OFFICE OF CLINICAL PHARMACOLOGY REVIEW

sNDA: 21-344 (S-013)	Submission Date: 17 Nov 2010
Brand Name	Faslodex®
Generic Name	Fulvestrant
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ORM division	Metabolism and Endocrinology Products
Sponsor	AstraZeneca
Submission Type; Code	Pediatric Written Request; Pediatric Exclusivity
Formulation; Strength(s)	250 mg / 5 mL single-use barrel
Indication	Adults: Treatment of hormone receptor positive metastatic breast cancer in postmenopausal women with disease progression following antiestrogen therapy. Pediatrics: None.

List of Tables and Figures:

1 Executive Summary

AstraZeneca has submitted a request for a 6-month pediatric exclusivity determination in response to FDA's Pediatric Written Request dated October 21,2002, amended May 7, 2004; amendment #1 and May 17, 2005; amendment #2, which requested the submission of information on the safety, efficacy, and pharmacokinetics of FASLODEX® (fulvestrant) in female patients with McCune Albright Syndrome (MAS). This supplemental NDA provides safety, efficacy and pharmacokinetic information on the use of FASLODEX® (fulvestrant) in female patients with McCune-Albright syndrome (MAS). No indication is being sought by the sponsor. Pediatric exclusivity has been granted to the sponsor for this application.

1.1 Recommendation

The Office of Clinical Pharmacology Divisions of Clinical Pharmacology 2 and Pharmacometrics have reviewed the information contained in sNDA 21-344 (S-013). This sNDA is considered acceptable provided that the agency and sponsor agree on the labeling.

1.2 Post Marketing Requirements

None.

1.3 Summary of Important Clinical Pharmacology Findings

Sponsor conducted a study to evaluate efficacy, safety and pharmacokinetics of fulvestrant in girls with progressive precocious puberty (PPP) arising from McCune-Albright Syndrome (MAS) in response to a formal written request by the US FDA. The sponsor is not seeking a new indication based on this pediatric study (D6992C00044, referred to as study 44). There are no currently approved treatments for this indication. The labels for Arimidex and Tamoxifen currently have a description of pediatric trials performed on girls with PPP associated with MAS.

The pharmacokinetics of fulvestrant were characterized using a population pharmacokinetic analysis with sparse samples obtained from 30 female pediatric patients aged 1 to 8 years with PPP associated with MAS receiving 4 mg/kg faslodex. Pharmacokinetic data from 294 postmenopausal women with breast cancer who received a 125 or 250 mg monthly dosing regimen (9238IL/0020 and 9238IL/0021, referred to as studies 20/21) were also included in the analysis. Pediatric patients receiving 4 mg/kg once monthly fulvestrant achieved lower exposures than adults receiving 250 mg once monthly dosing regimen. The mean (SD) predicted steady state C_{min} was 4.27 (0.867) ng/mL in pediatric patients receiving 4 mg/kg once monthly and was 7.70 (2.13) ng/mL in adults receiving the 250 mg monthly dose. Furthermore, it is important to note that 500 mg monthly dosing regimen in now approved for post-menopausal breast cancer patients which results in a mean (SD) steady state C_{min} of 12.2 (21.7) ng/ml.

Sponsor utilized bone age, growth velocity, and vaginal bleeding endpoints to assess fulvestrant efficacy in girls with PPP arising from MAS (Table 1). Sponsor reported a statistically significant reduction in annualized vaginal bleeding (medians = 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) and 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 was also reported.

There was lack of evidence of exposure-response relationship for efficacy. The two endpoints which demonstrated a statistically significant effect compared to baseline in the clinical study (reduction in bone age advancement and reduction in annualized vaginal bleeding at the end of 12 month compared to baseline) were used as the response variables in the exploratory exposure-response relationship analysis. The lack of an observed exposure-response relationship for either endpoint may be due in part to a narrow range of exposures at one dose level (C_{min} range: 2.5 - 6.3 ng/mL). For annualized vaginal bleeding endpoint, the baseline data was collected retrospectively based on patient's caregiver recollection of the 6-month pre-treatment period and thus is subjective; non-documented days of vaginal bleeding resulted in missing data in the prospective phase (baseline to 12 months).

2 Question Based Review

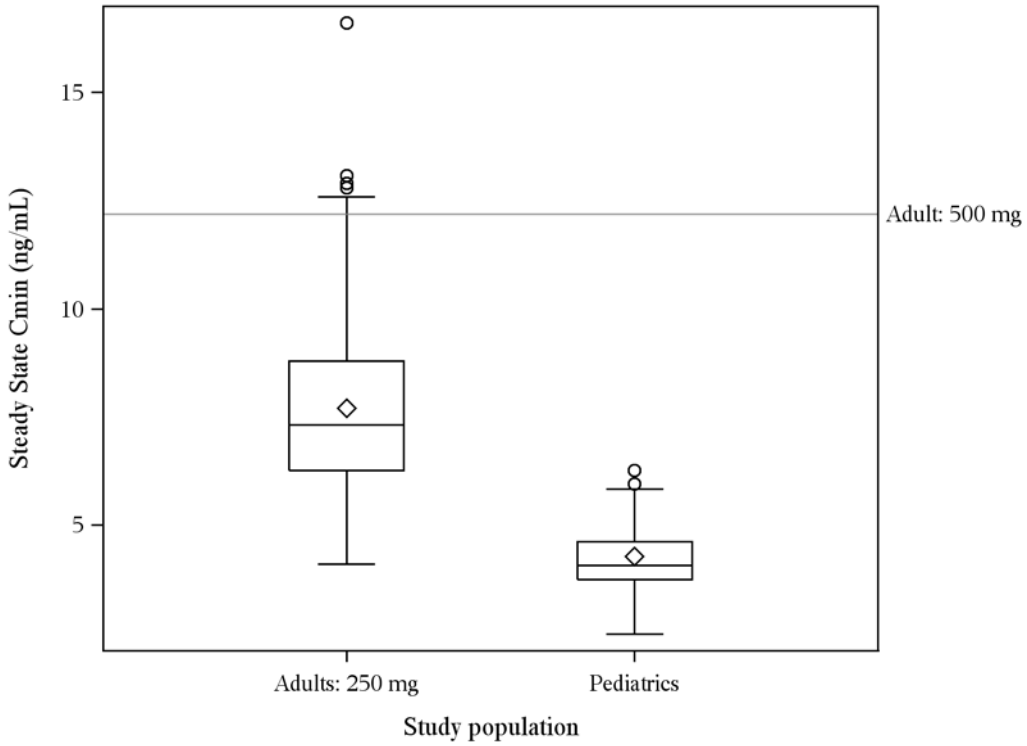
2.1 Key Questions

The purpose of this review is to address the following key questions.

