CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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CLINICAL PHARMACOLOGY REVIEW(S)

Office of Clinical Pharmacology Integrated Review

BLA Number	761148
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Submission Date	10/24/2019
Submission Type	351(a), Standard Review
Brand Name	Rolontis®
Generic Name	Eflapegrastim
Dosage Form and Strength	Subcutaneous Injection 13.6 mg
Proposed Indication	(b) (4)
Applicant	Spectrum Pharmaceuticals, Inc.
Associated IND	103461
OCP Review Team	Anusha Ande, Ph.D., Eliford Kitabi, Ph.D., Justin Earp, Ph.D., Sudharshan Hariharan, Ph.D.
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1. EXECUTIVE SUMMARY

This clinical pharmacology review is for an original Biologics License Application (BLA), submitted by Spectrum Pharmaceuticals to the Division of Non-malignant Hematology (DNH). The applicant is seeking approval for Rolontis® (Eflapegrastim) to decrease the incidence of infection, as manifested by febrile neutropenia, in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs associated with clinically significant incidence of febrile neutropenia. Eflapegrastim is a recombinant human granulocyte growth factor that binds to granulocyte-colony stimulating factor (G-CSF) receptors on myeloid progenitor cells and neutrophils, triggering signaling pathways that control cell differentiation, proliferation, migration and survival. There are currently two other myeloid growth factors (filgrastim and pegfilgrastim) that are approved in the U.S. for the same indication.

The proposed dose of eflapegrastim is a single injection of 13.2 mg administered subcutaneously via a single-dose prefilled syringe once per chemotherapy cycle. The applicant is relying on the efficacy and safety information from two pivotal multicenter, randomized, open-label, active-controlled Phase 3 studies in patients with early stage breast cancer (ESBC) receiving docetaxel and cyclophosphamide (TC) chemotherapy. The primary efficacy endpoint was met in both studies, with eflapegrastim demonstrating non-inferiority to pegfilgrastim for the duration of severe neutropenia (DSN) in Cycle 1. All secondary analyses in both pivotal studies showed that the efficacy of eflapegrastim was not different than pegfilgrastim.

The primary focus of this review is to evaluate the acceptability of general dosing recommendations and to explore the need for dose optimization based on extrinsic and intrinsic factors.

1.1 Recommendations

The Office of Clinical Pharmacology review team has reviewed the information submitted in BLA 761148 and recommends approval of eflapegrastim to decrease the incidence of febrile neutropenia in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs.

Key review issues with specific recommendations and comments are summarized below:

Review Issues	**Recommendations and Comments**
Pivotal or supportive evidence of effectiveness	The primary evidence of effectiveness is from two pivotal Phase 3 multicenter, randomized, open-label, active-controlled studies in patients with ESBC receiving TC chemotherapy (SPI-GCF-301 and SPI-GCF-302). The primary efficacy variable was the DSN which showed non-inferiority for eflapegrastim compared to pegfilgrastim in Cycle 1.

	An additional Phase 2 multicenter, sequentially enrolled, open-label, active-controlled, dose-ranging study in patients with ESBC receiving TC chemotherapy (SPI-GCF-12-201) provided supportive evidence. A dose proportional effect in DSN was observed across the three eflapegrastim dosing cohorts, with mean DSN values generally decreasing with increasing dose.
General dosing instructions	The recommended dosage of Rolontis is a single subcutaneous injection of 13.2 mg administered once per chemotherapy cycle. Administer approximately 24 hours after cytotoxic chemotherapy. Do not administer between 14 days before and 24 hours after administration of cytotoxic chemotherapy.
Dosing in patient subgroups (intrinsic and extrinsic factors)	No dose adjustments are needed based on age, race, sex, bodyweight, renal or hepatic impairment. Metabolic/transporter mediated interactions or impact of food does not apply for eflapegrastim.
Labeling	Pending agreement with the Applicant
Bridge between the to-be-marketed and clinical trial formulations	NA. The to-be-marketed formulation is the same as the clinical trial formulation.

