DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF BIOSTATISTICS

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/Serial Number:	21-344/S-013
Drug Name:	Faslodex™ (fulvestrant) Injection
Indication(s):	Pediatric girls with McCune-Albright syndrome with progressive precocious puberty
Applicant:	AstraZeneca Pharmaceuticals LP
Date(s):	Received 11/17/10; user fee (6 months) 05/17/11
Review Priority:	Priority (pediatric exclusivity)
Biometrics Division:	Division of Biometrics II (HFD-715)
Statistical Reviewer:	Cynthia Liu, MA
Concurring Reviewer(s):	Todd Sahlroot, Ph.D., Statistical Team Leader and Deputy Director of Biometrics II
Medical Division:	Division of Metabolic and Endocrine Products (HFD-510)
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Keywords:	NDA review, clinical study, pediatric exclusivity

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1. EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

Based on the results from the submitted clinical study, Faslodex was shown to be effective in slowing progression of puberty in pediatric girls with progressive precocious puberty (PPP) associated with McCune-Albright Syndrome (MAS). However, the efficacy was moderate. Additionally, the efficacy shown by Faslodex in this single-arm, uncontrolled study may have been compromised by the potential limitation in the quality of the pre-treatment data. These data were provided retrospectively, not collected prospectively, by the parent/guardian, local consultant, mother's diary, or medical notes. (Note that Written Request Amendment #2 was complicit in encouraging these data since it permitted the collection of retrospective and/or prospective pre-treatment data.) The most direct impact of these data was on the three main efficacy endpoints (vaginal bleeding, bone age, and linear growth) which were evaluated primarily as changes from pre-treatment.

With these limitations in mind, results showed that the median annualized vaginal bleeding days were significantly decreased from 12 days in the pre-treatment period to 1 day over the entire 12-month treatment period. Among the 23 patients with prior vaginal bleeding history at entry, 74% of them had at least 50% reduction in the frequency of vaginal bleeding days and 35% of them experienced a complete cessation over the 12-month treatment period. The bone age advancement and growth velocity were also declined over the 12 months of treatment as well as the 1st 6-month of treatment with Faslodex when compared with the pre-treatment period. The decline over the 12-month treatment period was statistically significant for the bone age advancement, but not for the growth velocity. Nevertheless, after treatment with Faslodex, the mean growth rate of study girls with PPP associated with MAS became closer to that of age-matched girls in the National Center for Health Statistics (NCHS) FELS study.

There were no marked changes in the breast and pubic hair Tanner staging, ovarian volume, and predicted adult height after 12 months of treatment with Faslodex when compared with baseline. There was, however, a beneficial reduction in uterine volume seen after 12 months of treatment.

Labeling Comments: Since the sample size and power were not formally calculated for the study, statistical results should only include the summery statistics, not the statistical significance. In addition, the potential limitation in the quality of the pre-treatment data that may have impacted the efficacy should also be mentioned.

1.2 Brief Overview of Clinical Studies

Faslodex™ (fulvestrant) injection is currently indicated (under NDA 21-344) for the treatment of hormone receptor positive metastatic breast cancer in postmenopausal women with disease progression following antiestrogen therapy. The sponsor has submitted a supplemental NDA containing the results from Study D6992C00044, which was conducted in response to the Pediatric Written Request Amendment #2 issued by the Agency on June 17, 2005, to study the use of fulvestrant for the treatment of progressive precocious puberty (PPP) in girls with McCune-Albright Syndrome (MAS). The sponsor does not plan to seek the investigative indication for the pediatric population studied. The submission is mainly to fulfill the Written Request so that the pediatric exclusivity for Faslodex™ (fulvestrant) injection can be obtained.

Study D6992C00044 (01/31/2006 – 12/08/2009) was a Phase 2, 12-month, open-label, single-arm, multicenter (15 centers), international (6 countries) trial, conducted in 30 girls aged between 2 and 9 years with PPP associated with MAS. The efficacy of Faslodex in this study was mainly assessed based on the change from baseline measurements relating to vaginal bleeding, bone age, and growth velocity as specified in the Written Request (WR). Data for uterine volume, ovarian volume, Tanner stage, and predicted adult height were also collected and evaluated as additional assessments as listed in the WR.

According to the sponsor, all the 30 enrolled subjects had classical MAS (i.e., having at least 2 of a triad of symptoms of precocious puberty, café au lait spots or fibrous dysplasia) and had retrospective data on height, weight, bone age, Tanner staging assessment, and vaginal bleeding history for at least 6 months prior to entry (see the Statistical Issues and Findings section below for issues regarding the retrospective pre-treatment data).

Approximately 87% (= 26/30) of the enrolled subjects were Caucasian. The mean chronological and bone ages at entry were 5.9 and 8.5 years, respectively. The mean ratio of change in bone age (Δ BA) to change in chronological age (Δ CA) over the 6-month period prior to the start of treatment (i.e., bone age advancement during the pre-treatment period) was 2.0. The mean growth rate in the pre-treatment period was around 9 cm/year and most (73%) of the subjects had a higher growth rate than the mean rate of the age-matched girls in the National Center for Health Statistics (NCHS) FELS study. The median vaginal bleeding days during the pre-treatment period was 6 days. Among the 30 enrolled subjects, 23 of them (77%) had at least 1 vaginal bleeding day over the last 6 months prior to entry.

1.3 Statistical Issues and Findings

The pre-treatment data in this study were all obtained retrospectively by the parent/guardian (for 26 patients) or local consultant/mother's diary/medical notes (for 4 patients). Therefore,

the quality and validity of the data could be in question. The protocol specified the retrospective pre-treatment bone age assessments to be at least 6 months but no more than 15 months apart. However, no definitions regarding the collection time frame for the pre-treatment growth velocity and vaginal bleeding episodes were mentioned (a 6-month pre-treatment period and a minimum of 6 months pre-treatment period were used interchangeably in the sponsor's clinical study report). The annualized pre-treatment vaginal bleeding frequency was obtained by multiplying the pre-treatment data by 2, assuming the pre-treatment data were collected within the 6-month time frame. The actual pre-treatment periods for bone age advancement and growth velocity varied from patient to patient as well as for any given patient. Specifically, the pre-treatment period for bone age advancement ranged from 0.1 years to 1.3 years (mean and SD = 0.7 and 0.2 years, respectively). The pre-treatment period for growth velocity ranged from 0.2 years to 1.2 years (mean and SD = 0.6 and 0.2 years, respectively).