2.1.1 Is PK at steady state similar between adult (post-menopausal women with breast cancer) and pediatric patients?

No. Pediatric patients receiving 4 mg/kg once monthly fulvestrant achieved 45% lower exposures than adults receiving 250 mg once monthly (see Figure 1). Model-based Cmin was calculated for the pediatric patients since the final concentration measurement in this group was obtained before steady state was achieved. The mean (SD) predicted steady state C_{min} was 4.27 (0.867) ng/mL in pediatric patients receiving 4 mg/kg once monthly and was 7.70 (2.13) ng/mL in adults receiving the 250 mg monthly dose. Furthermore, it is important to note that the recently approved 500 mg monthly dosing regimen for post-menopausal breast cancer patients results in a mean (SD) steady state C_{min} of 12.2 (21.7) ng/mL.

Figure 1. Boxplot of Observed C_{min} at Steady State for Adults Receiving 250 mg Once Monthly and Predicted C_{min} at Steady State for Pediatric Patients Receiving 4 mg/kg Once Monthly



The middle, top, and bottom horizontal lines in the box represent median and interquartile range, the diamond sign represents mean. The studies 20/21 have combined n=103 patients who had observed C_{min} at steady state following the 250 mg dose, and pediatric study 44 has n=30 patients. Based on the current FASLODEX label, a C_{min} of 12.2 ng/mL is obtained following 500 mg monthly dosing regimen.

2.1.2 Is there exposure-response for efficacy?

No, there was lack of evidence of exposure-response relationship for efficacy. The two endpoints used in this analysis were reduction in bone age advancement and reduction in annualized vaginal bleeding since they both demonstrated a statistically significant effect compared to baseline in the clinical study. Figure 2 depicts the relationship between C_{min} and the percent change in the bone age / chronological age (BA/CA) ratio at 12 months compared to screening. Figure 3 and Figure 4 show the relationship between the percent change in annualized on-treatment vaginal bleeding days at 12 months compared to annualized pre-study retrospective period vaginal bleeding days for both best case and worst case scenario endpoint assessments and the corresponding C_{min} values. The lack of an observed exposure-response relationship may be due in part to a narrow range of exposures at one dose level (minimum and maximum C_{min} values near the 12^{th} month of study period were 2.5 and 6.3 ng/mL, respectively). Similar results are obtained for the 6-month bone age advancement assessments (see Figure 7).

Figure 2. Percent Change in Bone Age / Chronological Age Ratio at 12 Months Compared to Pre-Treatment Period Vs. Predicted Steady State C_{min}.

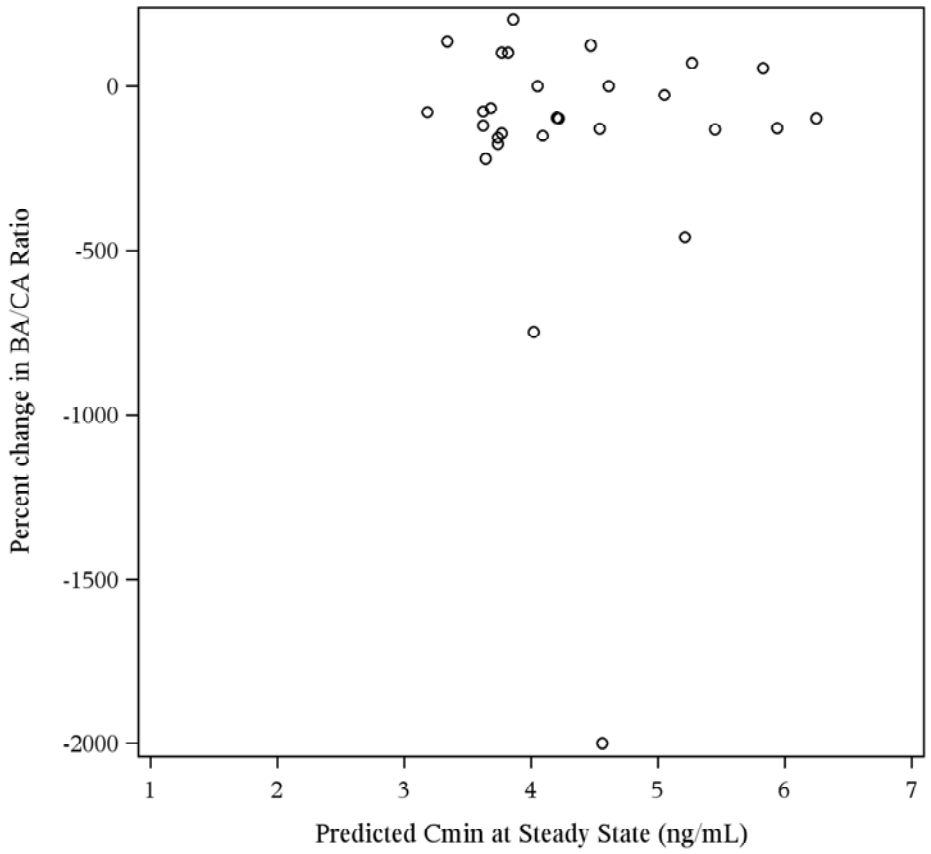


Figure 3. Percent Change of Annualized On-Treatment Bleeding Days from Retrospective Pre-Treatment Period – Best Case Scenario vs. Predicted Steady State C_{min}. Best case scenario data indicates that all non-documented days are assumed to have no bleeding events.