1.2 Post-Marketing Requirements and Commitments

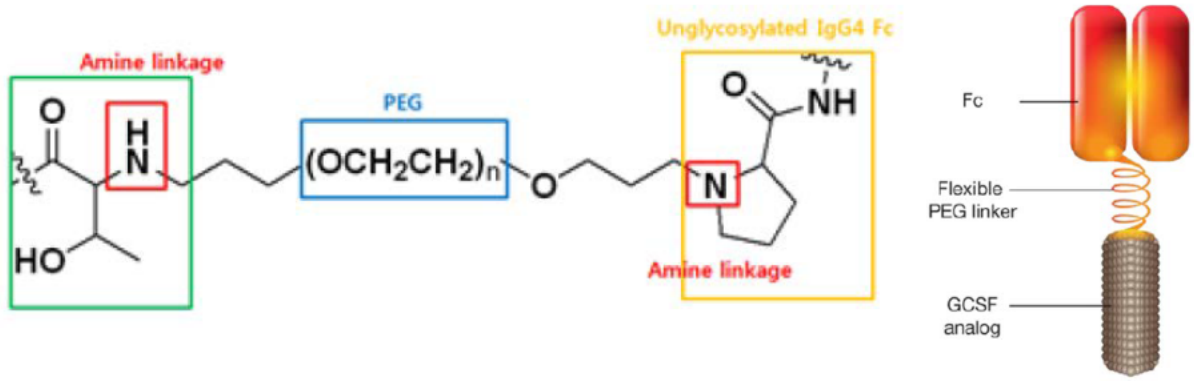
None.

2. SUMMARY OF CLINICAL PHARMACOLOGY ASSESSMENT

2.1 Pharmacology and Clinical Pharmacokinetics

Eflapegrastim (Rolontis®) is a long-acting granulocyte-colony stimulating factor (G-CSF) produced by covalent coupling of a human G-CSF analog and human immunoglobulin G4 (IgG4) Fc fragment, both derived from recombinant *Escherichia coli (E. coli)*, via a single 3.4 kDa polyethylene glycol (PEG) linker (***Figure 1***).

Figure 1 Structure Illustrations of Eflapegrastim



The Fc fragment of eflapegrastim is intended to increase the circulating half-life of G-CSF and the duration of biological response as compared to filgrastim, a recombinant methionyl human G-CSF, which has a half-life of 3.5 hours, potentially allowing for a longer dosing interval. While eflapegrastim has a half-life similar to that of pegfilgrastim, its dose in terms of G-CSF equivalence is lower than that of pegfilgrastim i.e., (b) (4) mg vs 6 mg. Eflapegrastim is eliminated primarily by internalization and degradation upon binding to the G-CSF receptors present on neutrophils. Therefore, eflapegrastim clearance decreases with increasing doses following single dose administration, suggesting target-mediated clearance of eflapegrastim by neutrophils. However, following repeat administration, clearance increases in Cycle 3 as compared to Cycle 1 resulting in lower plasma concentrations of eflapegrastim, potentially due to the subsequent treatment-mediated increase in neutrophils.

Pharmacology and ADME characteristics of eflapegrastim are summarized below in the table.

Pharmacology	
Mechanism of Action	Eflapegrastim is a recombinant human granulocyte growth factor that binds to G-CSF receptors on myeloid progenitor cells and neutrophils, triggering signaling pathways that control cell differentiation, proliferation, migration and survival.
General Information	