In general, this reviewer's results agree with the sponsor's findings. The results based on the PP population were similar to those based on the ITT population, which are summarized in Text Tables 1 and 2 below.

Over the 12 months treatment with Faslodex, the median number of vaginal bleeding days for girls with PPP arising from MAC was decreased from 12 days in the pre-treatment period (annualized) to 1 day for the worst case scenario (i.e., assuming bleeding occurred on the days with missing data). The decrease was associated with a moderate statistical significance ($p = 0.015$) according to the Sign test. Additionally, 74% of the 23 patients with vaginal bleeding history prior to entry had a $\geq 50\%$ reduction in the frequency of vaginal bleeding days and 35% experienced a cessation over the entire 12-month treatment period.

The mean rate of increase in bone age was also significantly decreased from a ratio (Δ BA / Δ CA) of 2.0 in the 6-month pre-treatment period to a ratio of 1.1 in the 12-month treatment period (change = -0.9, $p = 0.0007$), indicating a beneficial decline in bone age advancement after treatment with Faslodex. The mean growth velocity was also decreased from 8.8 cm/year in the 6-month pre-treatment period to 7.4 cm/year in the 12-month treatment period, but the change (-1.4 cm/year) was not statistically significant ($p = 0.05$). Nevertheless, when compared with the age-matched girls in the NCHS FELS study, the mean growth velocity (Z-score) was improved from 2.4 in the 6-month pre-treatment period to 1.2 in the 12-month treatment period (change = -1.1, $p = 0.14$).

Text Table 1 – Summary Results for Vaginal Bleeding, Bone Age Advancement, and Growth Velocity

Parameter	Fulvestrant (N=30)					
Visit or interval	N	Mean (SD)	Median	Range	p-value[a]	95% Confidence Intervals
Annualized vaginal bleeding episodes						
Change from pre-treatment to during treatment (Actual)	30	-8.4 (17.8)	-4.8	-42.0 to 52.9	0.0015	-16.0, 0
Change from pre-treatment to during treatment (Worst)	30	-1.5 (39.5)	-3.6	-42.0 to 185.2	0.0146	-10.1, 0
Rate of increase in bone age						
Change[c] from pre-treatment to during treatment	30[c]	-0.93 (1.343)	-0.83	-5.18 to 1.16	0.0007	-1.43, -0.43
Change[c] from pre-treatment to first 6 months of treatment	30	-0.83 (1.507)	-0.89	-5.64 to 1.28	0.0054	-1.39, -0.26
Change[c] from pre-treatment to second 6 months of treatment	29	-1.10 (1.383)	-1.12	-4.68 to 1.24	0.0002	-1.63, -0.58
Growth velocity (cm/year)						
Change from pre-treatment to during treatment	30	-1.4 (3.69)	-1.7	-8.4 to 8.6	0.0503	-2.75, 0.00
Change from pre-treatment to first 6 months of treatment	30	-1.7 (4.35)	-2.9	-8.2 to 8.8	0.0442	-3.29, -0.05
Change from pre-treatment to second 6 months of treatment	30	-0.8 (4.49)	-1.4	-9.0 to 12.3	0.3199	-2.51, 0.85
Growth velocity (Z-score)						
Change[c] from pre-treatment to during treatment	30	-1.14 (4.078)	-1.52	-8.58 to 9.63	0.1351	-2.67, 0.38
Change[c] from pre-treatment to first 6 months of treatment	30	-1.60 (4.616)	-3.06	-9.35 to 9.50	0.0683	-3.32, 0.13
Change[c] from pre-treatment to second 6 months of treatment	30	-0.64 (4.606)	-0.94	-9.26 to 9.53	0.4493	-2.36, 1.07

The 2-sided 95% CI for vaginal bleeding was a distribution-free CI for the median. The 2-sided 95% CIs for bone age advancement and growth velocity were based on the paired-t test.

Among the additional assessments in this study, an apparent reduction in uterine volume from baseline was observed at Month 12, as shown in Text Table 2. However, no marked changes in breast or pubic hair Tanner staging, ovarian volume, and predicted adult height from baseline to the end of the study were seen.

Text Table 2 – Summary Results for the Additional Assessments: Change from Baseline/Screening to Month 12

	Fulvestrant (N=30)			
	n	Mean (SD)	Median	Range
Tanner Staging (Breast)	30	-0.2 (0.92)	0.0	-3 to 2
Tanner Staging (Pubic)	30	-0.1 (0.55)	0.0	-2 to 1
Uterine Volume (cc)	27	-2.4 (4.2)	-2.4	-10.2 to 6.6
Ovarian Volume (cc)	21	-0.4 (7.5)	1.0	-22.3 to 10.4
Predicted Adult Height (cm)	17	0.5 (4.1)	1.9	-8.4 to 5.7

According to the method of Bayley and Pinneau, predicted adult height is not calculated at any time point when the patient's bone age is either <6 years, or between 6 and 7 years and categorised as advanced.

2. INTRODUCTION

2.1 Overview

Faslodex™ (fulvestrant) injection is currently indicated (under NDA 21-344) for the treatment of hormone receptor positive metastatic breast cancer in postmenopausal women with disease progression following antiestrogen therapy. The sponsor has submitted a supplemental NDA containing the results from Study D6992C00044, which was conducted in response to the Pediatric Written Request Amendment #2 issued by the Agency on June 17, 2005, to study the use of fulvestrant for the treatment of progressive precocious puberty (PPP) in girls with McCune-Albright Syndrome (MAS). The sponsor does not plan to seek the investigative indication for the pediatric population studied. The submission is mainly to fulfill the Written Request so that the pediatric exclusivity for Faslodex™ (fulvestrant) injection can be obtained.

Study D6992C00044 was entitled, "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 identifier	Objectives of the study	Study design and type of control	Test product; dosage regimen; route of administration	Number of patients	Diagnosis of patients	Duration of treatment	Study status, type of report	Location of study report in Module 5
Study 44	Safety and efficacy; Population PK analysis	Open label	Fulvestrant 50 mg/mL; 4 mg/kg[a] once monthly; im injection;	30 treated	Progressive precocious puberty in girls with MAS	12 months[b]	Complete[c], Full CSR; Population PK report	5.3.5.2; 5.3.3.5

[a] As per the study protocol, the first 10 patients received fulvestrant 2 mg/kg before being escalated to 4 mg/kg once predefined PK criteria were met by the first 6 patients.
[b] Patients who complete 12 months of study treatment can provide additional written consent continue study treatment (in the Extension phase) for as long as their treating physician considers it beneficial.
[c] Patients will be followed up during an Extension phase and 5-year safety surveillance.
MAS:McCune Albright syndrome; CSR:Clinical study report; im:intramuscular; PK:Pharmacokinetic(s).