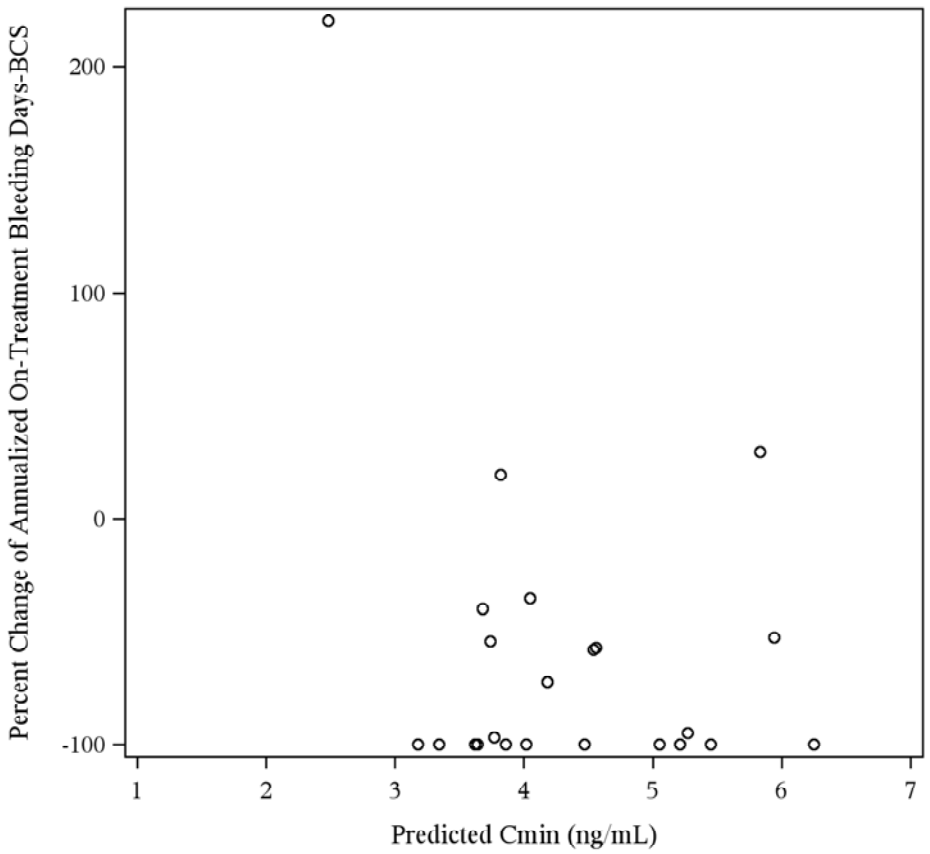
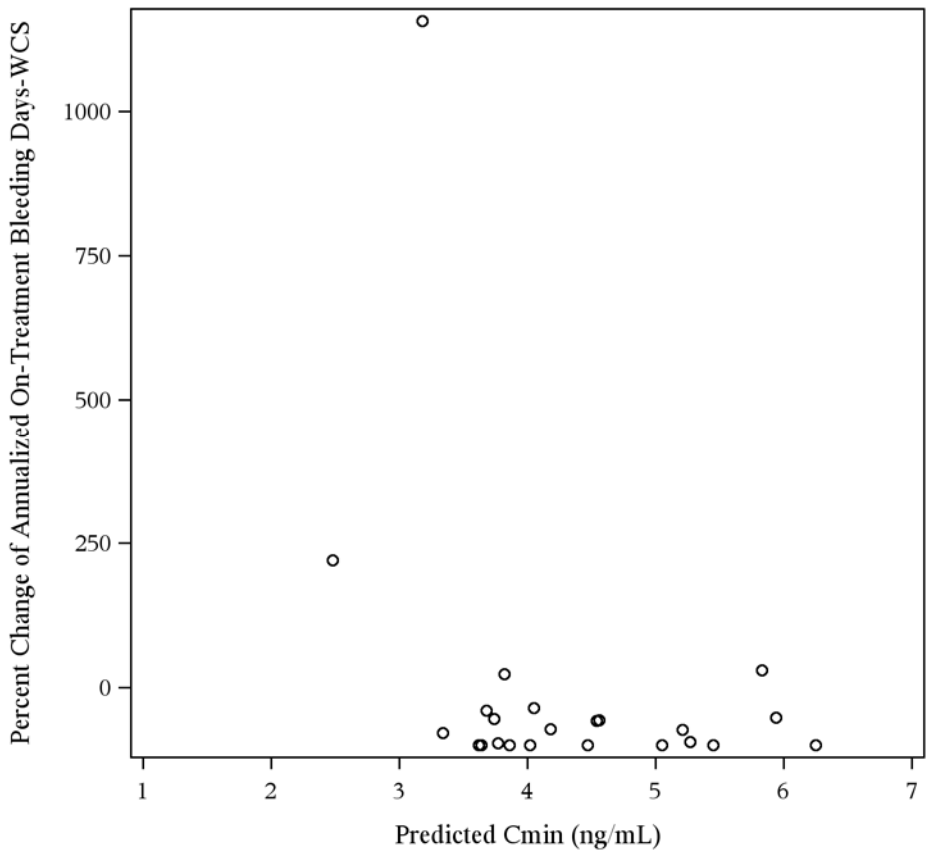


Figure 4. Percent Change of Annualized On-Treatment Bleeding Days from Retrospective Pre-Treatment Period – Worst Case Scenario vs. Predicted Steady State $C_{min.}$ Worst case scenario data indicates that all non-documented days are assumed to have bleeding events.



2.1.1 How are the active moieties identified and measured in the plasma/serum?

The analytical procedure for the determination of fulvestrant in human plasma, involved liquid-liquid extraction followed by reversed phase high performance liquid chromatography (HPLC) with tandem mass spectrometric detection (MS/MS). D6-fulvestrant was used as internal standard.