Bioanalysis	Eflapegrastim concentrations in serum samples were determined using a validated bioanalytical assay by [redacted] (b) (4). The samples were analyzed using an Enzyme-Linked Immunosorbent Assay (ELISA) assay with a lower limit of quantification (LLOQ) of 6.25 ng/mL.
Dose proportionality	After subcutaneous (SC) dosing, the pharmacokinetics of eflapegrastim was nonlinear and exposure increases were greater than dose-proportional over the dose range of 45 to 350 µg/kg.
Accumulation	After repeated dosing, the exposure of eflapegrastim in Cycle 3 was lower than in Cycle 1, with accumulation ratios for C_{max} and AUC_{last} of 0.35 and 0.38. The decrease in exposure over rounds of eflapegrastim treatment is potentially due to the subsequent treatment-mediated increase in absolute neutrophil count (ANC) concentration, as higher ANC is expected to result in lower plasma concentrations of eflapegrastim due to target-mediated elimination.
Immunogenicity	Antibodies to eflapegrastim were detected using bridging ELISA with sensitivity of 65 ng/mL. From the two Phase 3 studies, 28 of 297 (9.4%) patients treated with eflapegrastim and 10 out of 306 (3.3%) patients treated with pegfilgrastim developed antibodies following treatment. One out of 297 (0.3%) patients treated with eflapegrastim tested positive in the neutralizing antibody (Nab) assay. Due to the high prevalence of preexisting anti-PEG antibodies (60-70%), an approach involving evaluation of treatment-emergent anti-PEG antibodies was employed in which post dose titer had to increase by at least 4-fold to be assessed as positive. Treatment-emergent anti-PEG antibodies were detected by a direct binding ELISA in 126 out of 268 patients (47%) treated with eflapegrastim compared to 167 out of 263 patients (63.5%) treated with pegfilgrastim. No clinically significant differences in the pharmacokinetics, efficacy, or safety profile of eflapegrastim were observed in patients who tested positive for anti-drug antibodies (ADA).
Absorption	
T_{max}	The median T_{max} of eflapegrastim is 25 hours (6 to 144 hours) in patients with breast cancer following administration of the recommended dosage.

Distribution	
Volume of distribution	The volume of distribution of eflapegrastim is 1.44 L.
Elimination	
Half-life	The geometric mean half-life of eflapegrastim in patients with breast cancer is 36.4 hours (16.1 to 115 hours) during Cycle 1 and 57.3 hours (51.2 to 62.6 hours) during Cycle 3.
Metabolism/Excretion	Eflapegrastim is expected to be metabolized by endogenous degradation following receptor-mediated internalization by cells bearing the G-CSF receptor. Eflapegrastim was not detected in urine.

2.2 Dosing and Therapeutic Individualization

2.2.1 General dosing

The recommended dosage of Rolontis is a single subcutaneous injection of 13.2 mg administered once per chemotherapy cycle. Eflapegrastim should be administered approximately 24 hours after cytotoxic chemotherapy.

2.2.2 Therapeutic individualization

No dose individualization is recommended based on extrinsic/intrinsic factors. Neither renal nor hepatic impairment is expected to impact the pharmacokinetics of eflapegrastim. No extrinsic factors were evaluated in the clinical studies or in the population PK (popPK) analysis. Drug-drug interactions are not expected based on the mechanism of action and molecular properties of eflapegrastim.

2.3 Outstanding Issues

None.

2.4 Summary of Labeling Recommendations

The clinical pharmacology section of the proposed label was updated to reflect the current Guidance on Clinical Pharmacology Section of Labeling for Human Prescription Drug and Biological Products.

The following edits were suggested in section 12.3 to highlight specific PK characteristics of eflapegrastim and to indicate that the data is in patients with breast cancer wherever applicable:

- Absorption: The median T_{max} of eflapegrastim is 25 hours (6 to 144 hours) in patients with breast cancer following administration of the recommended dosage.
- Elimination: The geometric mean half-life of eflapegrastim in patients with breast cancer is 36.4 hours (16.1 to 115 hours) during Cycle 1. Following repeat administration, clearance increased in Cycle 3 as compared to Cycle 1, potentially due to the subsequent increase in neutrophils.
- Metabolism: Eflapegrastim is expected to be metabolized by endogenous degradation following receptor-mediated internalization by cells bearing the G-CSF receptor.