2.2 Data Sources

The clinical study report and electronic data files are located in the folders of EDR \\CDSESUB1\EVSPROD\NDA021344\0033. The data files are actually embedded several levels under the eCTD M5 'study report' folder …\m5\53-clin-stud-rep\535-rep-effic-safety-stud\pediatric-exclusivity\5352-stud-rep-uncontr\d6992c00044\crt. Except that variable names in the data files were difficult to follow, the quality and content of the sponsor's clinical study report and data were generally adequate for statistical review.

3. STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

3.1.1 Study Design and Endpoints

Study D6992C00044 (01/31/2006 – 12/08/2009) was a Phase 2, 12-month, open-label, single-arm, multicenter, international trial, conducted in girls aged between 2 and 9 years

with PPP associated with MAS. The efficacy of Faslodex in this study was mainly assessed based on the change from baseline measurements relating to vaginal bleeding, bone age, and growth velocity as specified in the Written Request (WR). Data for uterine volume, ovarian volume, Tanner stage, and predicted adult height were also collected and evaluated as additional assessments as listed in the WR.

According to the sponsor, since MAS is a rare disease, sample size and statistical power for this study could not be formally calculated. However, based on the results from a tamoxifen study in 28 girls with MAS (No. 6157US/0013 submitted in the Nolvadex application by the same sponsor), it was assumed that approximately 20 patients with complete 12 months of fulvestrant would provide useful exploratory information for this rare condition. Thus, 35 subjects were screened and 30 of them were enrolled and treated in this study.

Fulvestrant was given to patients via intramuscular injection once a month. The first 10 patients received 2 mg/kg initially and then 4 mg/kg thereafter once the dosage of the very first 6 patients was successfully escalated to 4 mg/kg after 2 months of the initial treatment. The rest of the 20 patients received 4 mg/kg from their study entry.

According to the sponsor, all the 30 enrolled subjects had classical MAS (i.e., having at least 2 of a triad of symptoms of precocious puberty, café au lait spots or fibrous dysplasia) and had retrospective data on height, weight, bone age, Tanner staging assessment, and vaginal bleeding history for at least 6 months prior to entry. The retrospective data were simply provided by their parent/guardian (for 26 patients) or local consultant/mother's diary/medical notes (for 4 patients). Note that the protocol specified that the 2 assessments of pre-treatment bone age (for calculating bone age advancement) had to be at least 6 months apart but no more than 15 months apart. However, no definitions regarding the collection time frame for the pre-treatment growth velocity and vaginal bleeding episodes were mentioned (a 6-month pre-treatment period and a minimum of 6 months pre-treatment period were used interchangeably in the sponsor's clinical study report).

A total of 15 centers from 6 countries participated in the clinical study: France (3), Germany (2), Italy (1), Russia (1), United Kingdom (1), and United States (7).

3.1.2 Statistical Methods

The primary analysis population for the efficacy variables consisted of all patients exposed to study treatment (i.e., ITT population). Depending on distribution of data, a 2-sided paired t-test (parametric test) or a Sign test/Signed Rank test (non-parametric test) was used to analyze change from baseline measurements.

The annualized pre-treatment vaginal bleeding frequency was obtained by multiplying the pre-treatment data by 2, assuming the pre-treatment data were collected within the 6-month time frame. The annualized on-treatment data was obtained by (number of bleeding days during treatment / number of days on-treatment) x 360. Missing diary days were treated as bleeding days for the worst case scenario for the purpose of analyzing the vaginal bleeding episode endpoint (1 bleeding episode = 1 bleeding day). Missing bone age and growth velocity at final visit were handled by the LOCF technique.

All p-values reported in this review and the sponsor's clinical study report were nominal. In other words, no p-value adjustments were made for multiple comparisons. Since this was a small clinical trial, statistical results should be interpreted with caution.

3.1.3 Subject Disposition

A total of 30 subjects were enrolled and treated with fulvestrant in this study. Among them, 1 subject withdrew from the study after Month 6 due to the worsening condition under investigation. All the 30 subjects were included in the ITT population for efficacy analyses.

3.1.4 Demographic and Baseline Characteristics

All patients were females in this study and 87% (= 26/30) of them were Caucasian. The mean chronological and bone ages at entry were 5.9 and 8.5 years, respectively. The mean ratio of change in bone age (Δ BA) to change in chronological age (Δ CA) over the 6-month period prior to the start of treatment (i.e., bone age advancement during the pre-treatment period) was 2.0, where 25 of the 30 subjects had a ratio > 1 and 5 had a ratio < 1. The mean growth rate in the pre-treatment period was around 9 cm/year and most (73%) of the subjects had a higher growth rate than the mean rate of the age-matched girls in the National Center for Health Statistics (NCHS) FELS study. The median Tanner stages for breast and pubic hair at baseline were 3 (further enlargement of breast mound; increased palpable glandular tissue) and 1 (preadolescent; vellus hair only and hair are similar to development over anterior abdominal wall), respectively. The median vaginal bleeding days during the pre-treatment period was 6 days. Among the 30 enrolled subjects, 23 of them (77%) had at least 1 vaginal bleeding day over the last 6 months prior to entry. The demographic and baseline statistics are summarized in Tables 1 and 2 below.