2.1.2 Have the analytical methods been sufficiently validated?

Yes. The lower and upper limits of quantification (LOQ) for the standard curve were 0.25 and 50 ng/mL for fulvestrant, respectively. No quantifiable interference was found at the retention times of fulvestrant and at the internal standard D6-fulvestrant. The coefficients of determination (r^2) of the calibration curves were above 0.95 (i.e. correlation coefficient (r) >0.99). Back-calculated concentrations of the calibration curves were within acceptable limits. Mean back calculated concentrations were between 98.9% and 102% of nominal with coefficients of variation (CV) in the range 1.8% and 6.3%.
Based on the quality control (QC) results, the precision (CV%) for fulvestrant at 0.50, 25, 45 and 80 ng/mL was 9.9%, 5.6%, 8.1% and 4.9%, respectively. The mean accuracy (% of nominal) was 103%, 98.7%, 98.2% and 96.5%, respectively.

2.2 General Attributes of the drug

Fulvestrant is an estrogen receptor antagonist that binds to the estrogen receptor in a competitive manner with affinity comparable to that of estradiol. Many breast cancers have estrogen receptors and the growth of these tumors can be stimulated by estrogen. Fulvestrant is indicated for the treatment of hormone receptor positive metastatic breast cancer in postmenopausal women with disease progression following anti-estrogen therapy. The recommended dose in this population is 500 mg to be administered intramuscularly into the buttocks slowly (1 - 2 minutes per injection) as two 5 mL injections, one in each buttock, on days 1, 15, 29 and once monthly thereafter. The intramuscular formulation was registered in the United States in 2002 under the trade name Faslodex.

2.3 Pertinent Regulatory Background

FASLODEX® has been approved in 2002 under an original NDA 21-344 for the treatment of hormone receptor positive metastatic breast cancer in postmenopausal women with disease progression following anti-estrogen therapy. The initial dosing regimen for the above mentioned indication was 250 mg monthly. The newer 500 mg monthly dosage regimen as described above was approved in 2010.

In response to the FDA's pediatric written request, the sponsor was required to submit two pediatric studies regarding the treatment of progressive precocious puberty (PPP) associated with McCune-Albright Syndrome (MAS) in female patients age ≤ 10 years; 1) a population pharmacokinetic study and 2) a safety and efficacy study.

Sponsor conducted study 44 which was an open-label, multi-center, non-comparative, exploratory phase II study to evaluate efficacy, safety and pharmacokinetics of fulvestrant in girls with PPP arising from MAS. Given the rarity of this condition and the age of the patients the sponsor determined it was not feasible to conduct a controlled study, and the nature of the study was exploratory rather than confirmatory. As there was no control arm in the trial, all comparisons are versus baseline. The design of Study 44 was such that no single endpoint was identified as being of primary importance. The efficacy endpoints are listed in Table 1.

Table 1. Efficacy endpoints in Study 44

Category in Written Request	Description	Methods of assessment and derivation
Study endpoints	Vaginal bleeding	Change in the frequency of annualized days of vaginal bleeding on treatment compared to baseline.
		Percentage of patients with baseline vaginal bleeding who experienced ≥50% reduction in the number of vaginal bleeding days on treatment compared to baseline.
		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.
	Bone age	Change in bone age advancement over a 6-month trial period and over the whole 12-month trial.
	Growth velocity	Change in growth velocity (annualized growth velocity, i.e., cm/y) over a 6-month trial period and over the whole 12-month trial.
Additional assessments	Uterine volume	Change in uterine volume from baseline to Month 12 / Final Visit by ultrasound
		Change in uterine volume from baseline to Month 6 by ultrasound
		Change in uterine volume from Month 6 to Month 12 by ultrasound.
	Ovarian volume	Change in mean ovarian volume from baseline to Month 12 / Final Visit by ultrasound
		Change in mean ovarian volume from baseline to Month 6 by ultrasound
		Change in mean ovarian volume from Month 6 to Month 12 by ultrasound
		Number and size of ovarian cysts at different time points.
	Tanner stage	Change in Tanner stage of breast from baseline to Month 12 / Final Visit
		Change in Tanner stage of pubic hair from baseline to Month 12 / Final Visit.
	Predicated adult height (PAH)	Change in PAH from baseline Month 12 / Final Visit

Source: clinical-overview.pdf, table 1, page 14/29

The 12 month duration of treatment in Study 44 was considered sufficient for clinical effects to be observed in MAS. Over the main 12 month treatment period in study 44, fulvestrant demonstrated efficacy for a number of MAS associated endpoints, most notably a reduction in the frequency of vaginal bleeding and a reduction in the rate of bone age advancement, compared to baseline.

The PK study was incorporated as a sub-study of the main safety and effectiveness study. Pharmacokinetic data collected in this study along with the adult PK data from studies 20/21 was used to describe the PK of fulvestrant in pediatric female patients using a non-linear mixed effects modeling approach. Studies 20 and 21 both utilize 125 mg as well as 250 mg doses.

There are no current approved treatments for this indication. The labels for Arimidex and tamoxifen currently have a description of pediatric trials performed on girls with PPP associated with MAS.

The sponsor is not seeking a new indication based on the pediatric studies and proposes to update the label to include the relevant clinical and PK information obtained from the pediatric study 44. Pediatric exclusivity has been granted to the sponsor.

3 Detailed Label Recommendations

8.4 Pediatric Use

Labeling statements for sNDA 21-344 to be removed are shown in ~~red strikethrough font~~ and suggested labeling to be included is shown in underline blue font.

Pharmacokinetics

(b) (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 ($C_{min,ss}$) and AUC_{ss} were 4.2 (0.9) ng/mL and 3680 (1020) ng*hr/mL, respectively.

4 PM Review

4.1 Sponsor's Analysis

Studies 20 and 21 had rich adult PK data while study 44 had sparse pediatric PK data. For study 44 , the first 10 patients received a 2 mg/kg dose and had a weekly blood sample (approximately 2.6 mL each) taken during the first month on a random day during the first, second and third weeks and just prior to the second dose (a total of 4 samples in the

1st month of dosing). The dose was escalated to 4 mg/kg monthly in the third month for all of the first 10 patients. The remaining 20 patients received 4 mg/kg monthly dose as a starting dose and did not have a blood sample drawn in the first month. For all patients, blood samples were randomly collected from each of these patients just prior to the monthly injection on one or two occasions between Month 7 and Month 9 with at least one month in between, in order to confirm the trough steady state plasma fulvestrant concentrations.

