Cross-Discipline Team Leader Review

Date	May 9, 2011
From	Dragos Roman MD
Subject	Cross-Discipline Team Leader Review
NDA/BLA # Supplement#	21-344/S-013
Applicant	AstraZeneca
Date of Submission	November 17, 2010
PDUFA Goal Date	May 15, 2011
Proprietary Name / Established (USAN) names	Faslodex/Fulvestrant
Dosage forms / Strength	Injectable solution; 250 mg/5ml
Proposed Indication(s)	Indication studied: treatment of progressive precocious puberty in girls with McCune-Albright Syndrome (the applicant, however, does not seek an indication)
Recommended:	The labeling changes negotiated with the applicant for the Pediatric Section (8.4) of the Faslodex label should be approved (b) (4)

1. Introduction

Faslodex (fulvestrant) is an injectable estrogen receptor antagonist currently approved for the treatment of metastatic estrogen receptor-positive breast cancer in postmenopausal women. A Written Request was issued to AstraZeneca, the maker of Faslodex, on October 21, 2002; it was twice amended, first on May 7, 2004 (Amendment #1) and next on June 17, 2005 (Amendment #2). In its final form, the Written Request contained two studies: 1) a single-arm clinical trial to be conducted in 20 patients with McCune-Albright syndrome and progressive precocious puberty, and 2) a pharmacokinetic (PK) study (in the end, this study was designed as a sub-study incorporated in the clinical trial). This supplemental NDA contains the final reports for the aforementioned WR studies. Following review of this submission, the Division concluded that AstraZeneca complied with the requirements formulated in the WR; in acknowledging that AstraZeneca fulfilled the terms of the WR, the Pediatric Exclusivity Board agreed with the Division's recommendation and granted AstraZeneca 6 months of marketing exclusivity for Faslodex.

This CTDL memorandum summarizes the findings and recommendations made in the clinical, statistical, and clinical pharmacology reviews of this NDA supplement. Of note, the applicant is not seeking a pediatric indication and, based on the data submitted, none of the reviewers recommends that such an indication (treatment of progressive precocious puberty in McCune-Albright syndrome) be approved. However, all reviewers recommend specific language to the Pediatric Section (8.4) of the Faslodex label summarizing the relevant PK and clinical knowledge gleaned from the studies submitted.

Reference ID: 2944030

2. Background

Faslodex is a steroidal antiestrogen; it exerts its effects via downregulating the estrogen receptor to which it binds with an affinity comparable to that of endogenous estradiol. It is asserted that Faslodex has no known partial agonistic effects, a feature which makes it an attractive therapeutic candidate from a safety standpoint, particularly over antiestrogens who retain such partial agonistic activity.

McCune-Albright syndrome (MAS) is a condition characterized, among others, by signs and symptoms of estrogen excess. The basic defect in this rare genetic syndrome (prevalence estimated between 1/100,000 and 1/1,000,000) consists in postzygotic activating mutations of the *GNAS* gene coding for the stimulatory subunit (Gsα) of the G protein; the latter is involved in signal transduction processes for a variety of hormones such as MSH (melanocyte stimulating hormone), LH (luteinizing hormone), TSH (thyroid stimulating hormone), GHRH (growth hormone stimulating hormone), and ACTH (adrenocrotical stimulating hormone). When expressed at the level of the ovary, such mutations result in loss of estrogen regulation, premature and autonomous estrogen output with subsequent manifestations of precocious puberty. Of particular relevance to this application - and to interpreting the results of any pharmacological intervention that attempts to reverse the estrogen excess in girls with McCune-Albright syndrome - is the recognition of the fact that ovarian estrogen production in MAS, although excessive, is neither steady nor continuous; in fact it waxes and wanes as estrogen-secreting ovarian cysts are recruited, develop, mature, and regress. The immediate consequence of this phenomenon is marked heterogeneity in the clinical manifestations of precocious puberty, with some patients experiencing episodic signs and symptoms of hyperestrogenism which may stabilize or even temporarily regress, while others exhibiting a more consistent and progressive course which may eventually result in premature epiphysial fusion and compromised adult height. The Faslodex clinical program targeted the latter population which, in the terms of the WR, was identified as MAS patients with"progressive precocious puberty".

