CLINICAL REVIEW

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Established Name	Fulvestrant
(Proposed) Trade Name	Faslodex
Therapeutic Class	Steroidal antiestrogen
Applicant	AstraZeneca
Formulation(s)	Injectable solution
Dosing Regimen	4 mg/kg once monthly
Indication(s)	None sought
Intended Population(s)	Girls with McCune-Albright Syndrome and precocious puberty

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1 Recommendations/Risk Benefit Assessment

Fulvestrant (Faslodex™) 50 mg/mL injection is a steroidal antiestrogen that has been approved for the treatment of estrogen-receptor positive breast cancer in postmenopausal women (NDA 21-344, approved April 25, 2002). The Sponsor has submitted this supplemental NDA as part of its request for a 6-month pediatric exclusivity determination in response to FDA's Written Request for pediatric information. This submission provides safety, efficacy and pharmacokinetic information on Faslodex in girls with McCune-Albright Syndrome with peripheral precocious puberty. The proposed clinical dose is 4mg/kg intramuscularly once a month.

1.1 Recommendation on Regulatory Action

No indication is being sought from this application. I am recommending revisions to the Sponsor's requested label changes; a summary and line-by-line labeling review will be submitted as an addendum to this review.

1.2 Risk-Benefit Assessment

On October 21, 2002, the Agency issued a Written Request (WR) for the study of Faslodex in girls with McCune-Albright Syndrome (MAS) and progressive precocious puberty (PPP). The rationale for using Faslodex, a steroidal estrogen receptor blocker, in this condition is to suppress estrogen action, and in so doing to suppress the manifestations of precocious puberty in girls with MAS. There are no available medical therapies to halt the progression of PPP in girls with MAS.

The foundation of the supplemental NDA (sNDA) submission was Study D6992C00044 (hereafter referred to as "Study 44"), an open-label, non-comparative Phase 2 study to evaluate the safety, efficacy, and pharmacokinetics of Faslodex in 30 girls with PPP associated with MAS. In Study 44, Faslodex was administered using the formulation approved for adult use, a 50 mg/mL solution for intramuscular injection. Patients were dosed on a mg/kg basis, and the study included a basic dose escalation protocol consistent with the WR. As there was no control arm in the trial, all comparisons were versus baseline.

The design of Study 44 was such that no single endpoint was identified as being of primary importance. The terminology and grouping of endpoints used in the WR was used in the Study 44 Clinical Study Report (CSR): these were described as "efficacy endpoints" and "additional assessments."

Overall, the Sponsor has demonstrated an acceptable safety profile of Faslodex for the treatment of PPP in girls with MAS. There were no new safety concerns for Faslodex arising from Study 44, and the AEs reported in the CSR were generally consistent with either the known safety profile of Faslodex or the pediatric population under investigation.

In terms of efficacy findings, the Sponsor argues that Faslodex treatment in girls with MAS improves symptoms of PPP based on results for a number of endpoints. Foremost, the Sponsor has presented data suggesting Faslodex-treated patients experience a

significant reduction in annualized vaginal bleeding (median 12.0 days pre-treatment vs. 1.0 days on treatment, p=0.0146). To bolster this argument, the Sponsor has presented data indicating that a majority of patients (73.9%) with baseline vaginal bleeding experienced a ≥50% reduction in vaginal bleeding, and that 34.8% experienced a complete cessation of vaginal bleeding while on treatment. Furthermore, the Sponsor has presented data that suggests a statistically significant reduction in the rate of bone age advancement; a clinically significant reduction in mean growth velocity Z-score; and no increase in median Tanner stage on treatment compared to pre-treatment.

These data are tempered by a number of important concerns regarding their interpretation. These are detailed in Section 6 of this review, and include: lack of a control arm; unorthodox plan for collection and interpretation of vaginal bleeding data; and the subjective nature of the evaluation method for multiple endpoints.

Since the Sponsor is not seeking an indication, these risks and benefits must be considered instead when reviewing the proposed label changes. It is this medical officer's opinion that the factors stated above limiting the efficacy evaluation should be mentioned as part of any changes made to the current Faslodex label.

1.3 Recommendations for Postmarketing Risk Management Activities

No additional postmarketing risk evaluation and mitigation strategies are being recommended. Note that Faslodex is already marketed at a 250 mg IM monthly dose for advanced breast cancer.

1.4 Recommendations for other Post Marketing Study Commitments

No postmarketing requirements or commitments are recommended.

2 Introduction and Regulatory Background

2.1 Product Information

Established name: Faslodex 50 mg/ml injection
Faslodex (fulvestrant) is a pure estrogen receptor antagonist administered via intramuscular injection. It is approved in the United States for the following indication:

- Treatment of hormone receptor-positive (HR+) metastatic breast cancer in postmenopausal women with disease progression following anti-estrogen therapy, at a dose of 250 mg IM once a month.

This submission is an efficacy supplement to add information to the current label on the effect of Faslodex on the progression of peripheral precocious puberty in girls with McCune-Albright Syndrome.

Applicant's Proposed Indication
No indication is being sought from this application

Applicant's Proposed Dosing Regimen
The proposed daily dose for Faslodex is 4 mg/kg administered by intramuscular (IM) injection to McCune-Albright Syndrome patients with precocious puberty. This dose was selected based on results of a pharmacokinetic (PK) dose-escalation substudy in the intended population.

Applicant's Proposed Age Groups
The Sponsor has not specifically proposed an age range for treatment. In Study 44, patients were required to be ≤ 10 years of age at the start of study therapy.

2.2 Tables of Currently Available Treatments for Proposed Indications

The sponsor is not seeking an indication with this application. There are no currently available treatments for the indication of peripheral precocious puberty in patients with McCune-Albright Syndrome[1].

2.3 Availability of Proposed Active Ingredient in the United States

Faslodex is already approved and marketed in the United States for the treatment of estrogen-receptor positive breast cancer in postmenopausal women at a dose of 250 mg IM monthly.

2.4 Safety Issues With Consideration to Related Drugs

Faslodex is a marketed drug in the United States for advanced breast cancer in postmenopausal women. As reflected in current product labeling, Faslodex may theoretically result in bleeding complications in patients with bleeding diatheses, thrombocytopenia, or anticoagulant use due to intramuscular route of administration. Among adult patients, the most frequent adverse events associated with fulvestrant use include gastrointestinal symptoms (nausea, vomiting, diarrhea, constipation, and abdominal pain), headache, back pain, hot flashes, pharyngitis, and musculoskeletal complaints. In addition, fulvestrant may cause an increase in hepatic transaminases which is generally low-grade and self-limited, even with continuation of fulvestrant.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

FDA Written Request and Amendments
On October 21, 2002, FDA issued a WR requiring the Sponsor to conduct 2 studies in order to obtain 6-month pediatric exclusivity for Faslodex: a PK study and a safety/efficacy study. Consistent with the WR, the PK study was incorporated as a sub-study of the main safety/efficacy study.

The Written Request was subsequently amended twice, on May 7, 2004 (Amendment #1), and on June 17, 2005 (Amendment #2), the latter of which requested the submission of information on the safety, efficacy, and pharmacokinetics of Faslodex in female patients with MAS.

[1] Nolvadex (tamoxifen citrate) and Arimidex (anastrozole) contain information in their labels as a result of studies conducted in girls with McCune-Albright syndrome and progressive precocious puberty under previous WRs, but no indication was granted in either case.

The Sponsor's response to the WR was presented in front of the FDA's Pediatric Exclusivity Board on February 2, 2011. Upon review, the Board granted 6-month exclusivity to the Sponsor.

2.6 Other Relevant Background Information

Peripheral Precocious Puberty in McCune-Albright Syndrome

MAS is a rare disorder characterized by the classic clinical triad of precocious puberty, polyostotic fibrous dysplasia, and cafe au lait spots. These symptoms can be fully present (classic form) or partially present ("forme fruste"). MAS is caused by an missense mutation in the gene coding for the stimulatory subunit of the G protein $G_s\alpha$ which is involved in intracellular signaling. The altered $G_s\alpha$ (which contains a substitution of arginine in coding amino acid 201 to a cysteine or histidine) causes autonomous activation of G-protein stimulated cAMP formation, a phenomenon known as "constitutive activation." This mutation is a post-zygotic event which leads to a mosaic distribution of the defect in affected endocrine and non-endocrine tissues. The resulting heterogeneity in clinical symptoms can be extreme.

Gonadal manifestations of the disease consist in waxing and waning estrogen secretion by ovarian cysts. This results in episodic uninhibited sex steroid production and subsequent sustained pubertal development in a subgroup of patients. Although initially independent of gonadotropin secretion, the MAS precocious puberty is followed by activation of the hypothalamus and a central (gonadotropin-dependent) component. Expression of the activating mutation in non-gonadal endocrine tissues may lead to hyperthyroidism, growth hormone excess, and Cushing's disease.

Available Treatment Options for PPP in MAS

There are no approved drugs for the indication of treatment of PPP in girls with MAS. Several drugs, in different pharmacological classes, have been used off label. They include drugs that inhibit various steps in the estrogen biosynthetic pathway such as ketoconazole (Syed and Chalew, 1999) and aromatase inhibitors, including testolactone (Feuillan et al,1986; Feuillan et al,1993), and more recently anastrazole and letrozole. Drugs that block estrogen activity at the level of the estrogen receptor, such as tamoxifen have been used successfully in small numbers of patients (Rodens et al, 1989; Eugster et al, 1999; DiMartino-Nardi, 2000; Eugster and Pescovitz, 2001). Medroxyprogesterone acetate has been used for control of menstrual bleeding but has no benefits in preventing skeletal growth and maturation.

Despite favorable results in published case reports, neither Arimidex (anastrazole) nor Nolvadex (tamoxifen) lived to expectations when tested in clinical trials. Therefore, the labels for both contain information on clinical trials for the treatment of PPP in patients with MAS, but this indication has not been approved for either drug. Because Faslodex is a pure antiestrogen with potent anti-estrogenic properties and no known partial agonistic effects, the Sponsor hypothesizes there is potential for improved efficacy (and therefore improved compliance) compared to other drugs that have been considered in the past.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

Data quality and completeness were adequate to permit review.

3.2 Compliance with Good Clinical Practices

The sponsor reports that the Pivotal Studies were conducted in accordance with the principles of good clinical practice (GCP), including the ethical review board (ERB) and informed consent.

No Division of Scientific Investigations (DSI) audit was felt to be necessary for this sNDA.

Table 1 below summarizes the major protocol violations in Study 44:

Table 1: Major Protocol Deviations – Study 44

Important protocol deviation	Faslodex N=30
	Number (%) of patients
Number of patients with at least one important deviation	2 (6.7)
Key assessments not completed at certain visits, or completed but outside time window	1 (3.3)
Use of prohibited concomitant treatments	1 (3.3)

Source: CSR, Table 11

The protocol deviations for the two patients identified above are as follows:

- **Patient E008001:** Received sandostatin as concomitant medication for excess growth hormone.
- **Patient E0010001:** Missed assessments due to a car accident.

3.3 Financial Disclosures

No financial relationships likely to have impacted the conduct or findings of the trial were disclosed for any of the investigators listed on the form 3454.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

No new chemistry data have been submitted with this supplemental NDA.

4.2 Clinical Microbiology

Not applicable – Faslodex is not an antimicrobial.

4.3 Preclinical Pharmacology/Toxicology

No new pharmacology/toxicology data have been submitted with this supplemental NDA.

4.4 Clinical Pharmacology

See Dr. Jaya Vaidyanathan's Clinical Pharmacology review and Dr. Nitin Mehrotra's Pharmacometrics review for full details.

The clinical pharmacology of fulvestrant has not been previously assessed in a pediatric population, although it has been extensively studied in adults. This application assessed the clinical pharmacology of fulvestrant in girls with MAS by a combined analysis of PK data from Study 44 (in girls with MAS) and Studies 20/21 (in postmenopausal women) using a population PK approach.