Table 1 – Demographic and Baseline Characteristics – for continuous measures

Parameter	n	Mean (SD)	Median	Range
Age at informed consent (fractional year)	30	5.9 (1.8)	6.1	1.7 – 8.5
Height at baseline (Month 0 visit) (cm)	30	123.5 (15.4)	125.8	81.5 – 144.1
Weight at baseline (Month 0 visit) (kg)	30	27.2 (8.1)	27.4	12.4 – 48.4
Bone age at baseline (screening visit) (years)	30	8.5 (2.0)	8.8	3.4 – 11.0
Bone age advancement during pre-treatment period	30	2.0 (1.0)	1.8	0.4 – 5.2
Growth rate during pre-treatment period (cm/year)	30	8.8 (3.5)	9.4	2.1 – 16.4
Growth rate during pre-treatment period (Z-score)	30	2.4 (3.3)	2.7	-4.3 – 7.5
Breast Tanner Staging	30	2.9 (0.8)	3	1 – 4
Pubic Tanner Staging	30	1.5 (0.7)	1	1 – 3
No. of vaginal bleeding days during pre-treatment period	30	7.2 (6.8)	6	0 – 21

Table 2 – Demographic and Baseline Characteristics – for categorical measures

Parameter	Subgroup	n (%)
Age Group	< 7 years	20 (66.7)
	≥ 7 years and ≤ 10 years	10 (33.3)
Race	Caucasian	26 (86.7)
	Black	1 (3.3)
	Other	3 (10.0)
Breast Tanner Staging	1-Preadolescent; only papilla are elevated	3 (10.0)
	2-Breast bud and papilla elevated and a small mound present	2 (6.7)
	3-Further enlargement of breast mound; increased glandular tissue	20 (66.7)
	4-Areola and papilla elevated to form a second mound above breast	5 (16.7)
Pubic Tanner Staging	1-Preadolescent; vellus hair only	20 (66.7)
	2-Sparse growth of long, curled, pigmented, downy hair along labia	6 (20.0)
	3-Darker, coarser, more curled hair along pubic junction	4 (13.3)
Vaginal Bleeding	Yes	23 (76.7)
	No	7 (23.3)

3.1.5 Efficacy Results and Discussion

Annualized Frequency of Vaginal Bleeding Days. As shown in Table 3, the mean and median of vaginal bleeding days during the 12-month treatment period were both decreased from that of the pre-treatment period (annualized), regardless of actual frequency or worst case scenario frequency (assuming bleeding occurred on the days with missing data) used. The median change in the annualized bleeding episodes from the pre-treatment period was -3.6 days for the worst case scenario, which was associated with a moderate statistical significance based on the Sign test ($p = 0.015$).

Table 3 – Results for Number (Frequency) of Vaginal Bleeding Days

	Mean ± SD (n)	Median	95% CI	Range
6-month pre-treatment period (annualized)	14.3 ± 13.6 (30)	12		0 – 42
12-month on-treatment period (annualized): Actual	6.0 ± 15.1 (30)	0		0 – 76.9
12-month on-treatment period (annualized): Worst	12.9 ± 38.6 (30)	1.0		0 – 201.2
Change in annualized frequency: Actual Sign test p-value = 0.0015	-8.4 ± 17.8 (30)	-4.8	(-16.0, 0)	-42.0 – 52.9
Change in annualized frequency: Worst Sign test p-value = 0.0146	-1.5 ± 39.5 (30)	-3.6	(-10.1, 0)	-42.0 – 185.2

Actual: Assuming no bleeding occurred on missing diary days.
Worst: Assuming bleeding occurred on missing diary days (worst case scenario).
The 2-sided 95% CI was a distribution-free CI for the median.

As shown in Table 4, 17 (74%) of the 23 subjects with vaginal bleeding history prior to entry had a ≥ 50% reduction in the vaginal bleeding frequency over the 12-month treatment period when compared with the annualized pre-treatment frequency for the worst case scenario. In addition, 8 (35%) of the 23 subjects with vaginal bleeding history prior to entry experienced a cessation in vaginal bleeding during the 1st 6-month treatment period. The same 8 subjects also had a cessation over the entire 12-month treatment period.

Table 4 – Responders for Vaginal Bleeding Episodes – worst case scenario

Proportion of patients with vaginal bleeding history who experienced:	Yes	No
A decrease in the number of vaginal bleeding episodes on treatment	19/23 (83%)	4/23 (17%)
≥ 50% reduction in the number of vaginal bleeding episodes on treatment	17/23 (74%)	6/23 (26%)
Cessation of menses over the 1st 6-month treatment period	8/23 (35%)	15/23 (65%)
Cessation of menses over the whole 12-month treatment period	8/23 (35%)	15/23 (65%)

Note that 2 of the 7 subjects who had no vaginal bleeding episodes prior to entry had vaginal bleedings on treatment for the worst case scenario.

Bone Age and Advancement (Rate of Increase). Bone age advancement (rate of increase in bone age) was calculated as the ratio of Δ BA (in years) to Δ CA (in years) over a time interval. As shown in Table 5 (copied from the sponsor's clinical study report), the mean rate of increase in bone age was decreased from approximately 2 in the pre-treatment period to approximately 1 in the 12-month treatment period as well as in the 1st and 2nd 6-month treatment periods. The mean reductions in bone age advancement from pre-treatment to those on-treatment intervals were all statistically significant based on the paired t-test (all $p < 0.01$). Note that there were a few subjects with negative bone age advancement (as depicted

in Figure 1, for example) which might be due to erroneous readings on bone age. This reviewer also analyzed the data without those negative rates and found similar results.

Figure 1: Bone Age Advancement
ITT Population

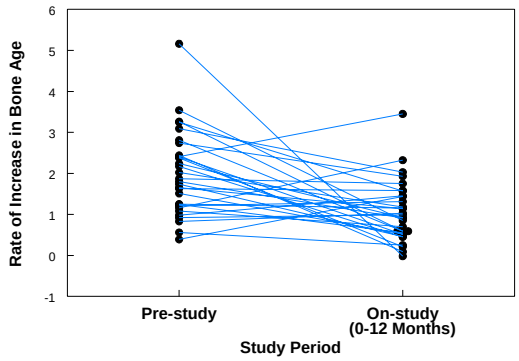


Table 5 – Results for Bone Age and Bone Age Advancement (the sponsor's table)

