AstraZeneca

Clinical Study Report Synopsis

Drug Substance	Fulvestrant; ZD9238
Study Code	D6992C00044
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An Open-label, Non-Comparative Trial to Evaluate the Safety, Efficacy and Pharmacokinetics of FASLODEX™ (fulvestrant) in Girls with Progressive Precocious Puberty Associated with McCune-Albright Syndrome

Study dates: First patient enrolled: 31 January 2006
Last patient last visit: 08 December 2009

Phase of development: Therapeutic exploratory (II)

This study was performed in compliance with Good Clinical Practice, including the archiving of essential documents

Study centre(s)

Patients were enrolled from 15 centres in 6 countries (United States [7 centres], France [3], Germany [2], Italy [1], Russia [1], United Kingdom [1]).

Publications

None at the time of writing this report.

Objectives and criteria for evaluation

Table S1 provides a summary of the primary and secondary objective and corresponding study endpoints.

Table S1 Primary and secondary objectives and study endpoints

Objectives	Endpoint	Type (category in FDA Written Request[a])
Primary		
The primary objective of the study was composed of two components: a safety and efficacy component and a PK component. All patients fulfilling the eligibility criteria were to participate in both components of the study. The safety of study treatment was evaluated by assessments of adverse events (AEs), withdrawals, laboratory data, ovarian volume as assessed by ultrasound, including the number of ovarian cysts and size of the largest cyst, and uterine volume. The efficacy of study treatment was assessed by change in frequency of vaginal bleeding days, rate of increase in bone age, and growth velocity. The second component will assess the PK of fulvestrant in girls with PPP associated with MAS.	Vaginal bleeding	Efficacy (study endpoints)
	Bone age[b]	Efficacy (study endpoint)
	Growth velocity[c]	Efficacy (study endpoint)
	Uterine volume	Efficacy[e](additional assessment)
	Ovarian volume	Efficacy[e] (additional assessment)
	Hormone levels	Efficacy[e] (NA)
	Pharmacokinetics[d]	Pharmacokinetics (study endpoints)
	Tolerability and safety	Safety (additional assessment)

Table S1 Primary and secondary objectives and study endpoints

Objectives	Endpoint	Type (category in FDA Written Request[a])
Secondary		
Secondary objectives included assessments of pubertal progression through Tanner Staging and predicted adult height (PAH) for children over 6 years old. The presence of a MAS associated Gsα mutation will be assessed by molecular analysis provided separate specific consent is obtained. No other genetic analysis will be performed with these specimens. The participation of patients and investigative sites in this analysis will be voluntary and any individual patient or site decision not to participate will not exclude them from this clinical study.	Tanner stage	Efficacy (additional assessment)
	Predicated adult height (PAH)[f]	Efficacy (additional assessment)
	Presence of Gsα mutation	Genetic (NA)

[a] FDA Written Request for pediatric studies for Faslodex (fulvestrant) injection, Amendment #2. NDA 21-344; IND 62,195; 17 June 2005.

[b] Defined as change in bone age (years) divided by the change in chronological age (years). Bone age was derived from blinded central read data.

[c] The growth velocity from the previous visit to the current visit, minus the mean growth velocity, 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.

[d] Mean clearance and volume of distribution, and exploration of race and body weight on fulvestrant PK.

[e] Ovarian volume, uterine volume and hormone levels are routinely reported as safety endpoints in fulvestrant studies and were therefore listed as such in the objectives in the CSP. However, these endpoints may also be considered a measure of efficacy in the patient population in this study (girls with MAS). Therefore, ovarian volume, uterine volume and hormone levels are reported as efficacy endpoints in this study.

[f] PAH equals the current height divided by a factor (the fraction of final adult height) based on current bone age (central read) 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.

Study design

This was an international multi-centre, open-label, non-comparative, exploratory phase II study to investigate the safety, efficacy and PK of fulvestrant in girls with PPP associated with MAS. The study compared efficacy endpoints on-treatment vs a 6-month pre-treatment baseline period.

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: females ≤ 10 years of age (prior to 11th birthday) at the start of therapy; diagnosed with MAS; had progressive precocious puberty manifested by physical signs of pubertal development; satisfying specific criteria regarding previous treatment; if central precocious puberty was present, treatment with 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 fulvestrant therapy. 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 (NOLVADEX™) in girls with MAS.

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

Fulvestrant was supplied in sterile, single patient, 5 mL pre-filled syringes (PFS). A pack was provided which contained the standard 5 mL PFS. For each 5 mL PFS, a sterile packed luer/luer connector and two sterile packed graduated syringes were also provided. Dependent on the location of the study centre, the volume of the sterile packed graduated syringes was either 3.0 ml (US) or 2.5 ml (outside US). The material was packaged by the Investigational Product Section at AstraZeneca and was not centre or patient specific.