4.4.1 Mechanism of Action

Fulvestrant is the first in a new class of steroidal antiestrogens called "pure antiestrogens." It displays potent antiestrogenic properties and a novel mode of action leading to downregulation of the estrogen receptor. In contrast to selective estrogen receptor modulators (SERMs), such as tamoxifen citrate, fulvestrant has no agonistic effect on the endometrium. This implies no increased risk of endometrial adenocarcinoma, a significant and well documented adverse event associated with tamoxifen that prompted the addition of a boxed warning to the tamoxifen drug labeling.

Fulvestrant showed superior binding affinity for the estrogen receptor when compared to tamoxifen (100 times higher) and similar binding affinity to estradiol. *In vitro* and *in vivo* tumor growth assays indicate that fulvestrant is superior to tamoxifen. Estrogen dependent skeletal maturation and endometrial proliferation are suppressed by fulvestrant in animal models.

4.4.2 Pharmacodynamics

In Study 44, fulvestrant was administered using the formulation that is approved for adult use (50 mg/mL solution for IM injection). Pediatric patients were dosed on an mg/kg basis and the study included a basic dose escalation protocol. This approach was consistent with the FDA Written Request, which indicated that the marketed formulation was suitable to fulfill the criteria for an age-appropriate formulation.

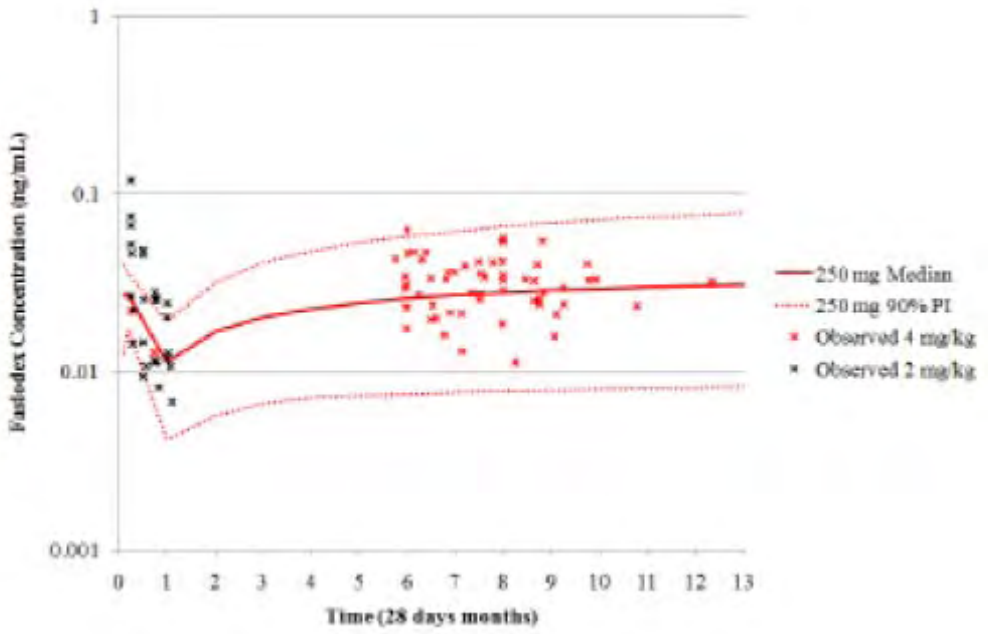
Approximately 30 female patients aged 10 years or less (prior to 11th birthday) who had the diagnosis of MAS, progressive precocious puberty associated with MAS were enrolled in Study 44's PK sub-study. The first ten patients enrolled into the study received an initial dose of 2 mg/kg. This dose was escalated to 4 mg/kg in all ten patients in the 3rd month of treatment because the estimate of C_{max} during the first month was $\leq$7.4ng/ml and C_{min} was $\leq$2.6 ng/mL. Subsequently patients were started at a dose of 4 mg/kg monthly.

4.4.3 Pharmacokinetics

The Sponsor used a two-compartment disposition model with a first order absorption process for the population PK analysis. The results from the combined analysis indicated that the apparent clearance (CL/F) was 32% lower in children than in postmenopausal women. Comparing results from this combined analysis with previous data for fulvestrant, the mean value of apparent clearance in children (estimated in the combined

analysis) was approximately 20% lower compared to the previously reported mean value in studies postmenopausal women with breast cancer (estimated from Studies 20/21 alone). The Sponsor has hypothesized that the release of compound from the depot may be faster in children than in postmenopausal women and that this has been observed as a change in clearance rather than a change in absorption. An increased release rate may occur due to increased motility in the muscle as children tend to be more physically active than postmenopausal women with advanced breast cancer. The Sponsor has indicated that there was no difference between children and postmenopausal women in dose-normalized C_{min} steady-state (Figure 1).

Figure 1: Dose normalized pediatric concentrations and adult prediction interval



Source: Sponsor's Clinical Overview

5 Sources of Clinical Data

This review uses clinical data derived from Sponsor's study D6992C00044 ("Study 44").

5.1 Tables of Clinical Studies

The tabular listing of studies (Table 2 below) is taken from the Sponsor's Clinical Study Report, Section 5.2.

Table 2: Overview of Study 44 (Main and PK Studies)

Type of Study	Objective (s) of the Study	Study Design and Type of Control	Test Product Dosage Regimen	Number of Subjects	Subjects	Duration of Tx
SAFETY AND EFFICACY (MAIN) STUDY						
Phase II	**Primary:** Characterize safety and efficacy of fulvestrant in girls with PPP associated with MAS. • Safety assessments: AEs, withdrawals, laboratory data, ovarian volume and uterine volume. • Efficacy assessments: change in frequency of vaginal bleeding days, rate of increase in bone age, and growth velocity. **Secondary:** Assess pubertal progression through Tanner Staging and PAH for children over 6 years old. Assess for presence of MAS Gsα mutation by molecular analysis.	Open label	Fulvestrant 50 mg/ml; 4 mg/kg once monthly via IM injection	30 treated	Girls with McCune-Albright Syndrome and progressive precocious puberty	12 months
PK STUDY						
Phase II	Assess the PK of fulvestrant in girls with PPP associated with MAS.	Open label				

Source: Study 44 CSR, Section 5.2

5.2 Review Strategy

The review of this sNDA was conducted by a single clinical reviewer. Sources of clinical data in this review are the original sNDA submission, the 4-month Safety Update, and the Sponsor's responses to the Agency's requests for information.

The primary assessment of the efficacy and safety of fulvestrant at the proposed 4 mg/kg IM monthly dose is derived from the original submission and 4 month Safety Update of Study 44. An independent review was performed by biostatistics, Dr. Cynthia Liu, and discussions from this review were used in this medical officer's final assessment.

The primary review activities for this sNDA included:

- Review of pre-NDA package and participation in pre-NDA internal/Sponsor meetings;
- Review of the electronic submission of the original sNDA and 4-month safety update;
- Review of Sponsor electronic submissions in response to FDA clinical queries;

- Reproduction and/or auditing of key efficacy and safety analyses with JMP using raw datasets provided by the applicant.
- Reading and incorporation of reviews written by fulvestrant reviewers from other Disciplines.

5.3 Discussion of Individual Studies

The phase 2 trial supporting this supplemental NDA, Study 44, is discussed in detail in Section 6.1.1.

6 Review of Efficacy

Efficacy Summary

See Dr. Cynthia Liu's Statistical Review for details of the safety/efficacy portion of Study 44. See Dr. Jaya Vaidyanathan's Clinical Pharmacology Review and Dr. Nitin Mehrotra's Pharmacometrics review for details of the PK portion of Study 44.

As part of its request for a 6-month pediatric exclusivity determination in response to FDA's Written Request for pediatric information, the Sponsor submitted the CSR for Study 44, which provides safety, efficacy and pharmacokinetic information on Faslodex in girls with McCune-Albright Syndrome with peripheral precocious puberty. Based on results from the PK study, the Sponsor studied a dose of 4mg/kg intramuscularly once a month.

Study 44 was an international multi-centre, open-label, non-comparative, exploratory phase II study to investigate the safety, efficacy and PK of fulvestrant in girls ≤10 years of age with PPP associated with MAS. The study compared efficacy endpoints on-treatment versus a 6-month pre-treatment baseline period. 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.

This review will focus on the safety/efficacy portion of Study 44.

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.

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 was assessed by molecular analysis in patients who provided separate consent.

A total of 30 patients received Faslodex 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 Faslodex injections and completed the main study period (one withdrew due to a worsening of her MAS symptoms).

The data provided from Study 44 show the following:

- A statistically significant reduction in annualized vaginal bleeding (median = 12.0 days pre-treatment vs 1.0 days on-treatment; median 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 increase in median Tanner stage on-treatment compared to baseline.

However, these results are tempered by a number of issues that affect the interpretation of the data:

- There was no control arm in the study; all comparisons are versus baseline.
- As part of the pre-specified analysis plan, baseline data consisted of a 6-month collection of height, weight, Tanner Stage, bone age, and vaginal bleeding data from each patient. This could be done either using documented retrospective data, or collected prospectively during a 6-month observation period. All 30 patients who were enrolled into the study had 6-months retrospective data available at baseline; therefore the method of collection for all baseline data (retrospective) differed from the method for all data collected during the study period (prospective). This complicates the analysis of each of these efficacy endpoints.
- Evaluation of each of the efficacy endpoints was subject to a degree of subjectivity, most notably the data on vaginal bleeding. Patients were asked to complete diary cards that indicated whether or not they had experienced vaginal bleeding on each day of the trial. First, “vaginal bleeding” may include either menses or bleeding of a different etiology, and this distinction may not be clear to the patients filling out the cards. Second, many patients did not fill out a diary card for each day they were enrolled in the trial. Therefore, the interpretation of the results depends upon whether one considers a missed day as a “bleeding”or a “non-bleeding” day. The Sponsor has submitted data for both scenarios, and the results are more favorable if one considers missed days to be “non-bleeding” days. Finally, the method of prospective collection (vaginal bleeding diary cards) was collected in a different manner from the retrospective data (vaginal bleeding days were based on the patient’s own recollection, and not recorded).

As the Sponsor is not seeking an indication from this application, it is this medical officer's opinion that these issues must be addressed as part of any changes to the current Faslodex label.

6.1 Indication

No new indication is sought with this supplemental NDA. New data regarding the treatment of PPP in girls with MAS is reviewed.

6.1.1 Methods

This section primarily reviews the safety and efficacy portion of the Phase II Study 44. The focus of the review for this trial is the effect on clinical symptoms associated with pubertal development and advancement. Some data from the PK portion of this study is presented as well.

6.1.1.1 Study Objectives

The primary objective of Study 44 was composed of two components: a safety and efficacy component and a PK component. 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.

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 was assessed by molecular analysis.

6.1.1.2 Study Endpoints

Primary and/or secondary endpoints were not defined by the Sponsor in this application. Instead, the Sponsor described endpoints as "study endpoints" or "additional assessments." For the Safety and Efficacy portion of Study 44, study endpoints included:

- 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 menses over a 6-month trial period and over the whole 12-month trial.
- Change in bone age advancement on treatment compared to change during baseline (provide data for both the 6-month and the 12-month timepoints).
- Change in growth velocity on treatment compared to change during baseline (provide data for both the 6-month and the 12- month timepoints).

Additional assessments included:

- Change in Tanner stage (breast and pubic hair) at the 12-month timepoint relative to baseline.