Parameter	Fulvestrant (N=30)					
Visit or interval	N	Mean (SD)	Median	Range	p-value[a]	95% Confidence Intervals
Bone age (years)						
6 months prior to treatment	30	7.07 (2.198)	7.75	1.32 to 9.90		
Screening	30	8.49 (1.980)	8.82	3.35 to 11.01		
Month 6	30	9.15 (1.860)	9.32	4.68 to 11.61		
Month 12/ Final visit	30	9.57 (1.755)	10.29	5.28 to 11.63		
Rate of bone age advancement[b]						
Pre-treatment	30	1.99 (1.031)	1.84	0.39 to 5.16		
During treatment (Month 0 to Month 12)	30[c]	1.06 (0.746)	0.96	-0.02 to 3.45		
During first 6 months of treatment (Month 0 to Month 6)	30	1.16 (0.891)	1.00	-0.48 to 3.45		
During second 6 months of treatment (Month 6 to Month 12)	29	0.87 (0.899)	0.48	-0.70 to 2.80		
Change[e] from pre-treatment to during treatment	30[c]	-0.93 (1.343)	-0.83	-5.18 to 1.16	0.0007	-1.43, -0.43
Change[e] from pre-treatment to first 6 months of treatment	30	-0.83 (1.507)	-0.89	-5.64 to 1.28	0.0054	-1.39, -0.26
Change[e] from pre-treatment to second 6 months of treatment	29	-1.10 (1.383)	-1.12	-4.68 to 1.24	0.0002	-1.63, -0.58

Data from blinded central read.
[a] From a 2-sided t-test at the 0.05 significance level.
[b] Defined as the change in bone age (years) divided by the change in chronological age (years).
[c] Patient E0035001 withdrew from study treatment at Month 7 and a bone age scan was not performed at their Final Visit (therefore they have no Month 12 / Final Visit data for bone age). In this instance, as detailed in Section 5.7.1, the last observed value (Month 6 bone age scan) has been carried forward when analysing the bone age of this patient across the whole treatment period.
[e] Median/mean changes are presented as the median/mean of the on-treatment vs pre-treatment changes and not the difference in the pre-treatment median/mean and the on-treatment median/mean.

Growth Velocity. As shown in Table 6 (copied from the sponsor's clinical study report), the mean growth rates during the 12-month treatment period, the 1st 6-month treatment period, and the 2nd 6-month treatment period were all smaller than that of the pre-treatment period. Similar findings were also observed for the standardized growth velocity data (Z-score) using the age-matched information from the National Center for Health Statistics (NCHS) FELS study. The mean decreases in growth rate (both in cm/year and in Z-score) from pre-treatment to those on-treatment intervals were all numerically evident, but not statistically

significant according to the paired t-test (except for change in cm/year from pre-treatment to the 1st 6-month treatment where p = 0.0442). Nonetheless, after treatment with Faslodex, the mean growth rate of study girls with PPP associated with MAS became closer to that of age-matched girls in the NCHS FELS study.

Figure 2: Growth Velocity (cm/year)
ITT Population

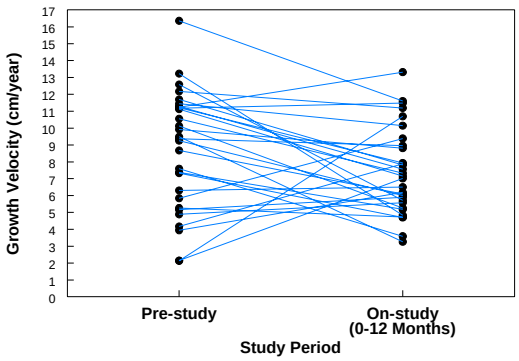


Figure 3: Growth Velocity (Z-score)
ITT Population

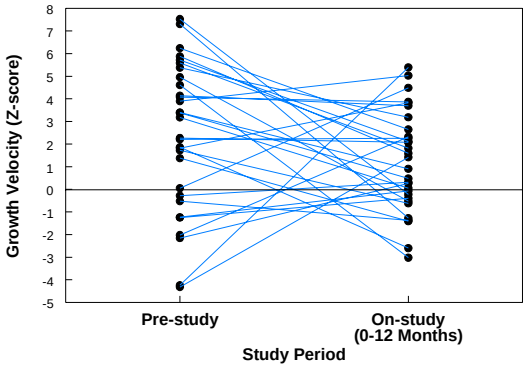


Table 6 – Results for Growth Velocity - in cm/year and in Z-score (the sponsor's table)

Parameter	Fulvestrant (N=30)					
Interval	n	Mean (SD)	Median	Range	p-value[a]	95% Confidence Intervals
Growth velocity (cm/year)						
Pre-treatment	30	8.8 (3.47)	9.4	2.1 to 16.4		
During treatment (Month 0 to Month 12)	30	7.4 (2.54)	7.1	3.3 to 13.3		
During first 6 months of treatment (Month 0 to Month 6)	30	7.1 (3.13)	6.9	1.7 to 15.9		
During second 6 months of treatment (Month 6 to Month 12)	30	7.9 (4.07)	6.8	2.5 to 23.5		
Change from pre-treatment to during treatment	30	-1.4 (3.69)	-1.7	-8.4 to 8.6	0.0503	-2.75, 0.00
Change from pre-treatment to first 6 months of treatment	30	-1.7 (4.35)	-2.9	-8.2 to 8.8	0.0442	-3.29, -0.05
Change from pre-treatment to second 6 months of treatment	30	-0.8 (4.49)	-1.4	-9.0 to 12.3	0.3199	-2.51, 0.85
Growth velocity (Z-score[b])						
Pre-treatment	30	2.35 (3.263)	2.73	-4.32 to 7.53		
During treatment (Month 0 to Month 12)	30	1.21 (2.211)	1.17	-3.02 to 5.39		
During first 6 months of treatment (Month 0 to Month 6)	30	0.76 (2.766)	0.63	-4.63 to 6.40		
During second 6 months of treatment (Month 6 to Month 12)	30	1.71 (3.330)	1.08	-3.99 to 11.35		
Change[c] from pre-treatment to during treatment	30	-1.14 (4.078)	-1.52	-8.58 to 9.63	0.1351	-2.67, 0.38
Change[c] from pre-treatment to first 6 months of treatment	30	-1.60 (4.616)	-3.06	-9.35 to 9.50	0.0683	-3.32, 0.13
Change[c] from pre-treatment to second 6 months of treatment	30	-0.64 (4.606)	-0.94	-9.26 to 9.53	0.4493	-2.36, 1.07

[a] From a 2-sided t-test at the 0.05 significance level.
[b] 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. See Appendix 12.2.6.3.3 for the reference table of age-dependent means and SDs of growth velocity.
[c] Median/mean changes are presented as the median/mean of the on-treatment vs pre-treatment changes and not the difference in the pre-treatment median/mean and the on-treatment median/mean.