There are no approved therapies for the treatment of precocious puberty (PP) in girls with McCune-Albright syndrome. Generally speaking, the clinical study experience in patients with MAS and precocious puberty has been restricted to a handful of antiestrogens and aromatase inhibitors evaluated in single-arm clinical trials of small size.[1] This was due largely to the rarity of MAS itself and to the fact that not all patients with MAS have progressive forms of puberty. It was further compounded by the need to validate candidate clinical trial endpoints and, no less importantly, enrollment criteria. To date, and appropriately, the clinical endpoints evaluated in MAS trials have been largely those investigated in pharmacological intervention trials conducted in patients with precocious puberty and non-MAS conditions.

[1] Two similar WRs issued for Nolvadex (an antiestrogen with partial agonist activity) and Arimidex (an aromatase inhibitor) had limited efficacy at the doses studied and were not granted an indication (the efficacy and safety results of these studies were described, however, in the pediatric section of the respective labels).

The WR included two study requests: a population pharmacokinetic (PK) study (Study 1 in the WR, the results of which will be summarized in Section 5 of this memorandum) and a clinical efficacy and safety study (Clinical trial D6992C00044 or "Study 2" in the WR, described in Section 7). The goal of conducting these studies was to seek evidence that Faslodex may indeed be beneficial for the treatment of girls with MAS and progressive precocious puberty as there is an unmet clinical need for this condition (no approved therapy, limited benefit demonstrated by all other therapies investigated to date). Viewed in the larger picture of a clinical development program, Study D6992C00044 had the general characteristics and goals of a phase II-III study. Specifically, predictions for pediatric doses were made on the basis of pharmacokinetic information accumulated in adults (women with breast cancer), and two such doses were evaluated pharmacokinetically and clinically in a one year study (2 mg/kg and 4 mg/kg administered once monthly intramuscularly). Due to the rarity of patients with MAS and progressive precocious puberty, the pharmacokinetic evaluations were nested within the clinical trial. The final dosing regimen was not known at the beginning of the trial and was established only after analysis in real-time of PK variables obtained with the lowest proposed dose of 2 mg/kg, at which time the decision to continue such a dose or to escalate to the next dose was made. Finally, in designing this trial, there was no planned investigation of the potential long term-effect of estrogen suppression on bone mineralization since the proof-of-concept that Faslodex is efficacious for this new indication has to be been proved first.

3. CMC/Device

The sponsor cross-references the original NDA (21-344) for CMC information regarding the drug substance and drug product. The presentation, formulation, and route of administration are the same as those currently approved and labeled for the adult breast cancer indication. The only difference between the Faslodex method of use in this study and that approved in adults is that a mg/kg dosing method was used instead of a fixed (250 or 500mg) dose. Administration of Faslodex does not require the use of a device. The applicant requested a categorical exclusion from the need to prepare an environmental assessment; this was granted by the CMC review which recommends approval.