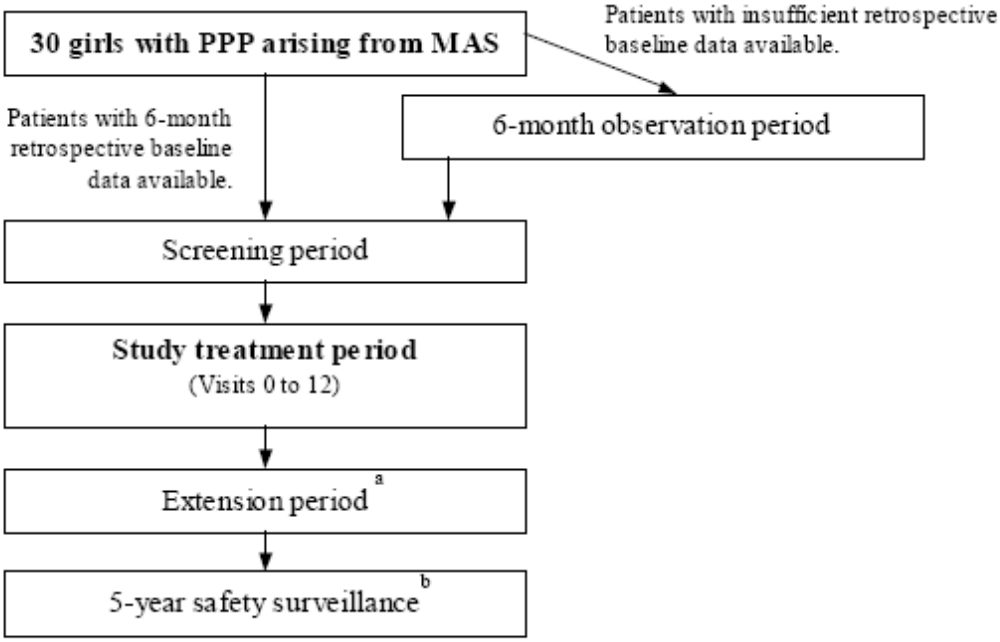
- Change in uterine volume at the 6-month and 12-month timepoints relative to baseline uterine volume.
- Change in ovarian volume at the 6-month and 12-month timepoints relative to baseline ovarian volume (categorization of the number and size of ovarian cysts should be attempted).
- Predicted adult height at the 12-month timepoint trial relative to baseline.
- Tolerability and safety data.

For the PK study, endpoints included mean clearance and volume of distribution of fulvestrant, and body weight and race effect on fulvestrant PK.

6.1.1.3 Study Design

Figure 2 shows a schematic representation of Study 44 taken from the Sponsor's Clinical Study Report.

Figure 2: Schematic representation of Study 44



[a] Patients were entered into the extension period at the investigators discretion. Separate consent was required.
[b] All patients enter into the 5-year safety surveillance period. Consent was included in the written consent for the main study.
PPP:Progressive precocious puberty; MAS:McCune Albright Syndrome.
From Study 44 CSR, Figure 1

Study 44 was a 12-month, open label, exploratory trial designed to allow for the identification and monitoring of safety parameters and efficacy outcome variables in all patients, as well as the evaluation of fulvestrant PK.

All 30 patients enrolled in the study had at least 6 months of retrospective data consisting of height, weight, bone age, Tanner staging assessment and vaginal bleeding history (ie, number of bleeding days). Patients who completed 12-months study treatment were given the option to continue treatment until the onset of natural puberty or until the patient

experienced a drug-related toxicity requiring treatment discontinuation. All patients who gave consent and received study medication will be followed as part of an ongoing five-year safety surveillance period.

The key features of the study design were chosen to address the FDA Written Request for pediatric information for fulvestrant.

Schedule of Assessments

Tables 3 and 4 depict the schedule of assessments for Study 44 for the safety/efficacy and PK portions, respectively.

Table 3: Schedule of Assessments – Study 44 (Safety/Efficacy)

Study period	6-month retrospective data / Screening		Enrolment	Study treatment period					
Visit	6-Month retrospective [a]	Screening [b]	Month 0	Month 1 to 2	Month 3	Month 4 to 5	Month 6	Month 7 to 11	Month 12
Visit number	100	99	0	1 to 2	3	4 to 5	6	7 to 11	12
Informed written consent of parent/legal guardian and patient assent		√							
History		√							
Physical Examination [c]	√	√	√		√		√		√
Height / Weight	√	√	√	√	√	√	√	√	√
Tanner Staging (Breast and Pubic Hair) [d]	√	√	√		√		√		√
Clinical chemistry [e]		√							√
Hormone assays [e]		√			√		√		√
Complete blood count [e]		√							
Pelvic ultrasound [f] (uterus and ovaries)		√					√		√
Bone age (wrist x-ray) [g]	√	√ [h]					√		√
Vaginal Bleeding Days	√								
Diary Cards [i]			√	√	√	√	√	√	√
Prior/Concomitant Meds		√	√	√	√	√	√	√	√
Adverse events (serious/non-serious) [j]			√	√	√	√	√	√	√
Pharmacokinetics [a]									
Administer study drug			√	√	√	√	√	√	[k]

[a] Visit 100 was not an actual visit. Retrospective data of at least 6 months were collected and recorded at the Screening Visit. Informed consent had to be obtained prior to the collection of any data.

Source: Study 44 CSR, Table 2

Table 4: Schedule of Assessments – Study 44 (PK Sampling)

Study Visit	Month 0	Month 1	Month 2	Month 3	Month 4	Month 5	Month 6	Month 7	Month 8	Month 9	Month 10	Month 11	Month 12
Dose	2 or 4 mg/kg[c]	2 or 4 mg/kg[c]	2 or 4 mg/kg[d]	2 or 4 mg/kg	2 or 4 mg/kg[f]	2 or 4 mg/kg	2 or 4 mg/kg	2 or 4 mg/kg	2 or 4 mg/kg	2 or 4 mg/kg	2 or 4 mg/kg	2 or 4 mg/kg	2 or 4 mg/kg
Week 1 [a]	√	[c]	√ [e]	[f]	[f]								
Week 2 [a]	√		√ [e]										
Week 3 [a]	√		√ [e]										
Week 4 [b]	√		√ [e]				√ [g]	[g]	[g]	√ [g]	√ [g]	√ [g]	√ [g]

Source: Study 44 CSR, Table 3

6.1.1.4 Study Eligibility Criteria

Inclusion Criteria:

1. Provision of written informed consent of parent/legal guardian and subject assent.
2. For patients who consented participate in the genetic portion of the study, provision of an additional written informed consent specific for DNA sampling and genetic analysis.
3. Females ≤10 years of age (prior to 11th birthday) at the start of study therapy (Visit 0).
4. Diagnosis of McCune-Albright Syndrome based on meeting the following clinical criterion:
    - Precocious puberty evident before the age of 8 years; and at least one of the following clinical criteria:
    - Café au lait spots
    - Fibrous dysplasia
    - Presence of Gsα mutation.
5. Progressive precocious puberty associated with MAS. Progressive precocious puberty was defined as:
    - An increase of at least one in the breast Tanner Stage over the observation period and/or
    - The development or persistence of vaginal bleeding during the observation period.
6. At least one of the following two criteria had to be fulfilled:
    - Advanced bone age (defined as bone age of at least 12 months beyond chronological age at the time of screening) and/or
    - Rapid growth velocity (a growth velocity over the observation period that was more than 2 standard deviations above the mean for age, where the growth velocity was defined as the change in height or length [in cm] divided by the change in time [annualized in years]).
7. Patients were eligible provided they were in one of the following categories:
    - Received no previous treatment and had documented retrospective data of at least 6 months for bone age, Tanner stage, height, weight, and vaginal bleeding (number of bleeding days);
    - Received no previous treatment and did not have documented retrospective data of at least 6 months for bone age, Tanner stage, height, weight and vaginal bleeding (number of bleeding days) but could be observed for 6 months without treatment (ie, a 6-month observation period);
    - Documented progression on treatment with anastrozole (or another aromatase inhibitor), tamoxifen, testolactone, an anti-androgen, or a progestin requiring immediate treatment provided there existed at least 6 months retrospective data for bone age, Tanner stage, height, weight, and vaginal bleeding (number of bleeding days) and the patient had 1 month washout period prior to the first dose of study drug;
    - Previously treated with any drug for PPP in which therapy was stopped for at least 6 months with subsequent clinical evidence of progression of disease meeting inclusion criteria 5 and 6 and retrospective data of at least 6 months for bone age, Tanner stage, height, weight, and vaginal bleeding (number of bleeding days).

8. If central precocious puberty (CPP) was evident, the patient had to have received treatment with a GnRH analogue (eg, Lupron) for at least 6 months prior to study enrollment (date of written consent of parent/legal guardian and patient assent).

Exclusion Criteria

1. Male gender.
2. Any prior treatment of PPP associated with MAS with fulvestrant.
3. Concomitant treatment of PPP associated with MAS, with the exception of bisphosphonates for fibrous dysplasia and GnRH analogs in the case of CPP.
4. Serum liver chemistry tests (AST, ALT) at screening ≥ 3× the upper limit of the reference range (ULRR) for age.
5. Platelet count at screening less than 100 × 109/L.
6. International normalized ratio (INR) greater than 1.6.
7. History of bleeding diathesis or long-term anticoagulant therapy (other than anti-platelet therapy).
8. Any severe concomitant condition that made it undesirable for the patient to participate in this study.
9. Known hypersensitivity to any component of the study drug product.

Restrictions

1. Patients were not to receive other investigational agents or begin any other treatment for PPP (except bisphosphonates for fibrous dysplasia and GnRH analogues in the case of CPP) while participating in this study.
2. Dosage of study drug was not be altered throughout the study except as per the dosing schedule (see Section 6.1.8 for complete details).

6.1.1.5 Study Enrollment

A total of 30 patients were enrolled between January, 2006 and October, 2008. Patients were enrolled from 15 centers in 6 countries: United States (7 centers), France (3), Germany (2), Italy (1), Russia (1), United Kingdom (1). Prior to enrolment, patients were screened to ensure they met the pre-defined inclusion and exclusion criteria for the study. All patients who were enrolled into the study had 6-months of retrospective data available at baseline; therefore no patients required a 6-month observational period prior to screening.

6.1.2 Demographics

Key demographic characteristics for patients in the full analysis set are summarized in Table 5 below:

Table 5: Baseline Demographics – Study 44

		Faslodex N=30
Age (years)	**Mean (SD)**	5.9 (1.8)
	Range	1.7; 8.5
Age group n (%)	**< 7 years old**	20 (66.7)
	≥ 7 and ≤ years	10 (33.3)
Height at Month 0 visit (cm)	**Mean (SD)**	123.5 (15.4)
	Range	81.5; 144.1
Weight at Month 0 visit (kg)	**Mean (SD)**	27.2 (8.1)
	Range	12.4; 48.4
Race n (%)	**Black**	1 (3.3)
	White	26 (86.7)
	Other	3 (10.0)
Ethnicity n (%)	**Hispanic/Latino**	3 (10.0)
	Not Hispanic/ Latino	4 (13.3)
	Not applicable	23 (76.7)

Source: CSR Table 13

The median age at informed consent was 6.10 years old (range: 1.7 to 8.5). All patients were <10 years of age; 66.7% of patients were <7 years old at informed consent.

The majority (86.7% [26/30]) of patients enrolled in the study were White (listed as Caucasian on the CRF). A total of 23 patients had Ethnicity listed as not applicable, which was an option on the CRF provided to the investigators; 22 of these patients had their Race listed as Caucasian/White.

As mentioned in section 6.1.1.4, patients with classical (ie, having at least 2 of a triad of symptoms of precocious puberty, café au lait spots or fibrous dysplasia) or atypical (precocious puberty with Gsα mutation confirmed by molecular diagnosis) MAS were eligible for inclusion in the study. All patients who were actually 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%].