The sponsor performed a population pharmacokinetic analysis of pooled concentration data including study 44 (n=30 pediatric MAS patients) as well as studies 20 and 21 (approximately 300 adult breast cancer patients, respectively) using the non-linear mixed effects modeling method. Modeling was performed using NONMEM version 6.0. The data were described by a two-compartment disposition model with 1st order absorption.

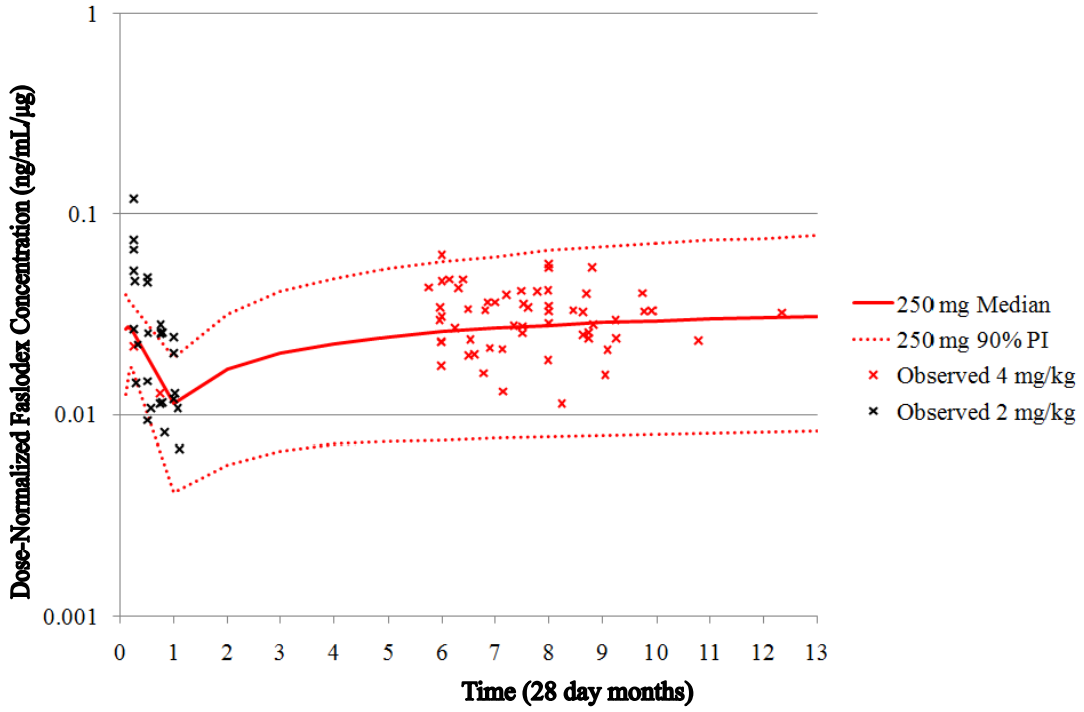
The sponsor estimated the population clearance (CL/F) to be 38.4 L/hr (CV 30.1%). CL/F increased with increasing body weight. Since body weight was found to be a significant covariate for CL/F, the final model incorporated allometric scaling with an allometric exponent estimated to be 0.402. The sponsor determined that CL/F in children was 32% lower than in postmenopausal women.

The population V_{ss}/F estimate (V1/F+V2/F) was 65700, where V1/F was estimated as 33000 L (CV 70.0%) and V2/F was estimated as 32700 L (CV 54.4%). The sponsor determined that CL/F and V1/F were positively correlated (0.85). Residual error was modeled using an additive error model on a log scale and had a standard deviation of 0.23.

The estimated half life is 70.4 ± 8.10 days. The median accumulation ratio was estimated by the sponsor to be 4.07 with a range of 3.49-5.18. Steady-state parameter estimates for the 4 mg/kg dose were: geometric mean C_{max} 6.81 ng/mL (CV 33.4%), median t_{max} 5 days (4-5 days min-max), geometric mean C_{min} 4.19 ng/mL (CV 20.3%), and geometric mean $AUC_{(0-\tau)}$ 3680 ng*hr/mL (CV 26%).

The sponsor demonstrated adult (study 20/21) dose-normalized predicted concentrations are similar to time-matched dose-normalized observed concentrations in children (study 44) occurring from approximately 6 months on-study until the end of the study (Figure 5).

Figure 5. Dose-normalized pediatric (Study 44) concentrations and adult (Studies 20/21) prediction interval (PI)