3. COMPREHENSIVE CLINICAL PHARMACOLOGY REVIEW

3.1 Clinical Pharmacology Questions

3.1.1. To what extent does the available clinical pharmacology program provide supportive evidence of effectiveness?

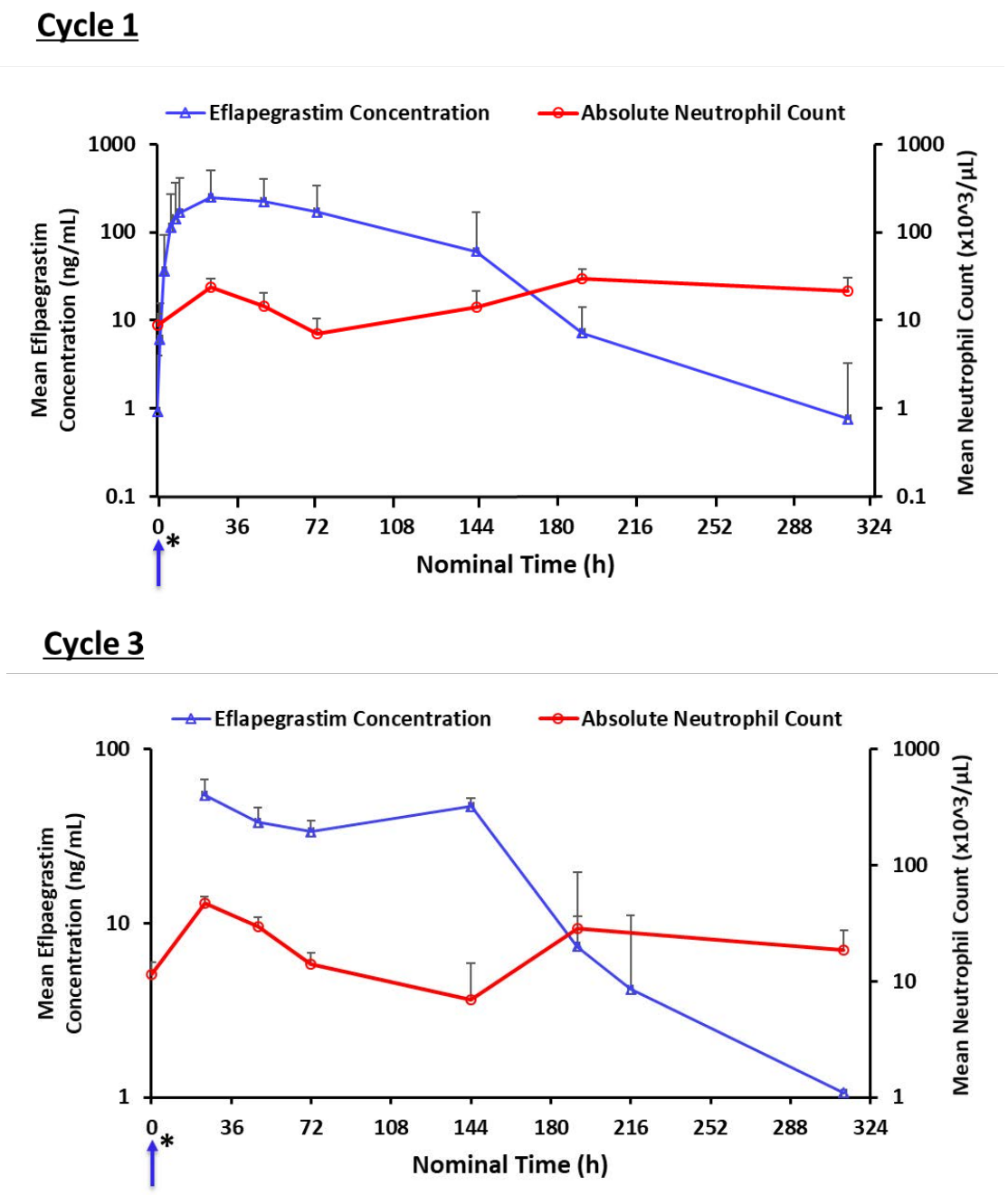
The primary evidence of effectiveness of eflapegrastim is based on two multicenter, randomized, open-label, active-controlled Phase 3 studies (SPI-GCF-301 and SPI-GCF-302) and a supportive Phase 2 study (SPI-GCF-12-201) in patients with ESBC receiving TC chemotherapy which are discussed in *3.1.2*. From a clinical pharmacology perspective, supportive evidence for effectiveness comes from the mechanistic description of PK and PD from the Phase 1 study and dose-response data from the Phase 2 study.