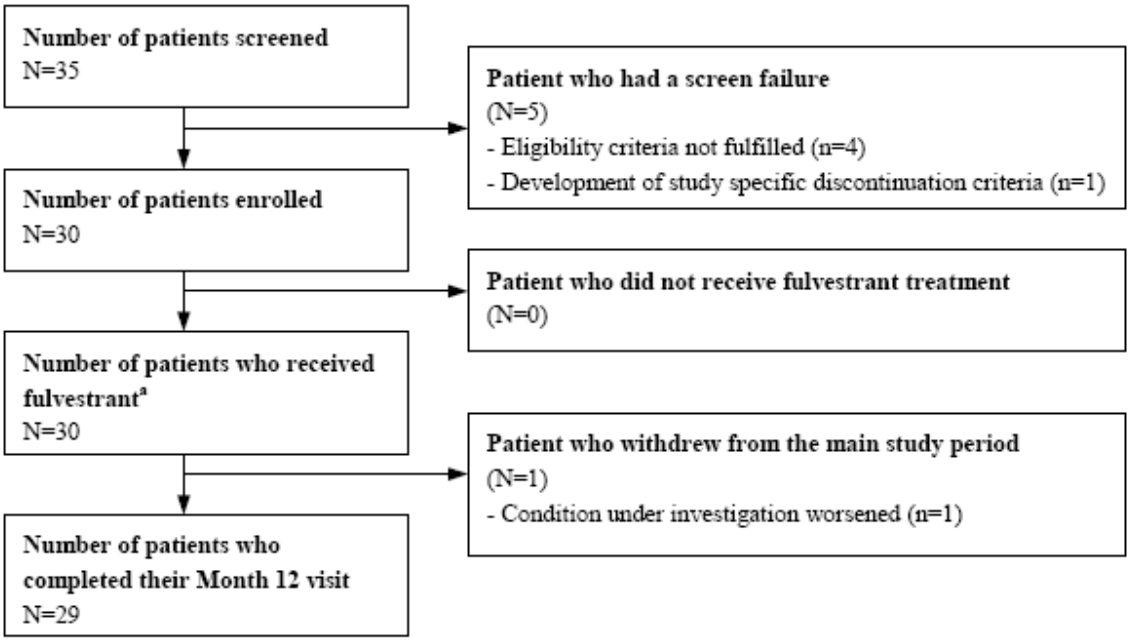
In addition to exhibiting at least 2 of the classic triad of MAS symptoms, 7 (23.3%) patients had a Gsα mutation confirmed by molecular diagnosis of peripheral blood (local analysis reported by investigators).

Baseline vaginal bleeding (bleeding days in the 6 months prior to treatment) was recorded on the CRF; for 26 patients (86.7%) this information was provided by the parent/guardian, for the remaining 4 patients the information was provided by a local consultant, mother's diary or medical notes. A total of 23 (76.7%) patients experienced at least 1 day of vaginal bleeding in the 6-months pre-treatment period.

6.1.3 Subject Disposition

See Figure 3 below for a representation of patient disposition for Study 44.
A total of 35 patients were screened for entry into the study, of which 30 were enrolled and received fulvestrant therapy. Overall, 29 patients completed 12 months study treatment; 1 patient (E0035001) withdrew due a worsening of the condition under investigation.

Figure 3: Patient disposition – Study 44



[a] Consistent with the dose escalation plan (see Figure 3), the first 10 patients initially received fulvestrant 2 mg/kg and were dose escalated to fulvestrant 4 mg/kg once the PK samples from the first 6 patients were analysed and met the criteria described in Figure 3. All subsequent patients received fulvestrant 4 mg/kg at all treatment visits .

Source : CSR, Figure 4

6.1.4 Analysis of Primary Endpoint(s)

As discussed in Section 6.1.1.2, the Sponsor has described study endpoints as "study endpoints" and "additional assessments," consistent with the format in which they are discussed in the Pediatric Written Request. Efficacy endpoints are described in this manner throughout this review; this section will include those described as study endpoints.

6.1.4.1 Baseline data (6-month retrospective data)

Table 6 below summarizes the height, number of vaginal bleeding days, and rates of increases in bone age[2] and growth velocity (Z-score)[3] for patients during the 6-month retrospective period. As previously mentioned, all patients provided retrospective data for these parameters, and therefore none were measured prospectively. Of note, retrospective data for bone age, height, and growth velocity were obtained from the patients' medical providers[4]. Bleeding history was determined based on the patients' recollection.

Table 6: Six-month retrospective data – Study 44

	Faslodex N=30		
	Mean (SD)	**Median**	**Range**
Rate of bone age advancement during pre-treatment period	2.0 (1.0)	1.8	0.4; 5.2
Height at baseline (month 0) (cm)	123.5 (15.4)	127.8	81.5; 144.1
Growth velocity during pre-treatment period (Z-score)	2.4 (3.3)	2.7	-4.3; 7.5
Number of vaginal bleeding days during pre-treatment period	7.2 (6.8)	6.0	0.0; 21.0

Source: CSR, Table 15

6.1.4.2 Vaginal bleeding

Patients were instructed to complete "diary cards" that asked them to mark whether they did or did not experience vaginal bleeding on each day of the treatment period. This differs from the method of collection for the baseline data, in which all 30 patients presented a 6-month history of vaginal bleeding days based on their own recollection. As per protocol, all pre-defined analyses of vaginal bleeding data were based on a worst-case scenario calculation, ie, missing diary card days were counted as bleeding days. The impact of this worst-case scenario assumption was investigated in a post-hoc 'best case' sensitivity analysis.

6.1.4.2.1 Change in frequency of annualized episodes of vaginal bleeding on treatment compared to baseline

Table 7 below shows the frequency of vaginal bleeding days for the full analysis set, when using a worst-case scenario calculation:

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

[3] Growth velocity from the previous visit to the current visit, minus the mean growth velocity, divided by the SD. Mean and SD are the age- and gender-specific statistics from the National Center for Health Statistics FELS study, and age is the age at the current visit.

[4] Height measured at screening and at least 6 months prior (for growth velocity determination as well); for bone age, two assessments at least 6 months, but no more than 15 months apart, were required

Table 7: Frequency of vaginal bleeding days (worst-case scenario calculation) – Study 44, Full Analysis Set

	Faslodex N=30				
	Mean (SD)	**Median**	**Range**	**p-value[a]**	**2-sided 95% CI**
Frequency pre-treatment[b]	14.3 (13.6)	12.0	0; 42		
Frequency during treatment[c]	12.9 (38.6)	1.0	0; 201		
Change in frequency from pre-treatment to during treatment[d]	-1.5 (39.5)	-3.6	-42; 185	0.015	-10.1; 0.0

[a]Data were non-normally distributed, therefore p-value is for a Sign test of the median
[b]Number of bleeding days in prior 6 months, annualized
[c]Number of bleeding days during 12 months,
[d]Annualized
Source: CSR, Table 16

The median frequency of vaginal bleeding was 12 days and 1 day for pre-treatment and treatment periods, respectively, whilst the median change in frequency is -3.6 days (95% CI: -10.10, 0.00]; p=0.0146). The results of the Per Protocol analysis (median change = -3.6 days [95% CI: -10.10, 0.00]; p=0.0106; were consistent with the results in the Full Analysis Set.

Over the time period from the 6-month retrospective data collection through the 12-month study period:

- A total of 19 patients with baseline vaginal bleeding experienced a reduction in the frequency of annualized bleeding days on study treatment compared to baseline.
- 5 other patients did not have vaginal bleeding at baseline and did not experience vaginal bleeding on-treatment.

Two patients (E0003002 and E0081006) did not have vaginal bleeding at baseline but experienced vaginal bleeding on-treatment (2 and 10 annualized days, respectively). Patient E0003002 did not actually report vaginal bleeding on-treatment, rather they had missing diary card data, which were classified as bleeding days under the pre-defined worst-case scenario calculation.

There were 4 patients (E0010001, E0016001, E0035001 and E0051002) who had baseline bleeding and experienced an increased frequency of annualized vaginal bleeding days on treatment:

- Patient E0010001 was involved in a car accident and was unable to provide vaginal bleeding data for a prolonged period of the main study period; these missing days (201 annualized days) were classified as bleeding days under the pre-defined worst case scenario calculation. This patient did not report any actual

bleeding days on treatment; the patient was excluded from the Per Protocol analysis set due to the number of missing assessments.

- ***Reviewer's comment: The Per Protocol analysis set excludes this patient, as well as Patient E008001, who received sandostatin as a concomitant medication for excess growth hormone. As shown in Table 8, below, compared with the Full Analysis Set, mean frequency of vaginal bleeding days is lower (12.9 days for the Full Analysis Set vs. 6.5 days for the Per Protocol Set), and mean change in frequency of vaginal bleeding days compared to baseline is greater (-1.5 days for the Full Analysis Set vs. -7.0 days for the Per Protocol Set). Median values, however, are similar.***

Table 8: Frequency of vaginal bleeding days (worst-case scenario) – Study 44, Per Protocol Set

	Faslodex N=30				
	Mean (SD)	**Median**	**Range**	**p-value[a]**	**2-sided 95% CI**
Frequency pre-treatment[b]	13.6 (13.5)	9.0	0; 42		
Frequency during treatment[c]	6.5 (15.5)	0.9	0; 77		
Change in frequency from pre-treatment to during treatment[d]	-7.0 (17.8)	-3.6	-42; 53	0.01	-10.1; 0.0

[a]Data were non-normally distributed, therefore p-value is for a Sign test of the median
[b]Number of bleeding days in prior 6 months, annualized
[c]Number of bleeding days during 12 months, annualized
[d]Annualized
Source: CSR, Table 11.2.1.6

- Patient E0016001 had 28 annualized days of bleeding in the pre-treatment period and 34 annualized days of bleeding during the study treatment period.
- Patient E0035001 had 24 annualized days of bleeding in the pre-treatment period and 77 annualized days of bleeding during the study treatment period. The patient was withdrawn from study treatment at the investigators discretion; the reason given was condition under investigation worsened.
- Patient E0051002 had 6 annualized days of bleeding in the pre-treatment period and 8 annualized days of bleeding during the study treatment period.

Impact of best-case scenario assumptions for annualized episodes of vaginal bleeding

As previously mentioned, all pre-defined analyses of vaginal bleeding data were based on a worst-case scenario calculation, i.e., missing diary card days were counted as bleeding days. The Sponsor performed a number of post-hoc analyses to assess the impact of this approach by applying a best-case scenario calculation where missing diary card days are counted as non-bleeding days; this analysis is presented in Table 9 below.

Table 9: Frequency of vaginal bleeding days (best-case scenario) – Study 44, Full Analysis Set

	Faslodex N=30				
	Mean (SD)	**Median**	**Range**	**p-value[a]**	**2-sided 95% CI**
Frequency pre-treatment[b]	14.3 (13.6)	12.0	0; 42		
Frequency during treatment[c]	6.0 (15.1)	0.0	0; 77		
Change in frequency from pre-treatment to during treatment[d]	-8.4 (17.8)	-4.8	-42; 53	0.002	-16.0; 0.0

[a]Data were non-normally distributed, therefore p-value is for a Sign test of the median
[b]Number of bleeding days in prior 6 months, annualized
[c]Number of bleeding days during 12 months, annualized
[d]Annualized
Source: CSR, Table 11.2.1.6

As expected, applying a best-case scenario calculation, the reduction in frequency of vaginal bleeding is greater on-treatment and a higher proportion of patients experienced reduction or cessation of vaginal bleeding compared to the main analysis using a worst-case scenario calculation. Results for the Per Protocol Set were similar to the Full Analysis Set for the best-case scenario calculations.

6.1.4.2.2 Percentage of patients with baseline vaginal bleeding who experienced ≥50% reduction in the number of vaginal bleeding days on treatment compared to baseline

Table 10 shows the number of patients with baseline vaginal bleeding days who experienced ≥50% reduction in the number of vaginal bleeding days on treatment compared to baseline, for the Full Analysis Set, using a worst-case scenario calculation. As seen below, the majority of patients (73.9%) with baseline vaginal bleeding experienced a ≥50% reduction in annualized vaginal bleeding days over the study.

