Drug product:	Arimidex	**SYNOPSIS**	
Drug substance(s):	Anastrozole		
Document No.:			
Edition No.:	Final		
Study code:	(D5394C00046)		
Date:	14 November 2006		

An Open-label Study Evaluating the Safety and Efficacy of Anastrozole (ARIMIDEX™) in the Treatment of Precocious Puberty in Girls with McCune-Albright Syndrome

Study center(s)

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).

Publications

None at the time of writing this report.

Study dates		**Phase of development**
First patient enrolled	23 October 2002	Therapeutic exploratory (II)
Last patient completed	6 February 2006	

Objectives

The primary objective of this study was to evaluate the safety and efficacy of anastrozole (daily 1 mg dose) for the treatment of McCune-Albright Syndrome (MAS) in girls up to the age of 10 years, receiving treatment for 1 year. The tolerability and safety of study treatment was assessed by assessment of adverse events, withdrawals and laboratory data. The efficacy of study treatment was assessed based on the change from baseline measurements relating to vaginal bleeding, bone age, and growth velocity.

Secondary objectives included assessments of pubertal progression through Tanner Staging and mean ovarian and uterine volume as assessed by ultrasound, bone growth by assessment of predicted adult height for children aged over 6 years and pharmacokinetic assessment.

The presence of a MAS associated gene coding for the stimulatory subunit of the G protein (Gsα) mutation was assessed by molecular analysis as a non-obligatory additional analysis. (This additional analysis is not linked to the study results and is outsourced to an independent party).

Study design

This was an international, multi-center, open-label, exploratory study to examine potential clinical efficacy, tolerability and safety of a 1 mg daily dose of anastrozole, given to girls with MAS, over a treatment period of 12 months.

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:

Key inclusion criteria: aged between 2 and 10 years; diagnosed with MAS; have progressive precocious puberty manifested by physical signs of pubertal development; satisfying specific criteria regarding previous treatment; if central precocious puberty exists, been on a gonadotrophin-releasing hormone (GnRH) analogue for at least 6 months.

Sample size: this exploratory study was designed to recruit approximately 30 patients in order to have a minimum of 20 patients completing 12 months of anastrozole. Since MAS is very rare, it was not possible to design a study based on formal statistical power calculations. However, with 20 patients and assuming the proportion of patients with a ≥50% reduction in the frequency of vaginal bleeding episodes over a 12-month study period was 0.67, an exploratory 95% confidence interval using the normal approximation was approximately 0.46 to 0.87. This assumed proportion was based on the results from a similar study conducted by AstraZeneca to investigate the use of tamoxifen in girls with MAS (Eugster et al 2003).

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

Anastrozole (ZD1033, ARIMIDEX™) 1 mg tablet, orally once-daily. The formulation numbers and batch numbers are shown in Table S1.

Table S1 Details of investigational product and any other study treatments

Investigational product or other treatment	Dosage form and strength	Manufacturer	Formulation number	Batch number
Anastrozole	1 mg oral tablet	AstraZeneca	F011292	12865H03, 22683I04, 82954C01, 82955K01, 90695F02, 93033A02, 93034I02, 93037K02

Table S1 Details of investigational product and any other study treatments

Investigational product or other treatment	Dosage form and strength	Manufacturer	Formulation number	Batch number
			MP001624	2000037400, 2000047082, 2000049687, 2000066148, 2000076213, 2000082747, 2000087319
			MP001625	2000059927, 2000067877, 2000076362, 2000086766

Duration of treatment

Patients received a 1 mg daily dose of anastrozole for a treatment period of 12 months.

Criteria for evaluation (main variables)

Efficacy and pharmacokinetics

- Primary variables: change in frequency of annualized episodes of vaginal bleeding on treatment compared to baseline, proportion of patients with baseline vaginal bleeding who experienced >50% reduction in the number of vaginal bleeding episodes on treatment, proportion of patients with baseline vaginal bleeding who experienced cessation of vaginal bleeding episodes over a 6-month study period and over the whole 12-month study, change in bone age advancement on treatment compared to change during baseline, change in growth velocity on treatment compared to change during baseline

- Secondary variables: change in Tanner Stage (measure of pubertal progression), Change in mean ovarian and uterine volumes by ultrasound, including the number of ovarian cysts and size of the largest cyst, predicted adult height for children over age 6 years, endpoints for the population PK analysis.

Safety

Tolerability and safety (including adverse events, withdrawals and laboratory data)

Statistical methods

The primary analysis population for the efficacy variables was all patients exposed to study treatment. The secondary analysis population for the efficacy variables included all patients exposed to study treatment who did not have major protocol violations or major deviations, the protocol-valid population. For the safety variables the data were summarized for all patients exposed to study treatment.

Primary or secondary endpoints based on binary or categorical measures were summarized using frequency counts and percentages of the corresponding analysis population. Endpoints that were continuous measures were summarized using mean, standard deviation, median, minimum, and maximum. Statistical tests performed were 2-sided and were tested at the 5% level of significance. No adjustment was made for the multiple comparisons.