PK-ANC relationship:

In both Phase 1 studies, PD endpoints were ANC and CD34+ cell counts in blood samples taken from pre-dose to 22 days after dosing. Single SC doses of eflapegrastim produced a dose-dependent increase in ANC and CD34+ over the dose range of 3.3 to 270 μg/kg.

The PK/PD relationship of eflapegrastim was evaluated using the data from one Phase 1 study (SPI-GCF-301-PK), conducted in patients dosed at the intended clinical dose (13.2 mg) once per chemotherapy cycle for 4 cycles. The mean eflapegrastim concentration and corresponding ANC over time are displayed in ***Figure 2***. The mean ANC-versus-time profiles in both Cycles 1 and 3 had an initial peak followed by a nadir, and then a recovery peak.

Figure 2 Mean Eflapegrastim Concentration Overlaid by Absolute Neutrophil Count



**Eflapegrastim was administered on Day 2 of each Cycle [Source: SPI-GCF-301-PK CSR]*

In Cycle 1, the mean pre-dose ANC was 8.7×10^9/L and the first peak (23.7×10^9/L) occurred at 24 hours after eflapegrastim administration (Cycle 1, Day 3). The nadir on Day 3 (Cycle 1, Day 5) was 7.1×10^9/L, or approximately 78% of the pre-dose mean ANC. The recovery peak (30.0×10^9/L) occurred on Day 8 (Cycle 1, Day 10) and remained >2-fold above pre-dose values

on Day 13 (Cycle 1, Day 15) (21.3×10^9/L). The first peak occurs due to a marked increase in peripheral blood neutrophil counts which is attributed to early release of neutrophils from the bone marrow granulocyte reserve, demargination of neutrophils, and prolongation of survival of neutrophils in circulation, which is followed by a neutrophil nadir caused by chemotherapy. The recovery peak occurs due to the rise in neutrophils as the bone marrow recovers.

In Cycle 3, the mean pre-dose ANC (11.5×10^9/L) was approximately 33% higher than in Cycle 1. The post-dose ANC peak (47.2×10^9/L) at 24 hours (Cycle 3, Day 3) was 2-fold higher in Cycle 3 than in Cycle 1. The mean ANC nadir (7.0×10^9/L) was approximately 50% of the pre-dose ANC and occurred on Day 6 (Cycle 3, Day 8). The recovery peak (28.3×10^9/L) occurred on the same day as in Cycle 1 on Day 8 (Cycle 3, Day 10). The Day 13 (Cycle 3, Day 15) mean ANC (18.5×10^9/L) was similar to the Cycle 1 recovery. Similar to Cycle 1, elimination of eflapegrastim in Cycle 3 appears to increase as mean ANC increases to its recovery peak.

The lower eflapegrastim exposures in Cycle 3 were likely due to higher ANC levels in the cycle. Higher ANC levels are expected to cause a decrease in plasma concentrations of eflapegrastim due to target-mediated elimination of eflapegrastim. Because of the complex relationship of ANC to the clearance of eflapegrastim, only a mechanistic description of PK and PD as outlined above was attempted as a formal exposure-response analysis will be confounded and uninterpretable.