Table 10: Patients with ≥50% reduction in the frequency of vaginal bleeding (worst-case scenario calculation) – Study 44

	Faslodex N=30	
	n (%)	**95% CI**
Patients with baseline vaginal bleeding	23 (100)	
Patients with baseline vaginal bleeding and ≥ 50% reduction	17 (73.9)	51.6%; 89.8%

Source: CSR, Table 17

Impact of best-case scenario assumptions for patients with ≥ 50% reduction in frequency of vaginal bleeding

Table 11 shows the number of patients with baseline vaginal bleeding days who experienced ≥50% reduction in the number of vaginal bleeding days on treatment compared to baseline, for the Full Analysis Set, using a best-case scenario calculation.

Table 11: Patients with ≥50% reduction in the frequency of vaginal bleeding (best-case scenario calculation)– Study 44

	Faslodex N=30	
	n (%)	**95% CI**
Patients with baseline vaginal bleeding	23 (100)	
Patients with baseline vaginal bleeding and ≥ 50% reduction	18 (78.3)	56.3; 92.5

Source: CSR, Table 11.2.1.7

As shown above, applying a best-case scenario calculation, the percentage of patients with a ≥ 50% reduction in frequency of vaginal bleeding is slightly greater on-treatment compared to the main analysis using a worst-case scenario calculation.

6.1.4.2.3 Percentage of patients with baseline vaginal bleeding who experienced cessation of vaginal bleeding over a 6-month trial period and over the whole 12-month trial

Table 12 shows the number of patients with baseline vaginal bleeding who experienced cessation of vaginal bleeding days over a 6-month study period and over the whole 12-month study, for the Full Analysis Set, using a worst-case scenario calculation. As shown below, of 23 patients with baseline vaginal bleeding, 18 (78.3%) experienced cessation for at least 6 months (≥180 consecutive days) on treatment. A total of 8 patients (34.8%) with baseline vaginal bleeding experienced cessation of vaginal bleeding for the whole of the main study period (Month 0 to Month 12).

Table 12: Patients with cessation of vaginal bleeding days (worst-case scenario calculation) – Study 44

	Faslodex N=30	
	n (%)	**95% CI**
Number of patients with baseline vaginal bleeding	23 (100)	
Patients with baseline vaginal bleeding and cessation for first 6 months of treatment	8 (34.8)	16.4%; 57.3%
Patients with baseline vaginal bleeding and cessation for a 6-month period during the main study period	18 (78.3)	56.3%; 92.5%
Patients with baseline vaginal bleeding and cessation for the entire main study	8 (34.8)	16.4%; 57.3%

Source: CSR, Table 18

Impact of best-case scenario assumptions for patients with cessation of vaginal bleeding

Table 13 shows the number of patients with baseline vaginal bleeding who experienced cessation of vaginal bleeding days over a 6-month study period and over the whole 12-month study, for the Full Analysis Set, using a best-case scenario calculation.

Table 13: Patients with cessation of vaginal bleeding days (best-case scenario calculation) – Study 44

	Faslodex N=30	
	n (%)	**95% CI**
Number of patients with baseline vaginal bleeding	23 (100)	
Patients with baseline vaginal bleeding and cessation for first 6 months of treatment	11 (47.8)	26.8%; 69.4%
Patients with baseline vaginal bleeding and cessation for a 6-month period during the main study period	19 (82.6)	61.2%; 95.0%
Patients with baseline vaginal bleeding and cessation for the entire main study	11 (47.8)	26.8%; 69.4%

Source: CSR, Table 11.2.1.7

As shown above, applying a best-case scenario calculation, the percentage of patients with baseline vaginal bleeding who experienced cessation of menses (for either 6 months or the entire study) is slightly greater on-treatment compared to the main analysis using a worst-case scenario calculation. Results for the Per

6.1.4.3 Bone Age

6.1.4.3.1 Change in bone age advancement over a 6-month trial period and over the entire 12-month trial

Table 14 below summarizes bone age data (determined by blinded central read) at the Month 6 and Month 12/Final Visit and the rate of bone age advancement for the full analysis set.

In the pre-treatment period, the mean rate of annualized bone age advancement was nearly twice the chronological age advancement (bone age advancement/chronological age advancement = 1.99). On-treatment, the mean rate of bone age advancement was approximately equivalent to chronological age advancement (bone age advancement/chronological age advancement = 1.06).

Table 14: Bone age and rate of bone age advancement – Study 44

		Faslodex N=30				
		Mean (SD)	**Median**	**Range**	**p-value[a]**	**2-sided 95% CI**
Bone age (years)	**6 months prior to treatment**	7.1 (2.2)	7.8	1.3; 9.9		
	Screening	8.5 (2.0)	8.8	3.4; 11.0		
	Month 6	9.2 (1.9)	9.3	4.7; 11.6		
	Month 12/Final Visit	9.6 (1.8)	10.3	2.3; 11.6		
Rate of bone age advancement	**Pre-treatment**	2.0 (1.0)	1.84	0.4; 5.2		
	Month 0 to Month 12	1.1 (0.7)	1.0	-0.02; 3.5		
	Month 0 to Month 6[b]	1.2 (0.9)	1.0	-0.5; 3.5		
	Month 6 to Month 12	0.9 (0.9)	0.5	-0.7; 2.8		
	Change from pre-treatment to during	-0.9 (1.3)	-0.8	-5.2; 1.2	0.0007	-1.4; -0.4
	Change from pre-treatment to 1st 6 months	-0.8 (1.5)	-0.9	-5.6; 1.3	0.005	-1.4; -0.3
	Change from pre-treatment to 2nd 6 mos.[b]	-1.1 (1.4)	-1.1	-4.7; 1.2	0.0002	-1.6; -0.6

[a]From a 2-sided t-test at the 0.05 significance level
[b]n=29
Source: CSR, Table 19

The data were found to be normally distributed and were therefore analyzed using a 2-sided t-test. There was a statistically significant reduction in the rate of bone age advancement during the 12-month study period compared to the pre-treatment period (mean change = -0.93 [95% CI = -1.43, -0.43]; p=0.0007). Furthermore, the reduction in the rate of bone age advancement was statistically significant for both the first 6-month study period (mean change = -0.83 [95% CI = -1.39, -0.26]; p=0.0054) and the second 6-month study period (mean change= -1.10 [95% CI=-1.63, -0.58]; p=0.0002), compared to baseline, indicated a progressive reduction in bone age advancement during the 12-month treatment period.

6.1.4.4 Growth velocity

6.1.4.4.1 Change in annualized growth velocity over a 6-month trial period and over the entire 12-month trial

Table 15 below summarizes growth velocity data (in cm/year and in Z-score) pre-treatment; during treatment (Months 0-12), during the first 6 months of treatment (Months 0-6) and during the second 6 months of treatment (Months 6-12).

Table 15: Growth Velocity – Study 44

		Faslodex N=30				
		Mean (SD)	**Median**	**Range**	**p-value[a]**	**2-sided 95% CI**
Growth velocity (cm/year)	**Pre-treatment**	8.8 (3.5)	9.4	2.1; 16.4		
	Month 0 to 12	7.4 (2.5)	7.1	3.3; 13.3		
	Month 0 to 6	7.1 (3.1)	6.9	1.7; 15.9		
	Month 6 to 12	7.9 (4.1)	6.8	2.5; 23.5		
	Change from pre-treatment to during	-1.4 (3.7)	-1.7	-8.4; 8.6	0.05	-2.75; 0.0
	Change from pre-treatment to 1st 6 months	-1.7 (4.4)	-2.9	-8.2; 8.8	0.04	-3.3; -0.05
	Change from pre-treatment to 2nd 6 mos.	-0.8 (4.5)	-1.4	-9.0; 12.3	0.3	-2.5; 0.85
Growth velocity (Z-score)	**Pre-treatment**	2.4 (3.3)	2.7	-4.3; 7.5		
	Month 0 to 12	1.2 (2.2)	1.2	-3.0; 5.4		
	Month 0 to 6	0.8 (2.8)	0.6	-4.6; 6.4		
	Month 6 to 12	1.7 (3.3)	1.1	-4.0; 11.4		
	Change from pre-treatment to during	-1.1	-1.5	-8.6; 9.6	0.14	-2.7; .04
	Change from pre-treatment to 1st 6 months	-1.6 (4.6)	-3.1	-9.4; 9.5	0.07	-3.3; .01
	Change from pre-treatment to 2nd 6 mos.	-0.6 (4.6)	-0.9	-9.3; 9.5	0.4	-2.4; 1.1

[a]From a 2-sided t-test at the 0.05 significance level
Source: CSR, Table 20

The data were found to be normally distributed and were therefore analyzed using a 2-sided t-test. There was a numerical reduction in growth velocity on study treatment compared to pre-treatment, when measured in either cm/year or Z-score. The reduction in growth velocity (cm/year) from the pre-treatment period to the first 6-months of study treatment was statistically significant (mean change = -1.7 [95% CI: -3.29, -0.05]; p=0.0442).

6.1.5 Analysis of Secondary Endpoint(s)

This section will review those endpoints the Sponsor has characterized as "additional assessments."

6.1.5.1 Change in mean uterine volume from baseline by ultrasound

Exposure to estrogens results in an increase in uterine volume; therefore, change in uterine volume can be used to assess overall estrogen exposure in this patient population. Table 16 below summarizes the mean uterine volume at the screening visit and at Month 6 and Month 12/Final Visit, for the Full Analysis Set.

Table 16: Uterine volume – Study 44

		Faslodex N=30			
		n	**Mean (SD)**	**Median**	**Range**
Uterine Volume (cc)	**Screening visit**	29	8.2 (5.0)	6.6	2.2; 20.5
	Month 6	30	6.0 (3.3)	4.6	2.4; 15.3
	Month 12/ Final Visit	28	5.5 (2.6)	4.4	2.6; 12.9
	Change: screening to Month 6	29	-2.4 (5.0)	-1.1	-15.1; 6.0
	Change: Month 6 to Month 12 /Final Visit	28	-0.5 (3.6)	-0.1	-11.8; 4.5
	Change: screening to Month 12/ Final Visit	27	-2.4 (4.2)	-2.4	-10.2; 6.6

Source: CSR, Table 21

As seen above, there was some evidence of non-normality in the distribution of the data. There was a numerical reduction in mean uterine volume at Month 12 / Final Visit compared to baseline (mean [SD] change = -2.38 [4.240]); there was also numerical

reduction in median uterine volume at Month 12 / Final Visit compared to baseline (median [range] change = -2.44 [-10.20 to 6.56]).

Fourteen patients had increases in uterine volume from the screening visit to Month 12. As a subanalysis to determine whether an increase in ovarian volume correlates with the results of the study endpoints, I have looked at the vaginal bleeding and bone age data for these individual patients. Of these 14, only 2 (14%) had increases in the number of vaginal bleeding days (range 10-185 days), while from baseline to Month 12, 3 (21%) had an increase in change in bone age from pre-treatment (range 0.2-0.47 years). Therefore, I conclude there is no strong clinical correlation between change in uterine volume and change in either number of vaginal bleeding days or bone age advancement.

6.1.5.2 Change in mean ovarian volume from baseline by ultrasound

Similar to uterine volume, exposure to estrogens results in an increase in ovarian volume, and change in ovarian volume can be used to assess overall estrogen exposure. Table 17 below summarizes the mean ovarian volume at the screening visit and at Month 6 and Month 12/Final Visit, for the Full Analysis Set.

Table 17: Ovarian volume – Study 44

		Faslodex N=30			
		n	**Mean (SD)**	**Median**	**Range**
Ovarian Volume (cc)	**Screening visit**	26	4.8 (6.8)	2.5	0.8; 32.6
	Month 6	28	3.4 (3.0)	2.1	0.4; 12.8
	Month 12/ Final Visit	24	4.6 (3.3)	3.8	0.6; 11.8
	Change: screening to Month 6	25	-1.2 (7.2)	0.1	-27.6; 8.0
	Change: Month 6 to Month 12 /Final Visit	24	1.1 (3.5)	0.8	-4.1; 10.0
	Change: screening to Month 12/ Final Visit	21	-0.4 (7.5)	1.0	-22.3; 10.4

Source: CSR, Table 22

Although there was some evidence of non-normality in the distribution of the data, there were no clinically meaningful changes in mean ovarian volume at Month 12/Final Visit compared to baseline.