4. Nonclinical Pharmacology/Toxicology

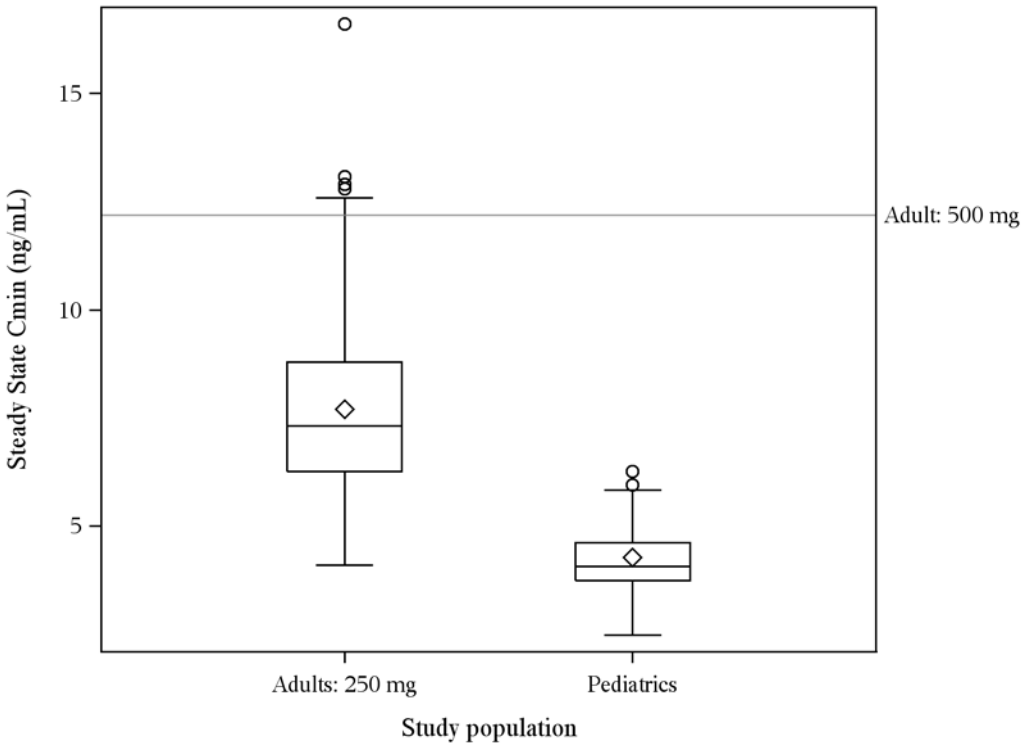
This application does not include any new pharmacology/toxicology data.

5. Clinical Pharmacology/Biopharmaceutics

The applicant characterized the pharmacokinetics of fulvestrant using a population pharmacokinetic approach. In such analysis the pediatric data derived from 30 female patients enrolled in the clinical study were combined with adult data collected from 294

postmenopausal women with breast cancer who received either 125 or 250 mg monthly in two previously conducted studies. Exposure analyses were done using trough (Cmin) fulvestrant levels; as these were observed data, they were felt to be more reliable than AUC data which were mostly calculated from predictions. Dose selection for the MAS clinical study was guided by several assumptions that led to the prediction that the approved adult dose of 250 mg and the 4 mg/kg pediatric dose are equivalent. The results of the population PK analysis indicate, however, that the exposure achieved with the pediatric dose of 4 mg/kg once a month was below initial predictions. Specifically, the mean Cmin was 4.27 ng/mL in pediatric patients and 7.70 ng/mL in adults who received the 250 mg dose (thus exposure was approximately 45% lower in children than in adults despite a 32% lower clearance observed in children). Moreover, this exposure is almost three times lower than the Cmin of 12.2 ng/ml for the recently approved adult Faslodex dose of 500 mg. These data are summarized in Figure 1 of the clinical pharmacology review, reproduced below.

Boxplot of C_{min} at Steady State for Adults Receiving 250 mg and Predicted C_{min} at Steady State for Pediatric Patients Receiving 4 mg/kg



These observations raise the question whether the predicted Faslodex doses that were selected for the clinical trial were indeed therapeutically adequate, and that, at least theoretically, doses higher than 4 mg/kg may reach serum concentrations closer to those proven to be efficacious in adults with breast cancer. On the other hand, the comparison of dose regimens in girls with MAS with dose regimens in adults with breast cancer, predicated on the assumption that similar serum drug levels will have similar efficacy in these two conditions, cannot be embraced with full confidence since MAS is a hyperestrogenic state while postmenopause is

quite the opposite. For these reasons, dose choices in further investigations will need to be made on the basis of disease-specific pharmacodynamic or efficacy responses.

Several analyses of exposure-response conducted by the pharmacology reviewer (Figures 2-4 of the clinical pharmacology review) did not find a relationship between drug exposure and efficacy responses such as change in bone age/chronological age ratio, or change in number of bleeding days (both endpoints showed statistically significant changes in applicant's analyses).

