasma testosterone concentrations increased from 5.55 ± 5.14 (3.43, 7.67) to 13.29 ± 7.40 nmol/L (10.24, 16.35); percent change was 285.9%.

  – serum estradiol concentrations decreased from 16.81 ± 15.39 (10.31, 23.31) to 11.17 ± 4.25 pmol/L (9.37, 12.96); percent change was -13.2%.

  – the testosterone/estradiol ratio increased from 377.79 ± 323.82 (241.05, 514.53) to 1227.84 ± 720.94 (923.41, 1532.27); percent change was 465.7%.

- serum follicle stimulating hormone concentrations increased from 1.98 ± 1.09 (1.53, 2.43) to 3.85 ± 2.04 IU/L (3.01, 4.69); percent change was 125.8%.

- serum luteinizing hormone increased from 1.55 ± 1.42 (0.96, 2.14) to 3.56 ± 2.06 IU/L (2.71, 4.41); percent change was 536.6%.

- sex-hormone binding globulin concentrations decreased from 21.64 ± 7.31 (18.62, 24.66) to 18.08 ± 7.29 nmol/L (15.07, 21.09); percent change was -11.9%.

Analysis of the efficacy data indicate that:

- The response rate (number of patients with a ≥50% reduction in total breast volume following 6 months of treatment) in the ITT population was 55.6% (20/36) as measured by ultrasound.

- An exploratory analysis of number of patients with a ≥50% reduction in total breast area following 6 months of treatment (in the ITT population) was 36.1% (13/36) as measured by ultrasound.

- No patients experienced complete regression of gynecomastia as assessed by ultrasound (ITT population).

- In the ITT population, the mean (± SD) breast volume by ultrasound was reduced by 126.6 ± 132.5 ml (percent change: 44.8%).

- An exploratory analysis indicated the mean (± SD) reduction in breast area was 40.6 ± 40.41 cm^2 (percent change: 39.8%) by ultrasound.

- The response rate in breast size measured by caliper was 77.8% (28/36).

- An exploratory analysis indicated 26/36 patients (72.2%) had ≥50% reduction in total breast area following 6 months of treatment by caliper.

- Using caliper, 3/36 patients (8.3%) were observed to have complete regression (ITT population).

- The mean (± SD) change in breast size measured by caliper was 1729.8 ± 2509.1 ml (percent change: 36.4%) (ITT population).

- Mean (± SD) reduction in breast area by caliper was 121.4 ± 173.88 cm^2 (percent change: 46.5%).

- Out of 5 patients in the ITT population who had symptomatic breast pain at baseline, 4 (80%) were pain free after 6 months of treatment.

- During the 6-month study period, the mean height increased by 3.4 ± 2.0 cm with preservation in mean height z-score (+0.02 ± 0.18). Mean weight increased by 2.9 ± 6.17 kg with a negligible change in mean weight z-score (-0.05 ± 0.3). There was no clinically relevant change in either the mean BMI (0.03 ± 2.18 kg/m^2) or the mean BMI z-scores (-0.11 ± 0.29).

- The results based on the PP population were consistent with the results obtained from the ITT analysis population.

Safety results

Safety data indicate that:

- Mean exposure to anastrozole was 166 days and mean compliance with dosing was 93.6%.

- A total of 78 AEs were reported by 30 patients (79.0%) in the safety population. There were 8 patients (21.1%) with treatment-related AEs and 2 patients (5.3%) with SAEs. Two patients (5.3%) withdrew due to AEs, 1 of whom had a SAE as well as an AE that led to withdrawal. There were no deaths in this study.

- Most of the AEs were typical of a pediatric population or were manifestations of gynecomastia. The most frequently reported (>10%) AEs were acne (23.7%), acanthosis nigracans (including acanthosis) (15.8%), vomiting (13.2%) and nasopharyngitis (10.5%). All AEs were mild or moderate except the case of epiphysiolysis (slipped capital femoral epiphysis [SCFE]) which was of severe intensity.

- Seven of the AEs that were considered by the investigator to be treatment-related were acne. The other 2 treatment-related AEs of arthralgia and epiphysiolysis (SCFE) were reported by the same patient.

- There were 2 SAEs. The case of epiphysiolysis (SCFE) required surgery and, together with the AE arthralgia, led to withdrawal of the patient from the study. This patient had a BMI of 34.3 kg/m^2 at baseline and was considered obese. Epiphysiolysis is known to occur in obese adolescents. The other SAE was gastroenteritis that required extension of a planned hospital stay.

- Anastrozole was well tolerated and there were very few patient withdrawals following AEs (n=2). One patient was withdrawn due to epiphysiolysis (SCFE), that was also considered serious, and arthralgia. The other withdrawal was a result of urticaria, which was present at entry to the study, and allergic rhinitis and wheezing, that had been reported in the patient's significant history.

- Changes in Tanner Stage (genital and pubic hair) were consistent with normal rates of pubertal progression.

- No new safety signals or concerns were raised based upon the results of liver function tests or clinical laboratory tests collected as part of the study.