There was positive, but weak, correlation between the change in growth rate and the change in bone age advancement. Figures 4 and 5 below show the Pearson correlations of 0.36 and

0.30 for the change in bone age advancement vs. the change in growth rate in cm/year and in Z-score, respectively.

Figure 4

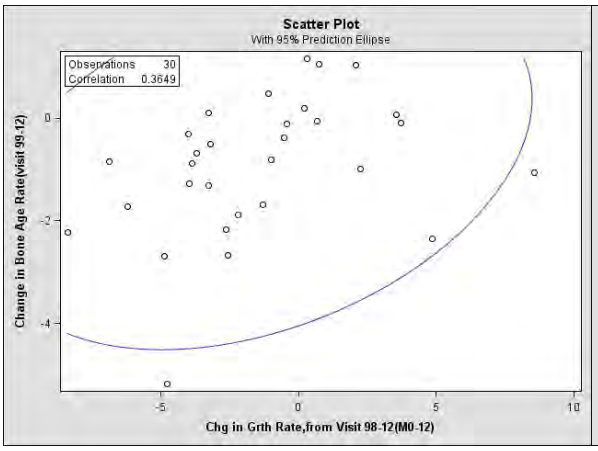
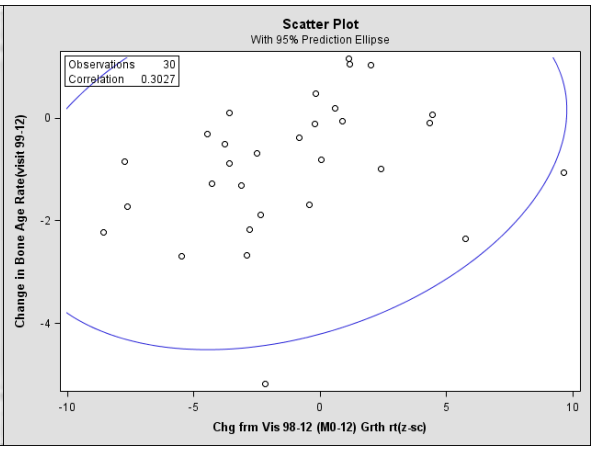


Figure 5



Tanner Staging for Breast and Pubic Hair. As shown in Table 7, there were no marked changes in breast or pubic hair Tanner stages from Month 0 to Month 12. Specifically, 21 (70%) and 24 (80%) of the enrolled subjects did not have their breast and pubic hair Tanner stages changed, respectively, while on treatment (see the diagonal lines on Table 8).

Table 7 – Results for Tanner Staging for Breast and Pubic Hair (the sponsor's table)

Parameter	Fulvestrant (N=30)			
	n	Mean (SD)	Median	Range
Tanner Staging (Breast)				
Month 0	30	2.8 (0.87)	3.0	1 to 4
Month 12/ Final visit	30	2.7 (1.06)	3.0	1 to 5
Change[a] from Month 0 to Month 12/ Final Visit	30	-0.2 (0.92)	0.0	-3 to 2
Tanner Staging (Pubic)				
Month 0	30	1.4 (0.77)	1.0	1 to 4
Month 12/ Final visit	30	1.4 (0.61)	1.0	1 to 3
Change[a] from Month 0 to Month 12/ Final Visit	30	-0.1 (0.55)	0.0	-2 to 1

[a] Median/mean changes are presented as the median/mean of the on-treatment vs pre-treatment changes and not the difference in the pre-treatment median/mean and the on-treatment median/mean.

Table 8 – Frequency in Transition of Tanner Staging (the sponsor's table)

Tanner Stage	Fulvestrant (N=30)				
	Month 12/ Final Visit				
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					
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

Uterine Volume. The mean and median uterine volumes at Months 6 and 12 were both smaller than that at the Screening visit, as shown in Table 9. The median reductions were statistically significant for both visits according to the Signed Rank test (p = 0.03 and 0.007, respectively).

Table 9 – Results for Uterine Volume (the sponsor's table)

	Fulvestrant (N=30)			
	n	Mean (SD)	Median	Range
Uterine volume (cc) at screening visit	29	8.16 (4.970)	6.58	2.18 to 20.54
Uterine volume (cc) at Month 6	30	6.04 (3.330)	4.55	2.44 to 15.27
Uterine volume (cc) at Month 12/ Final visit	28	5.49 (2.640)	4.43	2.58 to 12.89
Change[a, b] in uterine volume (cc) from screening to Month 6	29	-2.44 (4.954)	-1.10	-15.10 to 6.04
Change[a, b] in uterine volume (cc) from Month 6 to Month 12/ Final visit	28	-0.51 (3.595)	-0.13	-11.84 to 4.48
Change[a, b] in uterine volume (cc) from screening to Month 12/ Final visit	27	-2.38 (4.240)	-2.44	-10.20 to 6.56

[a] Calculated only for those patients with data at both time-points.
[b] Median/mean changes are presented as the median/mean of the on-treatment vs pre-treatment changes and not the difference in the pre-treatment median/mean and the on-treatment median/mean.
Ultrasound data from blinded central read. Volume was calculated as 0.5 multiplied by (longitudinal multiplied by anteroposterior multiplied by transverse), if all 3 linear dimensions were recorded; otherwise volume is missing.
N:Number; SD:Standard deviation; cc:Cubic centimetres.

Ovarian Volume. There were no significant changes in ovarian volume from Screening to Month 6, Screening to Month 12, and Months 6 to 12 according to the Signed Rank test (all p > 0.1).

Table 10 – Results for Ovarian Volume (the sponsor's table)

	Fulvestrant (N=30)			
	n	Mean (SD)	Median	Range
Average ovarian volume (cc) at screening visit	26	4.76 (6.840)	2.45	0.79 to 32.61
Average ovarian volume (cc) at Month 6	28	3.38 (3.043)	2.05	0.36 to 12.77
Average ovarian volume (cc) at Month 12/ Final visit	24	4.57 (3.304)	3.75	0.60 to 11.76
Change[a, b] in average ovarian volume (cc) from screening to Month 6	25	-1.21 (7.171)	0.10	-27.62 to 7.96
Change[a, b] in average ovarian volume (cc) from Month 6 to Month 12/ Final visit	24	1.14 (3.472)	0.76	-4.08 to 9.97
Change[a, b] in average ovarian volume (cc) from screening to Month 12/ Final visit	21	-0.42 (7.511)	1.01	-22.25 to 10.36

[a] Calculated only for those patients with data at both time-points.
[b] Median/mean changes are presented as the median/mean of the on-treatment vs pre-treatment changes and not the difference in the pre-treatment median/mean and the on-treatment median/mean.
Ultrasound data from blinded central read. Volume was calculated as 0.5 multiplied by (longitudinal multiplied by anteroposterior multiplied by transverse), if all 3 linear dimensions were recorded; otherwise volume is missing. Average volume was calculated as 0.5 multiplied by (volume of left ovary plus volume of right ovary) if both volumes were calculated; otherwise average ovarian volume is missing.
N:Number; SD:Standard deviation; cc:Cubic centimetres.