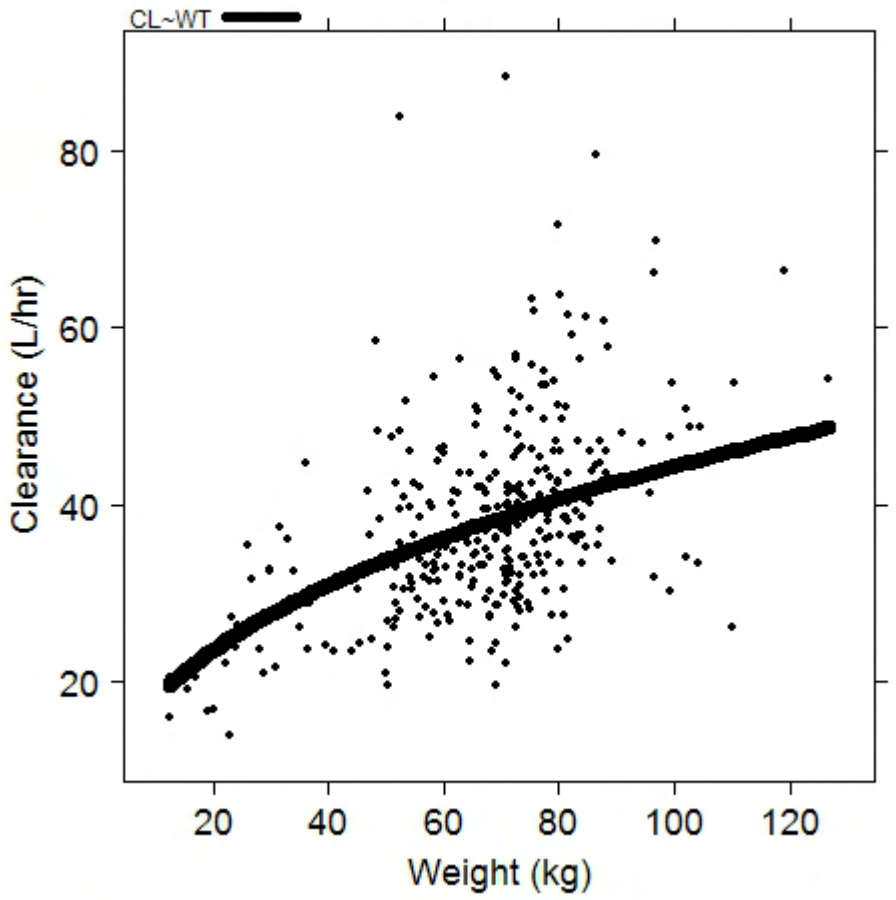


Source: population-pkpd-report.pdf, Figure 23,Page 36/71

Reviewer's Comments.

- *The pharmacokinetic analysis adequately described the fulvestrant concentration data. The oral clearance (Figure 6) was modeled as CL/F = 38.4 * (weight/71)^0.402, where weight is body weight in kilograms, 38.4 and 0.402 are the parameters representing mean population clearance (L/hr) and the allometric exponent, respectively. Due to the shallow allometric exponent (estimated to be 0.402) slope for the body weight-clearance relationship (Figure 6), the body weight dosing scheme (4 mg/kg) appears to under-dose children and thus result in lower achieved C_{min} than the assumed equivalent adult dose of 250 mg. Pediatric clearance was estimated to be 32% lower than adults.*

Figure 6. Clearance vs. Weight Scatterplot with Allometric Model Predictions. Black solid line is the population mean and black circles represent post-hoc individual clearance estimates.



- *While the sponsor demonstrates that adult dose-normalized concentrations are comparable to pediatric dose-normalized concentrations (see Figure 5), the sponsor's dose selection algorithm is guided by concentrations, not dose-normalized concentrations. This finding is also important as the sponsor assumed that the 250 mg monthly dose in adult patients corresponds to a dose of approximately 4 mg/kg in pediatric patients. The reviewer compared observed adult steady state C_{min} following a 250 mg monthly regimen to predicted pediatric steady state C_{min}. Pediatric patients receiving 4 mg/kg once monthly fulvestrant achieved 45% lower exposures than adults receiving 250 mg once monthly (Figure 1). The mean (sd) predicted steady state C_{min} was 4.27 (0.867) ng/mL in pediatric patients receiving 4 mg/kg once monthly and was 7.70 (2.13) ng/mL in adults receiving the 250 mg monthly dose.*
- *Furthermore, the concentrations depicted in Figure 1 represent steady state concentrations for adults as well as children, whereas the concentrations depicted in Figure 5 only represent steady state for adults after approximately 7 months ($t_{½,\ adult} \approx 40$ days, 5 half lives ≈ 200 days). For children, steady state is achieved after about 12 months ($t_{½,\ pediatric} \approx 70.4$ days, 5 half-lives ≈ 352 days). However, the mean time for pediatric concentration measurements is 213 days and the majority of the pediatric concentrations in* Figure 5 *are measured before 4 half-lives have been achieved (4 half lives ≈ 281.6 days). Thus, pediatric patients have achieved ~81% of the steady state Cmin by this time and it may not be appropriate to directly compare the pre-steady-state*

pediatric concentrations represented in Figure 5 with the adult steady-state concentrations.

- *Sponsor could potentially explore doses higher than 4 mg/kg since the exposures in pediatrics were lower than the 250 mg and the currently approved 500 mg monthly dosing regimen in adults.*
- *Sponsor could also explore the option of introduction of the additional dose on day 15 during the first month as is described in the current Faslodex® label (Section 2.1, "The recommended dose is 500 mg to be administered intramuscularly into the buttocks slowly (1 - 2 minutes per injection) as two 5 mL injections, one in each buttock, on days 1, 15, 29 and once monthly thereafter"). The additional dose given on day 15 after the initial dose allows for steady state concentrations to be reached within the first month of dosing in adults.*

4.2 Reviewer's Analysis

4.2.1 Introduction

This exploratory analysis was performed in order to determine if the clinical trial data support an exposure-response relationship for the annualized vaginal bleeding and bone age advancement efficacy endpoints.

4.2.2 Objectives

Analysis objectives are to determine if there is evidence of an exposure-response relationship for efficacy.

4.2.3 Methods

This analysis examined the relationship between these two endpoints which demonstrated statistically significant change from baseline in the clinical study and the C_{min} value. Bone age advancement is defined as change in bone age in years divided by the change in chronological age in years (page 14/29 of clinical overview). Both these bone age assessments were measured at 6 and 12 months in the trial. Percent change in bone age advancement at 6-months is the percent change in bone age advancement at 6-months into the treatment period compared to the value established during the 6-month pre-treatment period. A similar format is used to determine percent change in bone age advancement at 12 months. Annualized bleeding days during the 6-month pre-treatment period is the number of bleeding days multiplied by two. Percent change in annualized on-treatment bleeding days is the percent change in annualized bleeding days that occurred during treatment compared with the annualized bleeding days during the 6-month pre-treatment period.

4.2.4 Data Sets

Data sets used are summarized in Table 2.