On the basis of the observations made in Study 44, the clinical pharmacology reviewer recommends the following addition to the Pediatric Use Section of the Faslodex label (Section 8.4):

> The pharmacokinetics of fulvestrant were characterized using a population pharmacokinetic analysis with sparse samples per patient obtained from 30 female pediatric patients aged 1 to 8 years with PPP associated with MAS. Pharmacokinetic data from 294 postmenopausal women with breast cancer who received 125 or 250 mg monthly dosing regimen were also included in the analysis.
>
> In these pediatric patients receiving 4 mg/kg monthly intramuscular dose of fulvestrant, the geometric mean (SD) of the CL/F is 444 (165) mL/min which is 32% less than adults. The geometric mean (SD) of the steady state trough concentration (Cmin,ss) and AUCss were 4.2 (0.9) ng/mL and 3680 (1020) ng*hr/mL, respectively.

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical- Efficacy

Study D6992C00044 ("Study 2" in the WR, further referred to as Study 44) was an international (6 countries), multi-center (15), open-label, single-arm study whose main objective was to evaluate the efficacy and safety of Faslodex in girls with MAS and progressive precocious puberty (PPP). For the purpose of this study, PPP was defined as an association of pubertal development, menses, and/or advanced bone age. Bone age, which was centrally read, was considered advanced if it exceeded chronological age by at least 12-months. The reason for enrolling only patients with PPP was to exclude patients with milder forms of MAS who only display intermittent clinical signs or symptoms of precocious puberty; such patients are more likely to experience spontaneous reduction of estrogen secretion and involution or stabilization of clinical manifestations of precocious puberty. Patients were admitted in the study only if they if they had documented retrospective data of at least 6 months for the efficacy assessments (if not, they had to be observed for 6 months in order to collect such data before receiving Faslodex). Since the vast majority of patients with McCune-Albright syndrome are treated in clinical practice off-label with a variety of medications (antiestrogens, aromatase inhibitors, etc), such patients were allowed enrollment if they had evidence of disease progression on such therapies; if so, they had to complete a 1-month

washout period (4/30 patients fell in this category). Patients with concomitant central precocious puberty (an occurrence secondary to extended estrogen exposure in MAS) that required a GnRH agonist could be enrolled only if they had been on this medication for at least 6 months. Patients were allowed GnRH agonists if they developed secondary central puberty during the trial.

The duration of the study was 12 months. Of the 30 patients enrolled 29 were completers; 1 patient withdrew due a worsening of the condition despite treatment. All patients were treatment compliant. Faslodex was meant to be administered at an initial dose of 2 mg for the first 10 patients; subsequently, based on results of the plasma fulvestrant concentrations following the first and second administrations in the first 6 patients, dosing was escalated at 4 mg/kg in the third and subsequent months in this subgroup of 10 patients and in all remaining 20 patients. Faslodex was administered using the approved adult formulation (250 mg/5mL solution) once a month intramuscularly. In absence of a control group, all efficacy comparisons were between end-of-treatment and baseline (i.e. patients served as their own controls). Baseline variables were calculated mostly using retrospective information (standing height measurements for height velocity changes, wrist X-rays for bone age, and diaries for vaginal bleeding). Of importance, vaginal bleeding was recorded retrospectively for the previous 6 months on the basis of patient's and family's recollection of such events; the accuracy of such method of data collection imposes obvious limitations in the interpretation of the results for this particular endpoint.

At baseline, all patients were of prepubertal age, with a mean (SD) chronological age for the whole cohort of 5.9 (1.8) years (range of 1.7 to 8.5 years). All patients met diagnostic criteria for "classical" MAS, although the protocol allowed enrollment of atypical forms as well (classical MAS consists in the presence of at least two of the following: café au lait spots, polyostotic dysplasia and precocious puberty; as such, 100% of patients enrolled had precocious puberty, 80% café au lait spots, and 70% had fibrous dysplasia). Growth velocity during the baseline observation period was above normal but not exceedingly high: mean (SD) growth velocity Z-score was 2.4 (3.3) which corresponds to 8.8 (3.5) cm/year; the range of Z-score was quite wide, extending from below normal to highly accelerated rates (-4.32 to 7.53). Mean bone age was advanced relative to chronological age (8.5 years vs. 5.9 years, respectively); at baseline, the change in bone age was twice as fast as the change in chronological age, indicating that acceleration of growth maturation was ongoing at enrollment (range: 0.39 to 5.16). Secondary sexual characteristics were advanced for somebody of this chronological age and consistent with a diagnosis of precocious puberty: mean Tanner stage was 2.8 (0.9) for breast and 1.4 (0.8) for pubic hair. Patients had on average 7.2 (6.8) days of vaginal bleeding over the preceding 6 months. The mean screening serum estradiol was not particularly high: 20.5 (25.6) pmol/l (prepubertal levels are < 20 pg/ml).