Dose-DSN relationship:

The Phase 2 study (SPI-GCF-12-201) was an open-label, multicenter, dose-ranging study of eflapegrastim and pegfilgrastim for the management of neutropenia in adult patients with breast cancer, who were candidates for TC chemotherapy regimen. Eflapegrastim was administered at a dose of 45, 135, or 270 μg/kg and pegfilgrastim at a dose of 6 mg; both were administered once per chemotherapy cycle, on Day 2 (approximately 24 hours ± 2 hours after chemotherapy). ANC was measured to determine the primary efficacy endpoint, i.e., duration of severe neutropenia (DSN) in Cycle 1, with severe neutropenia defined as ANC $<0.5\times10^9$/L and DSN as the interval from the day of first observation of Grade 4 neutropenia to first ANC recovery to $\geq2\times10^9$/L. The ANC-time profiles, after treatment with eflapegrastim, exhibited biphasic patterns, and the maximum ANC value was higher in Cycle 3 than in Cycle 1. The first ANC peak occurred between 1 to 3 days after eflapegrastim dose and the second peak between 8 to 13 days post-dose. Elimination of eflapegrastim appeared to increase as the mean ANC values increased to its recovery peak. The efficacy results from Phase 2 study are presented in the ***Table 1***.

Table 1 Summary of efficacy results from Phase 2 study

	Eflapegrastim (45 µg/kg) N=39	Eflapegrastim (135 µg/kg) N=36	Eflapegrastim (270 µg/kg) N=36	Pegfilgrastim (6 mg) N=36
DSN (days)	1.03	0.44	0.03	0.31
Difference	0.72	0.14	-0.28	
95% CI Non-inferiority p-value	0.19, 1.27	-0.28, 0.64 0.002	-0.56, -0.06 <0.001	

[Source: SPI-GCF-12-201 CSR]

Both 135 and 270 µg/kg doses of eflapegrastim were found to be non-inferior to pegfilgrastim based on prespecified criteria (upper bound of 95% confidence interval [CI] <1 day). Furthermore, eflapegrastim, at a dose of 270 µg/kg, was statistically superior to pegfilgrastim (p=0.023).

To maximize the effectiveness of eflapegrastim in the Phase 3 study and stay within the well-tolerated dose range evaluated in SPI-GCF-12-201, an intermediate dose of approximately 188 µg/kg for a 70 kg patient was selected. This translated to a dose of 13.2 mg (b) (4) mg G-CSF), which is approximately (b) (4) the dose of the active comparator, pegfilgrastim 6 mg (6 mg G-CSF). The fixed dose of 13.2 mg eflapegrastim was chosen for both Phase 3 studies.

3.1.2 Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

Yes, the proposed dosing regimen of 13.2 mg administered SC once per chemotherapy cycle is acceptable to decrease the incidence of febrile neutropenia in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs. This dose was evaluated in the two Phase 3 studies.

SPI-GCF-301 (N=406) and SPI-GCF-302 (N=237) are two Phase 3 multicenter randomized, open-label, active-controlled studies in which patients with ESBC receiving TC chemotherapy were randomized to treatment with either eflapegrastim (13.2 mg) or pegfilgrastim (6 mg). These Phase 3 studies were identical in terms of their study design, primary endpoint, and statistical hypothesis and methodology, however, the studies differed in total numbers of patients and statistical power. After screening, eligible patients received TC chemotherapy (docetaxel 75

mg/m^2 IV and cyclophosphamide 600 mg/m^2 IV), on Day 1 of each of four 21-day cycles. On Day 2 of each cycle, approximately 24 to 26 hours after the last dose of TC chemotherapy, patients received either eflapegrastim 13.2 mg or pegfilgrastim 6 mg. The primary efficacy endpoint of the DSN in Cycle 1 was met in both studies, with eflapegrastim demonstrating non-inferiority to pegfilgrastim based on a prespecified non-inferiority margin (upper bound of 95% CI <0.62 days) (***Table 2***). The mean DSN in the eflapegrastim arm was non-inferior to that of pegfilgrastim arm in Cycles 2 though 4 (secondary). During Cycle 1 in SPI-GCF-301, eflapegrastim treatment significantly reduced the absolute risk of severe neutropenia by 8.5% compared to pegfilgrastim treatment and the relative risk reduction was 34.9%. There were also reductions in the absolute risk (3.2%) and relative risk (13.6%) in SPI-GCF-302, but these differences were not significant. The proposed dosing regimen is acceptable because both the Phase 3 studies met the primary endpoint and the effect on DSN was maintained through Cycles 2-4.