Table 2. Analysis Data Sets

Study Number	Name	Link to EDR
D6992C00044	r-bone	\\cdsnas\PHARMACOMETRICS\Reviews\Ongoing PM Reviews\Fulvestrant_NDA21344_MB\Sponsor Data and Reports\5352-stud-rep-uncontr\d6992c00044\crt\datasets\r-bone.xpt
D6992C00044	r-vbleed	\\cdsnas\PHARMACOMETRICS\Reviews\Ongoing PM Reviews\Fulvestrant_NDA21344_MB\Sponsor Data and Reports\5352-stud-rep-uncontr\d6992c00044\crt\datasets\r-vbleed.xpt
D6992C00044	nonmem44	\\cdsnas\PHARMACOMETRICS\Reviews\Ongoing PM Reviews\Fulvestrant_NDA21344_MB\Sponsor Data and Reports\5353-rep-analys-data-more-one-stud\stf-nonmem-d6992c00044\crt\datasets\nonmem44.xpt
D6992C00044	r-pkparm	\\cdsnas\PHARMACOMETRICS\Reviews\Ongoing PM Reviews\Fulvestrant_NDA21344_MB\Sponsor Data and Reports\5352-stud-rep-uncontr\d6992c00044\crt\datasets\r-pkparm.xpt

4.2.5 Software

The following software packages were used in the analyses.

- SAS version 9.2
- NONMEM version 6
- R version 2.10.1
- MS Excel 2003

4.2.6 Models

Percent change in bone age advancement assessed at 12-months on-treatment was plotted against the predicted steady state C_{min} values on a scatterplot. Since longitudinal endpoint data were available, the percent change in bone age advancement occurring during the first 6-months on treatment was plotted against the observed C_{min} occurring nearest to 6-months for each pediatric patient on a scatter plot. Scatter plots of the annualized vaginal bleeding and bone age advancement endpoints compared with the corresponding C_{min} were generated. An exposure-response relationship would be apparent if a reduction in annualized vaginal bleeding accompanied a fulvestrant concentration increase or if a reduction in bone age advancement accompanied a fulvestrant concentration increase.

4.2.7 Results

The bone age advancement efficacy endpoint (Figure 4) does not support an exposure response relationship (Figure 2). The narrow concentration range (minimum and maximum C_{min} values near the 12^{th} month of study period which were 2.5 and 6.3 ng/mL,

respectively) obtained from administration of only one dose level (4 mg/kg) may be partially responsible for lack of an observed exposure-response relationship.

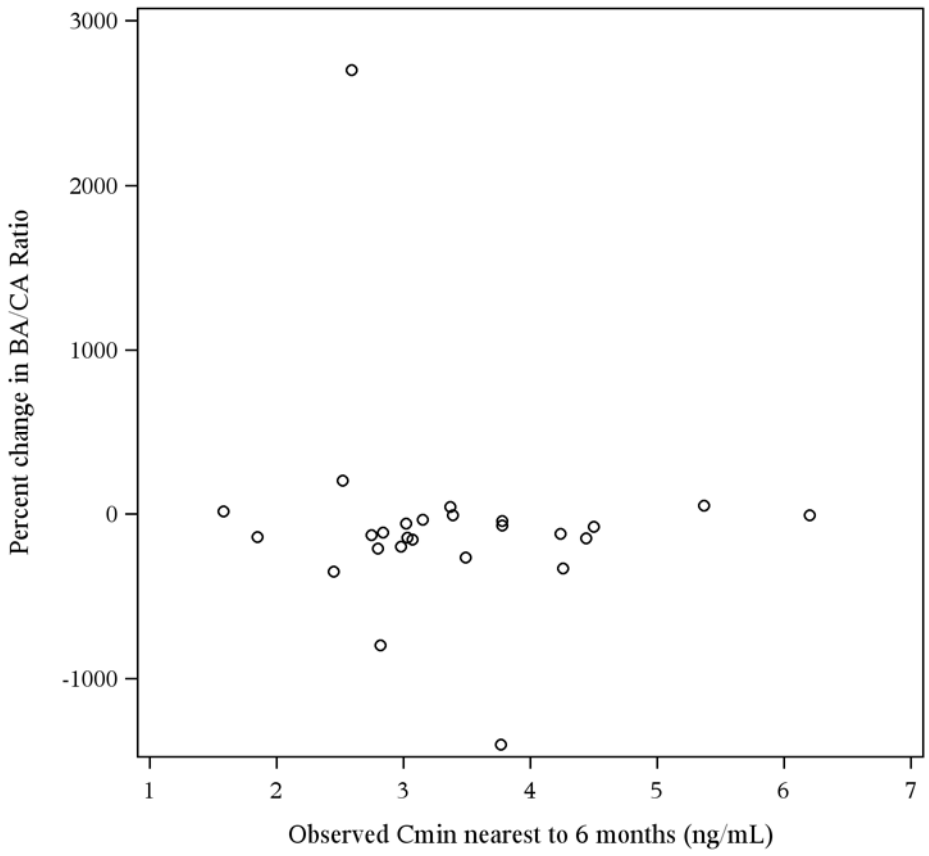
In addition to the 12-month assessments, the results of the exposure-response analysis for the percent change in bone age advancement at 6 months compared to the pretreatment period versus the observed C_{min} nearest to 6 months (Figure 7) do not support an exposure-response relationship.

The annualized vaginal bleeding efficacy endpoint does not support an exposure-response relationship (Figure 3 and Figure 4). There are two main limitations to the vaginal bleeding assessment method:

1. Baseline data was collected retrospectively based on patient's caregiver recollection of the 6-month pre-treatment period and thus is subjective
2. The prospective phase (baseline to 12 months) had missing data. Thus, the data were analyzed according to a best and worst case scenario. Worst case scenario data indicates that all non-documented days are assumed to have bleeding events. Best case scenario data indicates that all non-documented days are assumed to have no bleeding events.

Thus, these two limitations to the data collection scheme may have confounded the apparent presence of an exposure-response relationship.

Figure 7. Percent Change in Bone Age / Chronological Age Ratio at 6 Months Compared to Pre-Treatment Period Vs. Observed C_{min} Near 6-Months.