15 patients had increases in ovarian volume from the screening visit to Month 12. Of these 14, only 1 (6.7%) had an increase in the number of vaginal bleeding days (10 days), and similarly from baseline to Month 12, only 1 (6.7%) had an increase in change in bone age from pre-treatment (0.2 years). Therefore, I conclude there is no strong clinical correlation between change in uterine volume and change in either number of vaginal bleeding days or bone age advancement.

6.1.5.3 Hormone measurements: FSH, LH, TSH, free T4, serum estradiol, testosterone

Table 18 shows levels of FSH, LH, TSH, free T4, serum estradiol, and testosterone at the Screening Visit, Month 6 and Month 12/Final Visit for the Fully Analysis Set.

Table 18: Hormone measurements – Study 44

		Faslodex N=30			
	Visit	**n**	**Mean (SD)**	**Median**	**Range**
Free T4 (pmol/L)	**Screening**	30	14.4 (2.5)	14.7	8.6; 20.4
TSH (mU/L)	**Screening**	30	2.4 (3.3)	1.5	0.03; 18.0
Estradiol (pmol/L)	**Screening**	30	20.5 (25.6)	9.2	9.2; 95.4
	Month 6	29	36.1 (104.9)	9.2	9.2; 575.1
	Month 12/ Final Visit	26	26.0 (30.7)	9.6	9.2; 114.1
LH (IU/L)	**Screening**	30	0.8 (1.0)	0.5	0.1; 4.3
	Month 6	29	0.1 (0.02)	0.1	0.1; 0.2
	Month 12/ Final Visit	28	0.1 (0.04)	0.1	0.1; 0.3
FSH (IU/L)	**Screening**	30	3.9 (5.4)	2.0	0.3; 25.1
	Month 6	29	0.8 (0.8)	0.5	0.3; 3.6
	Month 12/ Final Visit	29	1.1 (1.0)	0.6	0.3; 3.8

Testosterone (nmol/L)	**Screening**	30	0.5 (.02)	0.5	0.4; 1.0
	Month 6	29	0.6 (0.2)	0.5	0.4; 1.1
	Month 12/ Final Visit	28	0.7 (0.3)	0.7	0.4; 1.3

Source: CSR, Table 23

Levels of FSH and LH were reduced on-treatment compared to screening; the reason for this change is unclear. There were no clinically meaningful changes in estradiol or testosterone on-treatment compared to baseline. Estradiol reference range specific to girls with MAS are not available, but the median values observed in this study are consistent with what might be expected in a population of pre-pubertal girls (ie, <20 pg/ml).

6.1.5.4 Change in Tanner stage of breast and pubic hair from baseline to Month 12/Final Visit

Table 19 summarizes the change in Tanner staging of breast and pubic hair for the Full Analysis Set.

Table 19: Tanner staging – Study 44

Tanner Staging		**Faslodex N=30**			
	Visit	**n**	**Mean (SD)**	**Median**	**Range**
Breast	**Month 0**	30	2.8 (0.9)	2.0	1; 4
	Month 12/ Final Visit	30	2.7 (1.1)	3.0	1; 5
	Change from Month 0 to Month 12/ Final Visit	30	-0.2 (0.9)	0.0	-3; 2
Pubic Hair	**Month 0**	30	1.4 (0.8)	1.0	1; 4
	Month 12/ Final Visit	30	1.4 (0.6)	1.0	1; 3
	Change from Month 0 to Month 12/ Final Visit	30	-0.1 (0.6)	0.0	-2; 1

Source: CSR, Table 24

Analysis of the data distribution for the Tanner endpoints found that they are non-normally distributed. For breast and pubic Tanner stage, the median change from Month 0 to Month 12 / Final Visit was 0.0 (range –3 to 2 for breast, -2 to 1 for pubic).

Table 20 summarizes the frequency in transition of breast and pubic Tanner Staging, from baseline to Month 12 / Final Visit, for the Full Analysis Set.

Table 20: Frequency in transition of Tanner staging – Study 44

		Faslodex N=30				
	Baseline	**Stage 1**	**Stage 2**	**Stage 3**	**Stage 4**	**Stage 5**
Breast	**Stage 1**	3	0	0	0	0
	Stage 2	0	2	0	0	0
	Stage 3	2	1	14	2	1
	Stage 4	1	0	2	2	0
	Stage 5	0	0	0	0	0
Pubic Hair	**Stage 1**	19	1	0	0	0
	Stage 2	1	4	1	0	0
	Stage 3	1	2	1	0	0
	Stage 4	0	0	0	0	0
	Stage 5	0	0	0	0	0

Source: CSR, Table 25

24/30 patients [80.0%], respectively) experienced no change in Tanner staging at Month 12 / Final Visit compared to baseline.

A total of 6 patients (20.0%) had a lower breast Tanner stage at Month 12 / Final Visit compared to baseline; 3 patients (10.0%) had a higher breast Tanner stage at Month 12 / Final Visit compared to baseline. Four (13.3%) patients had a lower pubic Tanner stage at Month 12 / Final Visit compared to baseline; 2 patients (6.7%) had a higher pubic Tanner stage at Month 12 / Final Visit compared to baseline.

6.1.5.5 Change in Predicted adult height from baseline to Month 12/Final Visit

Table 21 summarizes the predicted adult height (PAH), using the method of Bayley and Pinneau, at the screening visit and at the Month 12/ Final visit for the Full Analysis Set.

Table 21: Predicted adult height – Study 44

Predicted adult height (cm)	Faslodex N=30			
	N	Mean (SD)	Median	Range
Screening visit	17	163.0 (6.9)	163.0	149.0; 174.4
Month 12/Final Visit	17	163.5 (6.3)	161.7	149.5; 178.1
Change from screening to Month 12/Final Visit	17	0.5 (4.1)	1.9	-8.4; 5.7
Percent change from screening to Month 12/Final Visit	17	0.4 (2.5)	1.2	-5.0; 3.7

Source: CSR, Table 26

There were no clinically meaningful changes in PAH on-treatment compared to pre-treatment. The mean (SD) change in PAH at Month 12 / Final visit vs baseline was +0.5 cm (4.10), which corresponds to a 0.4% (2.48) increase in PAH.

6.1.6 Other Endpoints

None.

6.1.7 Subpopulations

The Sponsor has not included any data regarding subpopulation analyses with this submission.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

Both efficacy and PK data are available for fulvestrant 250 mg monthly in postmenopausal women with metastatic breast cancer after progression on antiestrogen therapy (Studies 0020/21). These studies included a 125 mg monthly dose regimen. In deciding on a starting dose, the Sponsor assumed that the dose of 250 mg monthly corresponds to a dose of approximately 4 mg/kg, and the dose of 125 mg corresponds to a dose of 2 mg/kg.

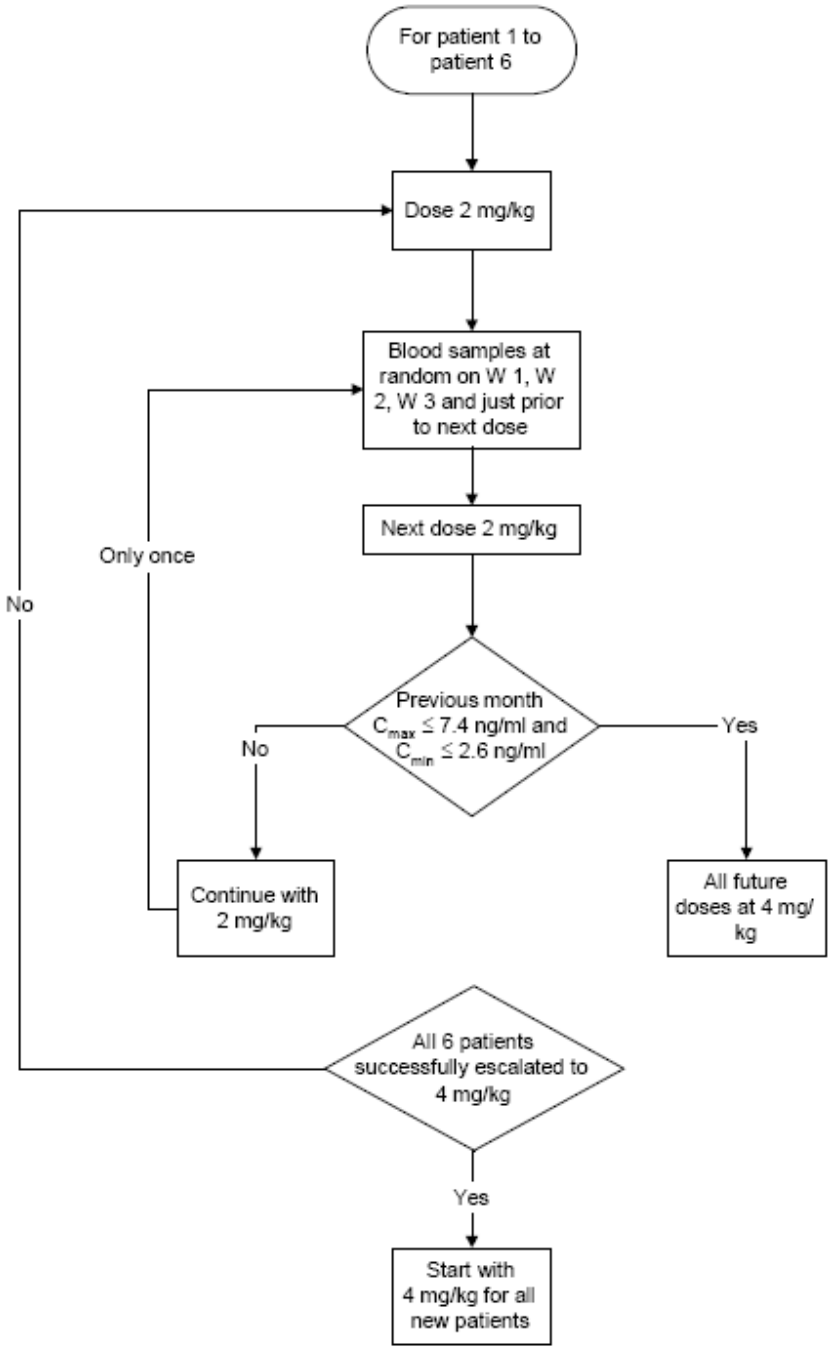
Per the pre-specified analysis plan, the Sponsor based its dose selection for the safety/efficacy trial on the initial findings from the PK study. For the first 6 patients, the first and second dose of fulvestrant was 2 mg/kg. For the third and subsequent doses, these patients received either 2 mg/kg or 4 mg/kg depending on whether the PK criteria specified in the CSP were met. For subsequent patients, the initial dose was to be either 2 mg/kg (with the option to increase during the trial to 4 mg/kg) or 4 mg/kg depending upon the outcome of the first 6 patients.

During Study 44, 10 patients received an initial fulvestrant dose of 2 mg/kg. Based on the results, the dose was escalated to 4 mg/kg in the third month in all 10 patients based on

plasma fulvestrant concentrations. The remaining 20 patients started at a dose of 4 mg/kg monthly.

See Figure 4 below for a schematic representation of the dosing schedule:

Figure 4: Dosing schedule flow chart



W:Week.
Note that patients entering the study before the PK data from the first 6 patients have been reviewed started on 2 mg/kg. Once the first 6 patients were successfully escalated to 4 mg/kg, any other patients who started on 2 mg/kg were also escalated and any new patients entering the study started on 4 mg/kg.
Source: CSR, Figure 3

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

Not applicable for this review.