Predicted Adult Height. Predicted adult height was calculated based on the method of Bayley and Pinneau. As shown in Table 11, there was no significant change in predicted adult height from Screening to Month 12 based on the paired t-test (p > 0.5 for both absolute change and % change).

Table 11 – Results for Predicted Adult Height (the sponsor's table)

Parameter	Fulvestrant (N=30)			
	n	Mean (SD)	Median	Range
Predicted adult height[a] (cm) at screening visit	17	163.0 (6.90)	163.0	149.0 to 174.4
Predicted adult height[a] (cm) at Month 12/ Final visit	17	163.5 (6.28)	161.7	149.5 to 178.1
Change[b] in predicted adult height[a] (cm) from screening to Month 12/ Final visit	17	0.5 (4.10)	1.9	-8.4 to 5.7
Percent change in predicted adult height[a] from screening to Month 12/ Final visit	17	0.4 (2.48)	1.2	-5.0 to 3.7

[a] 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. See Appendix 12.2.6.5.2 for the reference table of values for the calculation of predicted adult (mature) height attained at each bone age – method of Bayley and Pinneau.
[b] Median/mean changes are presented as the median/mean of the on-treatment vs pre-treatment changes and not the difference in the pre-treatment median/mean and the on-treatment median/mean.
According to the method of Bayley and Pinneau, predicted adult height is not calculated at any time point when the patient's bone age is either <6 years, or between 6 and 7 years and categorised as advanced.

3.2 Evaluation of Safety

In consultation with the reviewing medical officer, there were no aspects of safety that required review by a statistician. See Dr. Ali Mohamadi's report for safety evaluation.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race, and Age

No subgroup analyses for gender and race were performed since the 30 enrolled subjects were all females and 26 (87%) of them were Caucasian. As shown in Table 12, treatment effects on change from pre-treatment to post-treatment in bone age advancement and growth velocity were consistent between the subjects aged < 7 years and aged ≥ 7 years. Although the mean change in the annualized vaginal bleeding frequency was +5.1 days for the subjects aged < 7 years, the median change for this subgroup of subjects was -2.5 days. This discrepancy was due to 2 subjects with extreme positive change from baseline that skewed the whole data distribution. Particularly, Subject E0010001 had 0 bleeding episode recorded on-treatment (and 8 episodes pre-treatment), but since she had missing diary cards for 228 days (out of 408 days of exposure), her annualized bleeding episode for the worst case scenario became 201 days, resulting in a +185 days increase from baseline. When the actual frequency was analyzed for this subgroup, the mean change in the annualized vaginal bleeding frequency was -5.2 days (with SD = 18.3 days) and the median change was -4.0 days.

Table 12 – Summary Results for Subgroups of Age

From pre to 12-month treatment periods	Age	Mean ± SD (n)	Median	Range
Change in annualized vaginal bleeding frequency (worst case)	<7 years	5.1 ± 46.1 (20)	-2.5	-42.0 – 185.2
	≥7 years	-14.6 ± 15.7 (10)	-9.0	-40.0 – 1.8
Change in bone age advancement	<7 years	-0.9 ± 1.5 (20)	-0.8	-5.2 – 1.2
	≥7 years	-1.1 ± 1.1 (10)	-0.8	-2.7 – 0.1
Change in growth velocity (cm/year)	<7 years	-1.2 ± 4.0 (20)	-1.2	-8.4 – 8.6
	≥7 years	-1.8 ± 3.0 (10)	-2.4	-6.2 – 3.5
Change in growth velocity (Z-score)	<7 years	-0.7 ± 4.3 (20)	-0.3	-8.6 – 9.6
	≥7 years	-2.0 ± 3.6 (10)	-2.6	-7.6 – 4.4

4.2 Other Special/Subgroup Populations

No special/subgroup population analysis was requested by the reviewing medical officer and performed by this reviewer.

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

The pre-treatment data in this study were all obtained retrospectively by the parent/guardian or local consultant/mother's diary/medical notes. Therefore, the quality and validity of the data could be in question. The protocol specified the retrospective pre-treatment bone age assessments to be at least 6 months but no more than 15 months apart. However, no definitions regarding the collection time frame for the pre-treatment growth velocity and vaginal bleeding episodes were mentioned (a 6-month pre-treatment period and a minimum of 6 months pre-treatment period were used interchangeably in the sponsor's clinical study report). The annualized pre-treatment vaginal bleeding frequency was obtained by multiplying the pre-treatment data by 2, assuming the pre-treatment data were collected within the 6-month time frame. The actual pre-treatment periods for bone age advancement and growth velocity varied from patient to patient as well as for any given patient. Specifically, the pre-treatment period for bone age advancement ranged from 0.1 years to 1.3 years (mean and SD = 0.7 and 0.2 years, respectively). The pre-treatment period for growth velocity ranged from 0.2 years to 1.2 years (mean and SD = 0.6 and 0.2 years, respectively).

In general, this reviewer's results agree with the sponsor's findings. The results based on the PP population were similar to those based on the ITT population, which are summarized in Tables 13 and 14 below.

Over the 12 months treatment with Faslodex, the median number of vaginal bleeding days for girls with PPP arising from MAC was decreased from 12 days in the pre-treatment period (annualized) to 1 day for the worst case scenario (i.e., assuming bleeding occurred on the days with missing data). The decrease was associated with a moderate statistical significance ($p = 0.015$) according to the Sign test. Additionally, 74% of the 23 patients with vaginal bleeding history prior to entry had a $\geq 50\%$ reduction in the frequency of vaginal bleeding days and 35% experienced a cessation over the entire 12-month treatment period.