Table 2 Summary of efficacy results from Phase 3 studies

	SPI-GCF-301		**SPI-GCF-302**	
	Eflapegrastim N=196	**Pegfilgrastim N=210**	**Eflapegrastim N=118**	**Pegfilgrastim N=119**
DSN (days) Mean (SD)	0.2 (0.503)	0.35 (0.683)	0.31 (0.688)	0.39 (0.949)
ΔDSN (eflapegrastim - pegfilgrastim)	-0.148		-0.074	
95% Confidence Interval	(-0.264, -0.032)		(-0.292, 0.129)	
Non-Inferiority p-value	<0.0001		<0.0001	

[Source: SPI-GCF-301 CSR, SPI-GCF-302 CSR]

3.1.3 Is an alternative dosing regimen and/or management strategy required for subpopulations based on intrinsic factors?

No. Dose adjustment is not necessary based on intrinsic factors such as race, age, sex, body weight, BMI, renal or hepatic impairment. Population PK analysis was conducted on data from 329 subjects to evaluate the impact of intrinsic and extrinsic factors. Covariates that were found to be statistically significant in the model were weight on CL/F, ANC on CL/F, weight on Vz/F. The

finding of ANC as a covariate is consistent with results from SPI-GCF-201 and SPI-GCF-301-PK, in which ANC in Cycle 3 was found to be greater than Cycle 1 and eflapegrastim plasma concentration was lower in Cycle 3 than Cycle 1. No dose adjustment based on ANC is required as it is higher in Cycle 3 and the lower eflapegrastim exposures are a result of its target mediated clearance.

While weight has a significant effect on CL/F and Vz/F in the popPK analysis, it is not expected to have a clinically significant effect. The weight range in the Phase 3 studies was 40.3 to 171 kg, equivalent to a 328 and 77 μg/kg dose of eflapegrastim, respectively. In these subjects, there was no notable difference in incidence of severe neutropenia for subjects weighing >97.7 kg receiving 13.2 mg eflapegrastim (equivalent to <135 μg/kg, the lowest dose tested and shown to have non-inferiority to 6 mg pegfilgrastim in Cycle 1) compared to subjects weighing ≤97.7 kg in Cycles 1 to 3. In Phase 3 subjects who had severe neutropenia, there was no notable difference in DSN in any cycle for subjects weighing either above or below 97.7 kg (***Table 3***). The lack of difference in efficacy between weight groups and non-inferiority assessments support the use of a 13.2 mg eflapegrastim dose level across a broad body weight range.

Table 3 Duration of Severe Neutropenia by Weight in Phase 3 Studies

Characteristic	Statistic	>97.7 kg	≤97.7 kg	All Subjects
DSN in Cycle 1	N	10	46	56
	Mean (SD)	1.11 (0.57)	1.31 (0.48)	1.28 (0.49)
DSN in Cycle 3	N	5	23	28
	Mean (SD)	2.57 (0.87)	2.46 (0.73)	2.48 (0.74)

[Source: Integrated Pharmacokinetic Report]

Metabolism of eflapegrastim is mediated by endogenous degradation following receptor-mediated internalization by cells bearing the G-CSF receptor. Given that the excretion of eflapegrastim by kidneys is negligible, it is likely that the primary route of elimination of eflapegrastim is through ANC mediated degradation. Therefore, neither renal nor hepatic impairment is expected to affect eflapegrastim PK or response. No dedicated renal or hepatic impairment studies were conducted, and no dose adjustments are required in these patients.

3.1.4 Are there clinically relevant food-drug or drug-drug interactions and what is the appropriate management strategy?

Concomitant administration of eflapegrastim with other drugs is not expected to result in clinically relevant drug interactions. As eflapegrastim is expected to be metabolized by endogenous

degradation following receptor-mediated internalization by cells bearing the G-CSF receptor, it is unlikely to have an effect on drug metabolizing enzymes or transporters or be impacted by modulation of drug metabolizing enzymes or transporters. As a result, the applicant did not conduct in vitro studies to characterize its metabolism or evaluate drug interaction. Eflapegrastim is administered subcutaneously, and is not expected to be associated with clinically relevant food-drug interactions.