6.1.10 Additional Efficacy Issues/Analyses

Comparison of efficacy data for Faslodex with other drugs (Arimidex, Nolvadex)

A cross-study comparison of Study 44 with other studies in girls with MAS is presented in Table 22 below. In Study 44, Faslodex demonstrated greater efficacy than was observed with Arimidex (in Study 46 of its sNDA for treatment of PPP in girls with MAS), for a number of endpoints, most notably endpoints relating to vaginal bleeding. The efficacy of Faslodex appears to be comparable to that observed for Nolvadex (in Study 13 of its NDA) and importantly there is no evidence that Faslodex is associated with the estrogenic side effects (increased uterine and ovarian volume) observed with Nolvadex. The lack of an increase in uterine and ovarian volumes following Faslodex treatment is consistent with its mechanism of action and the absence of any known partial estrogenic activity.

Table 22: Comparison of efficacy findings – Faslodex vs. Arimidex vs. Nolvadex

Endpoint		**Faslodex N=30**	**Arimidex N=28**	**Nolvadex N=28**
Vaginal bleeding	**Median change in annualized bleeding days (95% CI)**	-3.6 (-10.1, 0.0)	1.9 (-6.0; 14.26)	Not calculated
	% with baseline bleeding who had ≥50% reduction (95% CI)	73.9% (51.6%; 89.8%)	28.0% (12.1%; 49.4%)	66.7% (43.0%; 85.4%)
	% with baseline bleeding who had cessation for 6 months (95% CI)	78.3% (56.3%; 92.5%)	40.0% (21.1%; 61.3%)	61.9% (38.4%; 81.9%)
Bone age	**Mean change in rate of advancement from pre-treatment (95% CI)**	-0.93 (-1.43; -0.43)	-0.25 (-0.65; 0.16)	-0.54 (NC)
Growth Velocity	**Mean change (cm/year) (95% CI)**	-1.4 (-2.75; 0.0)	-1.4 (-2.8; -0.1)	-1.7 (NC)
Tanner Stage	**Breast stage: mean change**	-0.2 (0.9)	0.1 (0.7)	NC

	Pubic hair: mean change	-0.1 (0.6)	0.4 (0.6)	NC
Predicted adult height	**Mean % change baseline to month 12 (SD)**	0.4 (2.5)	0.6 (2.4)	0.8 (2.4)
Average ovarian volume (cc)	**Mean change baseline to month 12 (SD)**	-0.4 (7.5)	-0.4 (4.9)	1.1 (11.3)
Uterine volume (cc)	**Mean change baseline to month 12 (SD)**	-2.4 (4.2)	1.2 (7.5)	12.0 (9.2)

Source: Sponsor's clinical overview, Table 2

7 Review of Safety

Safety Summary

The safety observations made during Study 44 in MAS patients with PPP are in general consistent with those known to be associated with Faslodex in women with estrogen-receptor positive breast cancer. Although 90% of patients reported an AE while on treatment (Table 23 below), in general these were mild in severity. Nine (30.0%) patients reported an SAE, most of which appeared to be background events. There were no deaths reported in Study 44. There were no discontinuations of study drug due to an AE.

Table 23: Frequency of patients with adverse events – Study 44

	Faslodex N=30
	Number (%) of patients
Number of patients with at least one AE	27 (90.0)
Number of patients with at least one treatment-related AE	8 (26.7)
Number of patients with at least one SAE	9 (30.0)
Number of patients with at least one treatment-related SAE	0
Number of patients who discontinued due to an AE	0
Number of deaths	0

Note: Patients may be included in more than one category
Source: CSR, Table 29

Most of the treatment-related adverse events that occurred with Faslodex were adverse reactions known to occur in association with the drug (e.g. injection site reactions, extremity pain, gastrointestinal disorders). The remainders of the TEAEs appear to be background adverse events.

A number of conditions were identified as drug-specific safety concerns in the FDA Written Request. These included: injection site reactions, gastrointestinal symptoms, headache, urinary tract infection, and pharyngitis. Overall, the majority of these AEs were of mild intensity, and the incidence was consistent with the known safety profile of Faslodex and the pediatric population under investigation.

In conclusion, there were no new safety concerns arising from this study.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The safety review covers Study 44 only. Only adverse events (AEs) that occurred on treatment are summarized. Any patients recording multiple occurrences of an AE under one treatment were only counted once in the AE category for that treatment.

7.1.2 Categorization of Adverse Events

Adverse events were coded with the Medical Dictionary for Regulatory Activities (MedDRA) by system organ class and preferred term. In the CSR, adverse events were categorized by intensity as "mild," "moderate," or "severe" as follows:

- **Mild:** awareness of sign or symptom, but easily tolerated.
- **Moderate:** discomfort sufficient to cause interference with normal activities.
- **Severe:** incapacitating, with inability to perform normal activities.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

Not applicable, as only one study has been submitted.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

Table 24 summarizes the duration of study treatment (defined as the number of days from the date of first dose until the date of the last visit or until the Month 12 visit) and the compliance rate for all patients, for the Full Analysis Set and for all patients who completed the Month 12 visit.

The mean duration of study treatment was approximately 360 days. This varied slightly between individual patients based on the exact timings of fulvestrant injection visits during the main treatment period (for example, one patient had a study duration of 421, explained by the wide range of acceptable visit windows). Compliance was 100% during the main study period, ie, each patient received all protocol-defined injections up until the point they either withdrew from the study (Patient E0035001; see Section 6.1), or completed the main study period.

Table 24: Duration of fulvestrant treatment and percent compliance – Study 44

	Duration of study treatment (days)		% Compliance	
	Full analysis set N=30	**Patients who completed Mo. 12 N=29**	**Full analysis set N=30**	**Patients who completed Mo. 12 N=29**
Mean (SD)	355.5 (38.5)	361.2 (22.8)	100 (0)	100 (0)
Median	358	359	100	100
Range	190; 421	336; 421	100; 100	100; 100

Source: CSR, Table 28

Consistent with the dosing schedule described in Section 6.1.8, the first 10 patients enrolled in the study received an initial dose of 2 mg/kg. Based on PK data from the their first month of treatment, each patient was then escalated to a dose of 4 mg/kg and all subsequent patients receive a dose of 4 mg/kg, starting at their first study visit.

7.2.2 Explorations for Dose Response

Although a subset of patients started at a dose of 2 mg/kg, all subjects eventually received a dose of 4 mg/kg. All safety evaluations in this supplement refer to the 4 mg/kg dose.

7.2.3 Special Animal and/or In Vitro Testing

Not applicable to this application.

7.2.4 Routine Clinical Testing

Routine clinical testing was adequate.

7.2.5 Metabolic, Clearance, and Interaction Workup

The Sponsor's testing of fulvestrant's metabolism, clearance, and potential for interaction has already been discussed in Section 4.4.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

There are no other drugs in this class currently available

7.3 Major Safety Results

7.3.1 Deaths

There were no deaths reported during Study 44.

7.3.2 Nonfatal Serious Adverse Events

All patients who had a serious adverse event (SAE), along with details pertaining to their respective SAEs, are listed in Table 25 below:

Table 25: Listing of all patients who had a serious adverse event – Study 44

Patient	Time to event (days)[a]	Start date (yy-mm-dd)	Stop date (yy-mm-dd)	Serious adverse event (preferred term)	Serious adverse event (investigator text)	Severity	Study treatment related	Outcome
E0002001	22	2006-03-09	2006-03-11	Dehydration	Dehydration	Severe	No	Resolved
	19	2006-03-06	2006-03-10	Pyrexia	Fever	Severe	No	Resolved
	19	2006-03-06	2006-03-11	Viral infection	Viral infection	Severe	No	Resolved
E008001	29	2006-10-16	2006-10-18	Neuromyopathy	Neuromuscular disorder	Moderate	No	Resolved
	29	2006-10-16	2007-03-02	Tic	Tics	Moderate	No	Resolved
E0035001	15	2008-04-04	2008-06-03	Femur fracture	Femur fracture right	Severe	No	Resolved
E0041002	155	2007-11-30		Bone pain	Increased bone pain	Moderate	No	Continuing
E0051002	132	2007-11-26		Ovarian cyst	Left ovarian cyst	Mild	No	Continuing
E0061006	92	2008-11-14	2008-11-26	Bronchitis	Acute bronchitis	Moderate	No	Resolved
E0081001	117	2008-01-11	2008-01-12	Arthralgia	Hip pain (fell from chair)	Severe	No	Resolved
	117	2008-01-11	2008-01-12	Pain in extremity	Left leg pain (fell off / from chair)	Severe	No	Resolved
E0081002	228	2008-05-01	2008-11-10	Dizziness	Feeling faint	Moderate	No	Resolved
E0081005	70	2008-10-26	2008-10-30	Wheezing	Viral wheeze	Severe	No	Resolved

[a] Number of days from start of study medication to start date of adverse event.

Source: CSR, Table 32

There were no SAEs reported by more than 1 patient. The SAEs reported in this study were consistent with the patient population and condition under investigation. None of the SAEs were considered by the investigator to be causally related to fulvestrant treatment.

7.3.3 Dropouts and/or Discontinuations

There were no discontinuations of study drug due to an AE reported in Study 44. One patient (E0035001) withdrew due a worsening of the condition under investigation.

7.3.4 Significant Adverse Events

Significant adverse events were described in Section 7.3.2.

7.3.5 Submission Specific Primary Safety Concerns

This section contains a detailed discussion of special safety concerns. The Sponsor identified injection site reactions, gastrointestinal symptoms, headache, urinary tract infections and pharyngitis as drug-specific safety concerns in the Pediatric Written Request.

7.3.5.1 Injection site reactions

AEs related to site reactions that were reported by the Sponsor included: injection site inflammation, injection site pain, injection site reaction, injection site hematoma, injection site pruritis and injection site rash. The frequency of these AEs is shown in Table 26 below:

Table 26: Frequency of patients with injection site reactions – Study 44

Adverse Event	Faslodex N=30
	Number (%) of patients
Injection site inflammation	4 (13.3)
Injection site pain	2 (6.7)
Injection site reaction	2 (6.7)
Injection site hematoma	1 (3.3)
Injection site pruritis	1 (3.3)
Injection site rash	1 (3.3)

Source: CSR, Table 11.3.2.2

Of these site reactions, the investigator considered all causally-related to study treatment. None was considered severe in intensity.

7.3.5.2 Gastrointestinal symptoms

AEs related to gastrointestinal symptoms that were reported by the Sponsor included: abdominal pain, upper abdominal pain, nausea, vomiting, and diarrhea. The frequency of these AEs is shown below in Table 27:

Table 27: Frequency of patients with injection site reactions – Study 44

Adverse Event	Faslodex N=30
	Number (%) of patients
Abdominal pain	8 (26.7)
Vomiting	8 (26.7)
Diarrhea	5 (16.7)
Upper abdominal pain	4 (13.3)
Nausea	2 (6.7)
Constipation	1 (3.3)

Source: CSR, Table 11.3.2.2

Of these site reactions, the majority were not considered by the investigator to be causally related to fulvestrant treatment, with the exception of 2/8 patients (25%) with abdominal pain and 1/8 patients (12.5%) with vomiting.

7.3.5.3 Headache

The investigator reported 8 patients (26.7%) as having developed headaches while on fulvestrant treatment. None of these cases was considered by the investigator to be causally-related to treatment.

7.3.5.4 Urinary tract infection

The investigator reported 3 patients (10%) as having developed urinary tract infections while on fulvestrant treatment. None of these cases was considered by the investigator to be causally-related to treatment.