Table S2 Details of investigational product and any other study treatments

Investigational product	Dosage form, strength, dosing schedule, and route of administration	Manufacturer	Formulation number
Fulvestrant	5% w/v solution, im injection into the buttock or thigh, 2 mg/kg or 4 mg/kg monthly[a].	AstraZeneca	F6521

[a] The first 10 patients initially received fulvestrant 2 mg/kg. Based on PK data from the first 6 patients, all 10 patients receiving 2 mg/kg were escalated to a dose of 4 mg/kg and all other patients received 4 mg/kg from study entry (this was consistent with a pre-defined study dose plan).

Duration of treatment

For the main study period, patients were scheduled to receive once monthly injections of fulvestrant for 12 months.

Statistical methods

The primary analysis population for the efficacy variables was the Full Analysis Set (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 important protocol deviations: the Per Protocol population (protocol valid). For the safety variables, data were summarized for the Full Analysis Set.

Primary or secondary endpoints based on binary or categorical measures were summarised using frequency counts and percentages of the corresponding analysis population. Endpoints

that were continuous measures were summarised 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. Individual patient data (including individual changes) were listed.

Patient population

A total of 30 patients received fulvestrant treatment and were included in the Full Analysis Set; of these 28 were included in the Per Protocol population. Twenty-nine patients received the protocol-defined 12 monthly fulvestrant injections and completed the main study period. One patient withdrew from study treatment due to a worsening of their MAS symptoms.

All patients who were enrolled in the study had classical MAS: ie, all 30 patients (100.0%) had precocious puberty before the age of 8 years old accompanied by: fibrous dysplasia (21/30 patients [70.0%]); and/or café au lait spots (24/30 patients [80.0%].

The patient population enrolled in the study was consistent with the intended patient population, ie, girls with PPP arising from MAS.

Summary of efficacy results

In this exploratory phase II study, fulvestrant has demonstrated efficacy in girls with PPP arising from MAS in terms of:

- A statistically significant reduction in annualised vaginal bleeding (medians =12.0 days pre-treatment vs 1.0 days on-treatment; median[1] change = -3.6 days [95% CI: -10.10, 0.00]; p=0.0146).

- The observation that a majority of patients (73.9% [95% CI: 51.6%, 89.8%) with baseline vaginal bleeding experienced a ≥50% reduction in vaginal bleeding over the course of the study and 34.8% (95% CI: 16.4%, 57.3%) of patients with baseline vaginal bleeding experienced a complete cessation of vaginal bleeding on-treatment (Month 0 to 12).

- A statistically significant reduction in the rate of bone age advancement during the 12-month study period compared to the 6-month pre-treatment period (mean change = -0.93 [95% CI=-1.43, -0.43]; p=0.0007).

- A numerical reduction in mean growth velocity Z-score on-treatment compared to pre-treatment.

- No advance in median Tanner stage (breast) on-treatment compared to baseline.

- A numerical reduction in mean uterine volume on-treatment compared to baseline.

There was no clinically meaningful changes in mean ovarian volume or PAH on-treatment compared to baseline.

Summary of pharmacokinetic results

A two-compartment model with a first order absorption and first order elimination process was fitted to the fulvestrant concentration-time data:

- CL/F was estimated at a mean of 38.4 L/hr (CV 30.1%). Body weight explained 14% of the variation in CL/F. The mean population clearance of a child weighing 27.4 kg (median weight in this study), was estimated to be 26.2 L/hr i.e. CL/F increased with increasing weight.

[1] Vaginal bleeding data were found to be non-normally distributed, therefore the median values were analysed. Note that median change is the median of the on-treatment vs pre-treatment changes and not the difference in the pre-treatment median and the on-treatment median.

- The mean estimate of Vss/F (V1/F + V2/F) was 65700 L (V1/F 33000, CV 70.0%; V2/F 32700, CV 54.4%). CL/F and V1/F were found to be positively (0.85) correlated.

- Residual variability was proportional in nature (CV 23%) and parameters were generally well estimated (relative standard errors (RSE) were <30% and were on average 15%).

Although weight was found to significantly explain some of the variation in CL/F, the observed dose normalised[2] steady-state fulvestrant concentrations ($C_{min, ss}$) in paediatric girls with MAS was similar to predicted dose normalised steady-state fulvestrant concentrations ($C_{min, ss}$) in postmenopausal women with breast cancer

Summary of safety results

- A total of 27 (90.0%) patients exposed to study treatment experienced at least one AE. Nine (30.0%) patients reported an SAE. No patients discontinued study treatment due to an AE and no patients died.

- There were no new safety concerns arising from this study.

- The adverse events reported in this study were generally consistent with either:

  – the known safety profile of fulvestrant (eg, injection site reactions); or,

  – the paediatric population under investigation (eg, pyrexia, rhinitis, nasopharyngitis); or,

  – the condition under investigation, ie, MAS (eg, 1 SAE of ovarian cyst).

- There was no evidence of increased uterine or ovarian volume on-treatment compared to the pre-treatment period.

[2] Concentration divided by the total dose administered eg, the observed concentration in a girl weighing 27.4 kg and received 4 mg/kg, was divided by 110 mg.