Patient population

A total of 28 patients received study treatment with anastrozole 1 mg, and were included in the all patients exposed to study treatment population. Of these, 27 patients were included in the protocol-valid analysis population.

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

Table S2 summarizes the age, height, weight and race at entry, for all patients exposed to study treatment.

Table S2 Age, height, weight and race of patients at entry: all patients exposed to study treatment

Demographic characteristic	Anastrozole 1mg (N=28)
Age at informed consent (fractional year)	
n	28
Mean (SD)	5.9 (2.03)
Median	5.6
Range	3.2 to 11.0
Height (cm) at Month 0 visit	
n	27
Mean (SD)	121.23 (14.86)
Median	119.70
Range	99.50 to 150.60
Weight (kg) at Month 0 visit	
n	26
Mean (SD)	25.33 (8.59)
Median	24.25
Range	14.80 to 53.00
Race (n [%])[a]	
Black	0
Caucasian	26 (92.9)
Oriental	1 (3.6)

Table S2 Age, height, weight and race of patients at entry: all patients exposed to study treatment

Demographic characteristic	Anastrozole 1mg (N=28)	
Other	1	(3.6)

[a] Percentages are based on the number of patients who received study treatment.
N Number of patients.
SD Standard deviation.
Data derived from Summary Tables 11.1.2 and 11.2.6.3.

Patients who participated in this study were representative of girls with MAS.

One patient who received treatment discontinued study treatment.

Efficacy and pharmacokinetic results

Analysis of the efficacy data indicate that:

- There was a slight increase in the frequency of bleeding days during treatment compared to baseline (median increase of 1.9 days) but this was not statistically significant
- Seven (28%) of the 25 patients with baseline vaginal bleeding experienced a ≥50% reduction in the frequency of vaginal bleeding days on treatment
- Ten (40%) of the 25 patients with baseline vaginal bleeding experienced a cessation in vaginal bleeding on treatment over a 6-month (ie, ≥180 days) study period. Three (12%) of those 10 patients experienced a cessation in vaginal bleeding on treatment over the whole 12-month study period (ie, from Day 1 to Day 360)
- The mean (and median) rate of increase in bone age decreased from the 6-month pre-baseline period over the 12-month on treatment period, with a slightly greater decrease in rate over the second 6 months of treatment. The change in rate of increase was not statistically significant for pre-treatment to during treatment, pre-treatment to the first 6 months of treatment, or for pre-treatment to the second 6 months of treatment
- Growth rate (in cm/year) was significantly reduced ($p<0.05$) from pre-treatment to during treatment (Month 0 to Month 12) (median change –2.1 cm/year; $p=0.0356$), and from pre-treatment to the second 6 months of treatment (median change -2.2 cm/year; $p=0.0186$). Growth rate (in Z-score) changes were not statistically significant but showed a trend in reduction consistent with the growth rate in cm/year
- There was no clinically significant change in breast or pubic Tanner staging from pre-treatment to end of treatment

- There was no clinically significant change in mean ovarian volume or mean uterine volume compared to screening, although marked variations in recordings were observed

- There was no clinically significant change in mean predicted adult height compared to screening. An increase of 0.9 cm in mean predicted adult height was observed following 12 months of study treatment, which corresponds to a 0.6 percent change

- Serum estradiol and serum estrone levels appeared to decrease over the first 6 months and then increase slightly during the second 6-month interval, while little to no change in dehydroepiandrosterone (DHEA) sulfate and testosterone was observed. Although follicle-stimulating hormone (FSH) is not as strong a marker as luteinzing hormone (LH) for central puberty, there was no obvious reason for their changes over time

- A detailed presentation of the population PK analysis of anastrozole in the pediatric MAS population will be located in an accompanying stand-alone population PK report entitled: Population pharmacokinetic analysis of anastrozole in pediatric girls with McCune-Albright syndrome and pubertal boys with gynecomastia

- The results based on the protocol-valid population confirmed the results obtained from the primary analysis population.

Safety results

Safety data indicate that:

- All except one of the 28 patients exposed to study treatment had a duration of study treatment that was greater than 360 days (ie, 12 months), and the median duration was 371 days

- A total of 24 (85.7%) patients exposed to study treatment experienced at least one adverse event. The most frequently reported (>10%) adverse events 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%), which, with the exception of arthralgia, all commonly occur in children

- A total of 5 (17.9%) patients experienced adverse events that were considered by the investigator to be possibly due to study medication

- Two (7.1%) patients reported adverse events that were classified as severe in intensity. All other adverse events reported were classified as mild to moderate and the majority of them resolved

- There were no deaths. Three (10.7%) patients reported at least one serious adverse event. None of the serious adverse events were considered by the investigators to be due to study medication
- No patients discontinued study treatment due to an adverse event.