4.2.8 Listing of Analysis Data, Code, and Output

File Name	Description	Location in \\cdsnas\pharmacometrics\ (b) (4)
cmin_plot_ generation_final.sas	Creates plots of C_{min} values, also creates an input data file for generating nonmem concentration prediction (IPRE). Also, creates an input file for the exposure response scripts.	
run30.csv	A modification of the NONMEM44.xpt file, which includes additional observations occurring one-month after the final dose in order to generate IPRE values at those times. This file is created from the cmin_plot_generation.sas file.	
final-mod.txt	Sponsor's final NONMEM model file.	
run30.mod	Modification of sponsor's final nonmem script (final-mod.txt), altered to match Waban requirements, and used with run30.csv to generate predictions.	
sdtab30	The output of this NONMEM run for the run30.csv dataset. sdtab30 is used as an input to the cmin_plot_generation file.	
combin_inp_nm_ sdtb_out_spon_ pred.sas7bdat	manipulated data file created by cmin_plot_generation.sas, used as an input to exposure-response scripts.	
exposure-response - bleed.sas	Create exposure-response plots for the vagnial bleeding data	
exposure-response - bone age.sas	Create exposure-response plots for the bone age advancement data	
2 - Intrasubject mean Cmin 7+ months adult 250 mg - CMINSS ped study 44.png	Box plot of C_{min} values for adults receiving 250 mg and pediatric patients. Data presented are intrasubject mean C_{min} value for all concentrations measured at 7+ months in adults, and predicted C_{min} at steady state values for pediatric patients.	
ER bleed - Percent Change of Annualized On-Treatment Bleeding Days - CMINSS - Best Case Scenario.png	Plot of the percent change of annualized on-treatment bleeding days compared to the retrospective pre-treatment period versus predicted C_{min} at steady state. Best case scenario data indicates that all	

	non-document days are assumed to have no bleeding events.	(b) (4)
ER bleed - Percent Change of Annualized On-Treatment Bleeding Days - CMINSS - Worst Case Scenario.png	Plot of the percent change of annualized on-treatment bleeding days compared to the retrospective pre-treatment period versus predicted C_{min} at steady state. Worst case scenario data indicates that all non-document days are assumed to have bleeding events.	
ER bone - Percent Change in BA-CA Ratio at 6 Months Compared to Screening - Concs Near 6-Months. png	Plot of the percent change in the ratio of bone age to chronological age assessed at 6 months compared to the ratio established throughout the retrospective study period until screening versus concentrations occurring near 6 months.	
ER bone - Percent Change in BA-CA Ratio at 12 Months Compared to Screening - CMINSS. png	Plot of the percent change in the ratio of bone age to chronological age assessed at the 6-to-12 months time-frame compared to the ratio established throughout the retrospective study period until screening versus sponsor predicted steady state concentrations.	
POPPK Tool	Used to generate NONMEM diagnostic plots, in particular, CL.vs.WT.Cov.jpg.	
CL.vs.WT.Cov.jpg	Scatter plot of clearance versus body weight with allometric clearance predictions. Generated using POPPK tool.	

5 OCP Filing Forms

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA/BLA Number	**21-344**	**Brand Name**	**Faslodex**
OCP Division (I, II, III, IV, V)	**II**	**Generic Name**	**Fulvestrant**
Medical Division	**Metabolic and Endocrine Products**	**Drug Class**	**Steroidal anti-estrogen**
OCP Reviewer	**Jaya bharathi Vaidyanathan, Ph.D.**	**Indication(s)**	**No indication is being sought in this application**
OCP Team Leader	**Sally Choe, Ph.D.**	**Dosage Form**	**Injection, 50 mg/mL**
Pharmacometrics Reviewer	**Nitin Mehrotra, Ph.D.**	**Dosing Regimen**	**Solution for injection**
Date of Submission	**11/17/10**	**Route of Administration**	**Intramuscular**
Estimated Due Date of OCP Review	**3/17/11**	**Sponsor**	**Astra Zeneca**
Medical Division Due Date	**4/17/11**	**Priority Classification**	**P**
PDUFA Due Date	**5/17/11**		

Clinical Pharmacology Information

	"X" if included at filing	**Number of studies submitted**	**Number of studies reviewed**	**Critical Comments If any**
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	**X**			
Tabular Listing of All Human Studies	**X**			
HPK Summary	**X**			
Labeling	**X**			
Reference Bioanalytical and Analytical Methods	**X**			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:				
multiple dose:				
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD -				

Phase 2:				
Phase 3:				
PK/PD -				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:		**X**	**1**	
II. Biopharmaceutics				
Absolute bioavailability				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies				
Bio-waiver request based on BCS				
BCS class				
Dissolution study to evaluate alcohol induced dose-dumping				
III. Other CPB Studies				
Genotype/phenotype studies				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies		**1**	**1**	

On **initial** review of the NDA/BLA application for filing:

	Content Parameter	Yes	No	N/A	Comment
Criteria for Refusal to File (RTF)					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?			X	
2	Has the applicant provided metabolism and drug-drug interaction information?			X	
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?			X	
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?	X			
5	Has a rationale for dose selection been submitted?			X	
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?	X			
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	X			
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?	X			

Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
Data					
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	X			
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			X	
Studies and Analyses					
11	Is the appropriate pharmacokinetic information submitted?	X			
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?			X	
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?			X	
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?			X	
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			X	
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?	X			
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?	X			
General					
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?			X	
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?		X		

4.1 Signatures

Nitin Mehrotra, Ph.D . Pharmacometrics Reviewer Division of Pharmacometrics	Jayabharathi Vaidyanathan, Ph.D. Metabolism Endocrinology Reviewer Division of Clinical Pharmacology 2
Sally Choe, Ph.D. Team Leader, Metabolism Endocrinology Division of Clinical Pharmacology 2	Christine Garnett, Pharm.D. Team Leader, Pharmacometrics Division of Pharmacometrics

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

/s/

NITIN MEHROTRA
04/15/2011

JAYABHARATHI VAIDYANATHAN
04/15/2011

CHRISTINE E GARNETT
04/18/2011

SALLY Y CHOE
04/19/2011