Consistent with the experience accumulated from two similar WRs (Nolvadex and Arimidex) issued in the past for the same indication, and the exploratory nature of the study, Study 44 did not provide a rigid hierarchy of clinical endpoints but rather divided them in two categories based on general importance: "study endpoints" (which included growth rate, bone age advancement, frequency of annualized episodes of vaginal bleeding) and "additional assessments" (included Tanner stage, uterine and ovarian volume, hormone levels, PK

endpoints, safety and tolerability, predicted adult height, and genetic testing). From a statistical perspective the WR asked that paired t tests be used to compare relevant endpoints and that the rest of the data be presented descriptively. Due to the exploratory nature of the study, the clinical trial was not formally powered for any specific efficacy variable (although some exploratory power calculations were conducted).

As requested in the WR, efficacy analyses were conducted for the Full Analysis Set (30 patients; included all patients who received at least one dose of study medication) and for the Per Protocol population (28 patients; one patient was excluded because of use of prohibited medication, sandostation, which could have interfered with growth velocity results; another patient missed several key assessments due to being involved in a car accident). The efficacy analyses showed generally a favorable trend but seen in the context of the disease the results were not particularly robust. From a minimally advanced Z-score of 2.4, growth velocity slowed down into the normal range as indicated by a reduction of 1.1 ($p = 0.1351$); when expressed in cm/year, growth velocity reduction was only 1.4 cm/year ($p = 0.0503$). Figures 2 and 3 of the statistical review (reproduced below) show a variety of individual responses, with more seeming to trend downward. Such small treatment changes did not affect the predicted adult height (this should not be surprising because, generally, predicted adult height tends to change with longer treatment durations).

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

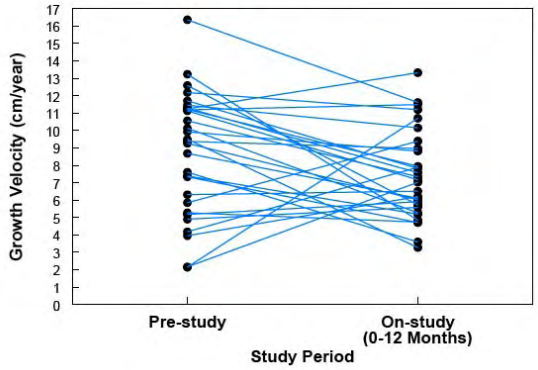
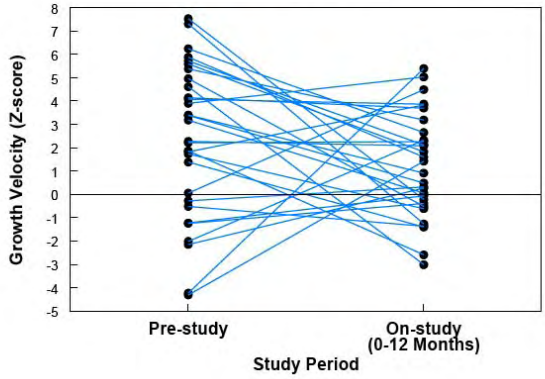
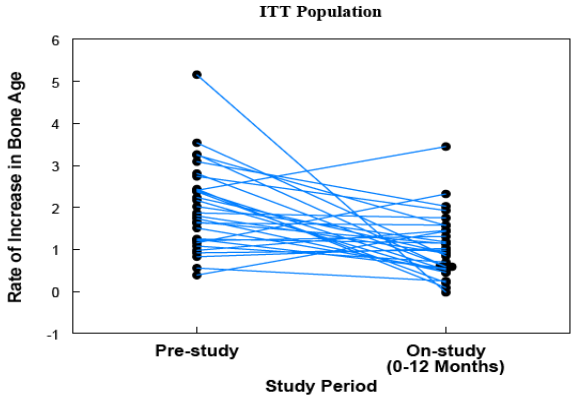