7.3.5.5 Pharyngitis

A number of patients reported AEs related to pharyngitis, including: nasopharyngitis (4 patients, 13.3%); pharyngitis (2, 6.7%), and streptococcal pharyngitis (2, 6.7%). None of these events were considered by the investigator to be causally-related to fulvestrant treatment.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

A summary of common AEs that occurred during Study 44 and were reported by ≥2 patients is presented in Table 28 below:

Table 28: Summary of adverse events occurring during the main study period, reported by ≥2 patients – Study 44

MedDRA system organ class[a]	Number (%) of patients[b]			
Preferred term	Fulvestrant (N=30)			
	Total	Maximum severity		
		Mild	Moderate	Severe
Ear and labyrinth disorders				
Ear pain	4 (13.3)	4 (13.3)	0	0
Gastrointestinal disorders				
Abdominal pain	8 (26.7)	5 (16.7)	2 (6.7)	1 (3.3)
Vomiting	8 (26.7)	6 (20.0)	2 (6.7)	0
Diarrhoea	5 (16.7)	4 (13.3)	1 (3.3)	0
Abdominal pain upper	4 (13.3)	4 (13.3)	0	0
Toothache	3 (10.0)	3 (10.0)	0	0
Nausea	2 (6.7)	2 (6.7)	0	0
General disorders and administration site conditions				
Pyrexia	14 (46.7)	11 (36.7)	2 (6.7)	1 (3.3)
Injection site inflammation	4 (13.3)	2 (6.7)	2 (6.7)	0
Fatigue	2 (6.7)	2 (6.7)	0	0
Injection site pain	2 (6.7)	2 (6.7)	0	0
Injection site reaction	2 (6.7)	2 (6.7)	0	0
Infections and infestations				
Rhinitis	6 (20.0)	6 (20.0)	0	0
Upper respiratory tract infection	5 (16.7)	5 (16.7)	0	0
Nasopharyngitis	4 (13.3)	3 (10.0)	1 (3.3)	0
Bronchitis	3 (10.0)	2 (6.7)	1 (3.3)	0
Ear infection	3 (10.0)	2 (6.7)	1 (3.3)	0
Gastroenteritis	3 (10.0)	2 (6.7)	1 (3.3)	0
Tonsillitis	3 (10.0)	2 (6.7)	1 (3.3)	0
Urinary tract infection	3 (10.0)	2 (6.7)	1 (3.3)	0
H1N1 Influenza	2 (6.7)	2 (6.7)	0	0
Otitis Media	2 (6.7)	2 (6.7)	0	0
Pharyngitis	2 (6.7)	2 (6.7)	0	0
Pharyngitis streptococcal	2 (6.7)	2 (6.7)	0	0

Sinusitis	2 (6.7)	2 (6.7)	0	0
Vaginal infection	2 (6.7)	2 (6.7)	0	0
Varicella	2 (6.7)	1 (3.3)	1 (3.3)	0
Metabolism and nutrition disorders				
Decreased appetite	3 (10.0)	3 (10.0)	0	0
Musculoskeletal and connective tissue disorders				
Pain in extremity	5 (16.7)	4 (13.3)	0	1 (3.3)
Bone pain	3 (10.0)	2 (6.7)	1 (3.3)	0
Arthralgia	2 (6.7)	1 (3.3)	0	1 (3.3)
Neck pain	2 (6.7)	2 (6.7)	0	0
Nervous system disorders				
Headache	8 (26.7)	7 (23.3)	1 (3.3)	0
Lethargy	2 (6.7)	2 (6.7)	0	0
Respiratory, thoracic and mediastinal disorders				
Cough	7 (23.3)	7 (23.3)	0	0
Oropharyngeal pain	4 (13.3)	4 (13.3)	0	0
Productive cough	2 (6.7)	2 (6.7)	0	0
Skin and subcutaneous tissue disorders				
Rash	3 (10.0)	3 (10.0)	0	0
Eczema	2 (6.7)	2 (6.7)	0	0
Vascular disorders				
Hot flush	2 (6.7)	2 (6.7)	0	0

[a] Adverse events are included if they started during study treatment or within 60 days of the last day of study treatment. A patient may have had more than one AE.
[b] If patients experienced the same event on more than one occasion, the most severe intensity is summarized.

Source: CSR, Table 30

The most commonly reported AEs were pyrexia (14 patients, 46.7%), abdominal pain, vomiting and headache (8 patients, 26.7% each). The majority of AEs were reported as being of mild intensity.

Table 29 lists the treatment-related Adverse Events (TEAEs), as determined by the investigator, that occurred during the main study period of Study 44.

Table 29: Treatment-related adverse events during the main study period – Study 44

Adverse Event	Faslodex N=30
	Number (%) of patients
Injection site inflammation	4 (13.3)
Abdominal pain	2 (6.7)
Injection site pain	2 (6.7)
Injection site reaction	2 (6.7)
Contusion	1 (3.3)
Tachycardia	1 (3.3)
Hot flush	1 (3.3)
Injection site hematoma	1 (3.3)
Injection site pruritis	1 (3.3)
Injection site rash	1 (3.3)
Extremity pain	1 (3.3)
Vomiting	1 (3.3)

Source: CSR, Table 31

A total of 8 patients (26.7%) reported an AE that the investigator considered possibly related to fulvestrant treatment. The causally related AEs reported in this study were consistent with the known safety profile of fulvestrant.

7.4.2 Laboratory Findings

Hematology
A complete blood count (CBC) assessment was performed for each patient at the screening visit (see Table 27, below), but not during the treatment period. There were no clinically meaningful abnormalities in CBC results in any patients at the time of evaluation.

Serum liver chemistry tests
Table 30 below shows the serum liver chemistry tests at the screening and Month 12/ Final Visit the Full Analysis Set.

Table 30 Serum liver chemistry values – Study 44

		Faslodex N=30			
	Visit	**n**	**Mean (SD)**	**Median**	**Range**
ALT (U/L)	**Screening**	30	20.3 (10.7)	16.0	10; 56
	Month 12/ Final Visit	28	21.5 (12.7)	18.0	9; 77
AST (U/L)	**Screening**	30	28.0 (7.0)	26.5	19; 48
	Month 12/ Final Visit	28	27.6 (8.4)	25.5	18; 59

Source: CSR, Table 33

Hormone measurements: FSH, LH, TSH, free T4, serum estradiol, testosterone
See Section 6.1.5.3 for data related to hormone levels in Study 44. No specific safety concerns arose from evaluation of these data.

7.4.3 Vital Signs
Data relating to vital signs were not routinely collected for patients in this study.

7.4.4 Electrocardiograms (ECGs)
Data relating to vital signs and ECG were not routinely collected for patients in this study.

7.4.5 Special Safety Studies/Clinical Trials
No information regarding special safety studies was included in this submission.

7.4.6 Immunogenicity
No information regarding immunogenicity was included in this submission.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events
Not applicable, since Study 44 only evaluated the clinical effect of the 4 mg/kg dose of FASLODEX.

7.5.2 Time Dependency for Adverse Events
No time dependency for adverse events was noted.

7.5.3 Drug-Demographic Interactions
All patients enrolled in Study 44 were girls between the age of 1-12 years. While baseline patient characteristics, including age, race, and ethnicity, have been listed and summarized, the demographics of the enrolled population make it impossible to comment on the effect of these categories on fulvestrant activity.

7.5.4 Drug-Disease Interactions
From the approved Faslodex label:

"In the advanced breast cancer trials, fulvestrant concentrations in women with estimated creatinine clearance as low as 30 mL/min were similar to women with normal creatinine."

"Fulvestrant is metabolized primarily in the liver. Subjects with severe hepatic impairment (Child-Pugh C) have not been evaluated. Modeled intramuscular mean steady state plasma concentrations of fulvestrant in subjects with Child-Pugh category A and B hepatic impairment fall within the upper range of concentrations expected for patients with normal hepatic function given the intramuscular formulation. In clinical trials in patients with locally advanced or metastatic breast cancer, pharmacokinetic data were obtained following administration of a 250 mg dose of Faslodex to patients with alanine aminotransferase concentration greater than the upper limit of the normal range [ULN] but less than twice the ULN. The safety profile was similar to that seen in patients with no hepatic impairment. Safety and efficacy have not been evaluated in patients with moderate to severe hepatic impairment."

7.5.5 Drug-Drug Interactions
See Dr. Jaya Vaidyanathan's Clinical Pharmacology review for details.

From the approved Faslodex label:

"There are no known drug-drug interactions. Fulvestrant does not significantly inhibit any of the major CYP isoenzymes, including CYP 1A2, 2C9, 2C19, 2D6, and 3A4 *in vitro*, and studies of co-administration of fulvestrant with midazolam indicate that therapeutic doses of fulvestrant have no inhibitory effects on CYP 3A4 or alter blood

levels of drug metabolized by that enzyme. Although fulvestrant is partly metabolized by CYP 3A4, a clinical study with rifampin, an inducer of CYP 3A4, showed no effect on the pharmacokinetics of fulvestrant. Also results from a healthy volunteer study with ketoconazole, a potent inhibitor of CYP3A4, indicated that ketoconazole had no effect on the pharmacokinetics of fulvestrant and dosage adjustment is not necessary in patients co-prescribed CYP 3A4 inhibitors or inducers."

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

From the approved Faslodex label:

"A two-year carcinogenesis study was conducted in female and male rats, at intramuscular doses of 15 mg/kg/30 days, 10 mg/rat/30 days and 10 mg/rat/15 days. These doses correspond to approximately 1-, 3-, and 5-fold (in females) and 1.3-, 1.3-, and 1.6-fold (in males) the systemic exposure [AUC0-30 days] achieved in women receiving the recommended dose of 250 mg/month. An increased incidence of benign ovarian granulosa cell tumors and testicular Leydig cell tumors was evident, in females dosed at 10 mg/rat/15 days and males dosed at 15 mg/rat/30 days, respectively. Induction of such tumors is consistent with the pharmacology-related endocrine feedback alterations in gonadotropin levels caused by an antiestrogen.

Fulvestrant was not mutagenic or clastogenic in multiple *in vitro* tests with and without the addition of a mammalian liver metabolic activation factor (bacterial mutation assay in strains of Salmonella typhimurium and Escherichia coli, *in vitro* cytogenetics study in human lymphocytes, mammalian cell mutation assay in mouse lymphoma cells and *in vivo* micronucleus test in rat)."

7.6.2 Human Reproduction and Pregnancy Data

No cases of pregnancy were observed. Faslodex is Pregnancy Category D.

7.6.3 Pediatrics and Assessment of Effects on Growth

In the clinical development program, Faslodex was studied in subjects between the ages of 1-12. There is no clear unmet medical need for Faslodex in children less than 1 year, and given that normal puberty occurs by age 12, there is no unmet need for children greater than 12. In order to comply with the Pediatric Research and EquityAct (PREA), the Division has planned to grant a pediatric waiver for children <1 and >12 years old.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

Overdose

Faslodex doses above 4 mg/kg were not evaluated in Study 44, and there were no reports of overdose among these patients. The approved Faslodex label states that "there is no clinical experience with overdosage in humans."

Drug Abuse Potential

The potential for drug abuse was not specifically studied.

Withdrawal and Rebound
These effects were not studied.

7.7 Additional Submissions / Safety Issues

Four Month Safety Update: The four-month safety update was submitted electronically by the Sponsor on February 25, 2011 and provided updated information on SAEs and deaths recorded following the original data cut-off date of September 3, 2010 to the 4-month safety update data cut-off date of February 12, 2011. At the data cutoff for the 4-month safety update, 30 patients (100%) exposed to study treatment had experienced at least one AE. Eleven (36.7%) patients reported an SAE. No patients discontinued study treatment due to an AE and no patients died. Consistent with the findings from the main study period alone, the SAEs reported up to the data cutoff for the 4-month safety update were consistent with the patient population and condition under investigation. None of the SAEs were considered by the investigator to be causally related to fulvestrant treatment.No new safety issues were identified.

8 Postmarketing Experience

All Annual Reports of Faslodex submitted to NDA 21344 were reviewed for safety information. These reports pertain to the indication of treatment of hormone receptor-positive metastatic breast cancer in postmenopausal women.

9 Appendices

9.1 Literature Review/References

Not applicable.

9.2 Labeling Recommendations

A summary and line-by-line labeling review will be added as an addendum to this Review.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ALI MOHAMADI
04/21/2011

DRAGOS G ROMAN
04/21/2011