The mean rate of increase in bone age was also significantly decreased from a ratio (Δ BA / Δ CA) of 2.0 in the 6-month pre-treatment period to a ratio of 1.1 in the 12-month treatment period (change = -0.9, $p = 0.0007$), indicating a beneficial decline in bone age advancement after treatment with Faslodex. The mean growth velocity was also decreased from 8.8 cm/year in the 6-month pre-treatment period to 7.4 cm/year in the 12-month treatment period, but the change (-1.4 cm/year) was not statistically significant ($p = 0.05$). Nevertheless, when compared with the age-matched girls in the NCHS FELS study, the mean growth velocity (Z-score) was improved from 2.4 in the 6-month pre-treatment period to 1.2 in the 12-month treatment period (change = -1.1, $p = 0.14$).

Table 13 – Summary Results for Vaginal Bleeding, Bone Age Advancement, and Growth Velocity

Parameter	Fulvestrant (N=30)					
Visit or interval	N	Mean (SD)	Median	Range	p-value[a]	95% Confidence Intervals
Annualized vaginal bleeding episodes						
Change from pre-treatment to during treatment (Actual)	30	-8.4 (17.8)	-4.8	-42.0 to 52.9	0.0015	-16.0, 0
Change from pre-treatment to during treatment (Worst)	30	-1.5 (39.5)	-3.6	-42.0 to 185.2	0.0146	-10.1, 0
Rate of increase in bone age						
Change[c] from pre-treatment to during treatment	30[c]	-0.93 (1.343)	-0.83	-5.18 to 1.16	0.0007	-1.43, -0.43
Change[c] from pre-treatment to first 6 months of treatment	30	-0.83 (1.507)	-0.89	-5.64 to 1.28	0.0054	-1.39, -0.26
Change[c] from pre-treatment to second 6 months of treatment	29	-1.10 (1.383)	-1.12	-4.68 to 1.24	0.0002	-1.63, -0.58
Growth velocity (cm/year)						
Change from pre-treatment to during treatment	30	-1.4 (3.69)	-1.7	-8.4 to 8.6	0.0503	-2.75, 0.00
Change from pre-treatment to first 6 months of treatment	30	-1.7 (4.35)	-2.9	-8.2 to 8.8	0.0442	-3.29, -0.05
Change from pre-treatment to second 6 months of treatment	30	-0.8 (4.49)	-1.4	-9.0 to 12.3	0.3199	-2.51, 0.85
Growth velocity (Z-score)						
Change[c] from pre-treatment to during treatment	30	-1.14 (4.078)	-1.52	-8.58 to 9.63	0.1351	-2.67, 0.38
Change[c] from pre-treatment to first 6 months of treatment	30	-1.60 (4.616)	-3.06	-9.35 to 9.50	0.0683	-3.32, 0.13
Change[c] from pre-treatment to second 6 months of treatment	30	-0.64 (4.606)	-0.94	-9.26 to 9.53	0.4493	-2.36, 1.07

The 2-sided 95% CI for vaginal bleeding was a distribution-free CI for the median. The 2-sided 95% CIs for bone age advancement and growth velocity were based on the paired-t test.

Among the additional assessments in this study, an apparent reduction in uterine volume from baseline was observed at Month 12, as shown in Table 14. However, no marked changes in breast or pubic hair Tanner staging, ovarian volume, and predicted adult height from baseline to the end of the study were seen.

Table 14 – Summary Results for the Additional Assessments: Change from Baseline/Screening to Month 12

	Fulvestrant (N=30)			
	n	Mean (SD)	Median	Range
Tanner Staging (Breast)	30	-0.2 (0.92)	0.0	-3 to 2
Tanner Staging (Pubic)	30	-0.1 (0.55)	0.0	-2 to 1
Uterine Volume (cc)	27	-2.4 (4.2)	-2.4	-10.2 to 6.6
Ovarian Volume (cc)	21	-0.4 (7.5)	1.0	-22.3 to 10.4
Predicted Adult Height (cm)	17	0.5 (4.1)	1.9	-8.4 to 5.7

According to the method of Bayley and Pinneau, predicted adult height is not calculated at any time point when the patient's bone age is either <6 years, or between 6 and 7 years and categorised as advanced.

5.2 Conclusions and Recommendations

Based on the results from the submitted clinical study, Faslodex was shown to be effective in slowing progression of puberty in pediatric girls with PPP associated with MAS. However, the efficacy was moderate. Additionally, the efficacy shown by Faslodex in this single-arm,

uncontrolled study may have been compromised by the potential limitation in the quality of the pre-treatment data. These data were provided retrospectively, not collected prospectively, by the parent/guardian, local consultant, mother's diary, or medical notes. (Note that Written Request Amendment #2 was complicit in encouraging these data since it permitted the collection of retrospective and/or prospective pre-treatment data.) The most direct impact of these data was on the three main efficacy endpoints (vaginal bleeding, bone age, and linear growth) which were evaluated primarily as changes from pre-treatment.

With these limitations in mind, results showed that the median annualized vaginal bleeding days were significantly decreased from 12 days in the pre-treatment period to 1 day over the entire 12-month treatment period. Among the 23 patients with prior vaginal bleeding history at entry, 74% of them had at least 50% reduction in the frequency of vaginal bleeding days and 35% of them experienced a complete cessation over the 12-month treatment period. The bone age advancement and growth velocity were also declined over the 12 months of treatment as well as the 1st 6-month of treatment with Faslodex when compared with the pre-treatment period. The decline over the 12-month treatment period was statistically significant for the bone age advancement, but not for the growth velocity. Nevertheless, after treatment with Faslodex, the mean growth rate of study girls with PPP associated with MAS became closer to that of age-matched girls in the NCHS FELS study.

There were no marked changes in the breast and pubic hair Tanner staging, ovarian volume, and predicted adult height after 12 months of treatment with Faslodex when compared with baseline. There was, however, a beneficial reduction in uterine volume seen after 12 months of treatment.

Labeling Comments: Since the sample size and power were not formally calculated for the study, statistical results should only include the summery statistics, not the statistical significance. In addition, the potential limitation in the quality of the pre-treatment data that may have impacted the efficacy should also be mentioned.

Primary Statistical Reviewer: Cynthia Liu, MA

Concurring Reviewer: Todd Sahlroot, Ph.D.
Statistical Team Leader and Deputy Director of Biometrics II

CC: HFD-510/JJohnson, DRoman, AMohamadi
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/s/

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