Figure 3: Growth Velocity (Z-score)
ITT Population



On the other hand, the ratio of change in of bone age/change in chronological age for the duration of the trial (-0.93) reached statistical significance (p=0007); this measurement indicates normalization of bone age advancement, which became concordant with the change in chronological age. Individual responses can be visually appreciated in Figure 1 of the statistical review, reproduced below; the trend was clearly downward (per statistical reviewer the data provided consistent results when a few patients with negative rates, reflecting measurement errors, were excluded). This finding could be consistent with the antiestrogenic effect of Faslodex, although, in absence of a control group one has to interpret the data with caution.

Figure 1: Bone Age Advancement



Interpretation of the efficacy data for the vaginal bleeding endpoint is challenging for two reasons. First of all, baseline data were not prospectively collected and patients and families had to provide such information from personal records that go back for 6 months prior to enrollment. Secondly, some patients did not have complete data collected during the trial: patients recorded the presence or absence of vaginal bleeding for each day on trial on "diary cards" and some had missing days. To address this deficiency, the applicant conducted two different types of analyses: under a "worst-case" scenario (assuming vaginal bleeding in each of the missing days) and under a "best-case" scenario (assuming that there was no bleeding on such days). Under the most conservative estimate (worst-case scenario) the study reports a statistically significant reduction in annualized vaginal bleeding days (median change = -3.6 days; p=0.0146). The results for the Full Analysis Set and for the Per Protocol population were concordant. In this analysis the range of changes was quite wide: -45 days to 185 days; some patients improved (19 patients with vaginal bleeding at baseline experienced a reduction in the frequency of annualized bleeding days on study treatment); other remained unchanged (5 patients who did not have vaginal bleeding at baseline did not experience vaginal bleeding on-treatment); while some patients (4) experienced an increase in frequency of bleeding days (one of them should be probably be disregarded because she missed 201 days due to a motor vehicle accident and had no vaginal data recorded for this time period). Finally, 73.9% of the 23 patients with baseline vaginal bleeding experienced a ≥50% reduction over the course of the study and 34.8% experienced a complete cessation of vaginal bleeding on-treatment. This latter analysis is probably the most telling because the simple recollection of having had bleeding during the retrospective pretreatment period is likely to be more accurate than the quantitative assessment of number of bleeding days.

The rest of the efficacy analyses did not show any significant changes from baseline. There were small numerical reductions in uterine and ovarian volume, respectively. Mean Tanner stage (breast and pubic hair) remained virtually unchanged (70% of patients did not experience any change in Tanner stage for breast and 80% had no change in Tanner stage for pubic hair; the remainder had either reductions or progressions).

Finally, there was general agreement between applicant's efficacy analyses and those conducted by the FDA statistical reviewer.

In interpreting the efficacy results one has to keep in mind that Study 44 used clinical criteria in order to enroll patients with progressive forms of precocious puberty. Not all patients had, however, biochemical evidence of hyperestrogenism at baseline and, moreover, estrogen levels did not decline on treatment. Mean estradiol serum concentration was 20.5 pmol/L at screening (prepubertal levels are considered <20 pmol/L) and increased to 36.1 pmol/L and 26 pmol/L at Months 6 and 12, respectively. The range was quite wide: 9.18 to 95.42 pmol/L at screening, 9.18 to 575.09 pmol/L at Month 6 and 9.18 to 114.14 pmol/L at Month 12. A visual inspection of the individual list of estrogen values (Appendix 12.2.6.6) indicates that most of the baseline estrogen concentrations were below the 20 pmol/L level; in fact, 20/30 baseline values were less than 10 pg/ml and only 6/30 patients had baseline estrogen values > 20 pmol/kg, thus raising the question whether the assay was informative or whether the clinical criteria applied for puberty progression did indeed capture a true hyperestrogenic state. With regard to patients who started with high (pubertal) estradiol screening levels, some showed full regression, while some showed partial reductions. On the other hand, several patients with low estradiol levels at baseline had elevations during the trial, some even considerable, despite treatment. An analysis conducted by the statistical reviewer did not find a strong correlation between estrogen changes during treatment and changes in efficacy variables such as bone age, height velocity, and vaginal bleeding. Thus, the lack of estrogen suppression at Months 6 and 12 and the limited efficacy seen clinically raise questions about how effective this Faslodex regimen really is, especially in the face of 100% compliance with the treatment.

8. Safety

There were no safety findings of concern observed in this 12-month clinical trial, and Faslodex appeared to be relatively well tolerated. In absence of a control group, Dr. Mohamadi's review had to rely, appropriately so, on prior knowledge of the safety profile of Faslodex in adults, on the known background morbidity associated with McCune-Albright syndrome, and on the information provided by the study investigators who categorized adverse events by intensity and provided an opinion whether they were treatment-related or not. In his review he points out that there were no deaths, no treatment-related serious adverse events (SAEs), and no discontinuations of study drug due to an adverse event (AE). The SAEs observed reflected background disease-specific events or general pediatric illnesses. Injection site reactions occurred in several patients and were described under the following terms: inflammation, pain, reaction, hematoma, pruritus, rash; none was considered severe in intensity. Although 90% of patients reported an AE, these were, in general, considered mild in intensity. The most frequent adverse events were gastrointestinal (e.g. abdominal pain, vomiting), respiratory (rhinitis, URIs, nasopharyngitis) and pyrexia. The most frequent adverse events judged to be treatment-related were injection site reactions and gastrointestinal symptoms. Symptoms consistent with estrogen deprivation (hot flushes) were rare. Laboratory assessments were

limited to endocrine biomarkers and analytes (LH, TSH, free T4, serum estradiol, testosterone) and liver function tests. There no specific safety concerns raised by these results.

9. Advisory Committee Meeting

There were no Advisory Committee meetings for this application.

10. Pediatrics

On February 2, 2011 the Pediatric Exclusivity Board agreed that AstraZeneca fulfilled the terms of the Faslodex Written Request and granted the applicant 6-month of marketing exclusivity under Section 505A of the Federal Food, Drug, and Cosmetics Act as amended by the Best Pharmaceuticals for Children Act.

As the applicant does not seek an indication,PREA requirements do not apply.

11. Other Relevant Regulatory Issues

Dr. Mohamadi indicates that the data quality and completeness were adequate to permit review. Study 44 was conducted in accordance with good clinical practice standards, included informed consent/assent, and was scrutinized by ethical review boards. There were no significant deviations or violations of the protocol. There were no financial relationships between investigators and the applicant that could have impacted the conduct or findings of the trial, as evidenced by information provided in form 3454. No DSI inspections were conducted.

12. Labeling

Despite the fact that the sponsor does not seek an indication in MAS patients, a summary of the PK, clinical efficacy and safety data should be included in the Pediatric Section (8.4) of the Faslodex label. Specific language is currently being negotiated with the applicant.

13. Recommendations/Risk Benefit Assessment

- Recommended Regulatory Action

In accordance with the requirements of the Best Pharmaceuticals for Children Act, specific language summarizing the results of Study 44, which was conducted in response to the Faslodex Written Request, should be summarized in Section 8.4 of the Faslodex label. Faslodex should not be approved for the indication of treatment of progressive premature puberty in girls with McCune-Albright syndrome because the regimen studied in Study 44 showed limited evidence of efficacy.

- Risk Benefit Assessment

Unfavorable based on absence of a clinically meaningful treatment effect at the doses studied.

- Recommendation for Postmarketing Risk Evaluation and Management Strategies

Not applicable.

- Recommendation for other Postmarketing Requirements and Commitments

None.

- Recommended Comments to Applicant

None.

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/s/

DRAGOS G ROMAN
05/09/2011

MARY H PARKS
05/09/2011
concur with Dr. Roman's recommendations