3.1.5 Is the to-be-marketed formulation the same as the clinical trial formulation, and if not, are there bioequivalence data to support the to-be marketed formulation?

Yes, the to-be-marketed formulation is the same as the clinical trial formulation.

4. APPENDICES

4.1 Summary of Bioanalytical Method Validation

For the determination of plasma eflapegrastim concentrations, the applicant used a ligand binding ELISA method. Briefly, the assay depended on the capturing antibody, biotin labeled anti-HM10411 polyclonal antibody (pAb), being bound to streptavidin in wells of a streptawell 96-well plate. Following blocking and washing steps, eflapegrastim in serum samples was then bound to the anti-HM10411 pAb. After incubation and washing, the detection antibody, horseradish peroxidase (HRP)-mouse anti-human immunoglobulin G4 (IgG4), is bound to eflapegrastim. After incubation and washing step, a colorimetric substrate was added. Colorization was stopped and the optical density (OD) of each well was determined, using a microplate reader, set to 450nm. This method was developed and validated by the (b) (4) The ELISA method was validated in compliance with the standards set forth in the FDA Bioanalytical Method Validation guidance. Summary of the validation parameters are presented in ***Table 4***.

Table 4 Summary Review of Bioanalytical Method Measuring Plasma Eflapegrastim

Bioanalytical method validation report	Study report MC14I-0017
Method description	Validation of a Method for the Quantification of HM10460A in Human Serum using ELISA Detection
Validation assay range	6.25 – 200 ng/mL
QCs (ng/mL)	6.25, 10, 100, 160, 200

Inter-day precision (%CV)	8.62% to 12.2%
Inter-day accuracy (%DEV)	0.00% to 7.00%
Intra-day precision (%CV)	2.31% to 18.4%
Intra-day accuracy (%DEV)	-11.9% to 19.0%
Reference standard	Recombinant HM10460A Lot # PGC13001
Specificity	No interference in the blank matrix was seen
Freeze/thaw stability (-70°C/RT)	4 cycles: Precision (%CV): 3.04% – 7.53%; Accuracy (%DEV): -2.4% – 12.5%

[Source: MC14I-0017 Validation Report]

4.2 Evaluation of Effect of Immunogenicity on PK/Efficacy/Safety of Eflapegrastim

Immunogenicity to eflapegrastim was evaluated in the following 5 clinical studies:

- Two Phase 1 studies (08-HM10460A-101 and 09-HM10460A-102) in healthy volunteers
- One dose-ranging Phase 2 study (SPI-GCF-12-201) in patients with breast cancer undergoing TC chemotherapy, and
- Two pivotal Phase 3 studies (SPI-GCF-301 and SPI-GCF-302) in patients with breast cancer undergoing TC chemotherapy.

Immunogenicity to pegfilgrastim, used as a comparator in clinical studies, was evaluated for the Phase 2 and Phase 3 studies, utilizing the same immunoassays as used for eflapegrastim.

A bridging ELISA using labeled eflapegrastim was used to capture and detect antibodies to eflapegrastim and its protein domains (only to G-CSF for the Phase 1 and Phase 2 studies and to G-CSF and Fc fragment for the Phase 3 studies). A cell-based assay was used to detect NAb for all studies. A separate direct-binding ELISA was used to test samples from the Phase 3 studies for anti-PEG antibodies. Immunogenicity sample analysis for antibodies to eflapegrastim and its protein domains was performed following a standard tiered testing strategy. Samples were initially subjected to a screening assay, and putative positive samples from the screening assay were subjected to a confirmatory assay. Samples that were positive in the confirmatory assay were

subjected to a titer assay. In the Phase 3 studies, samples confirmed positive for ADA were also tested for reactivity to G-CSF and Fc domains and for cross reactivity to endogenous G-CSF (lenograstim). Samples reactive to the G-CSF domain or lenograstim were tested further in a NAb assay. OBP finds the validation of these ADA assays to be acceptable.

The immunogenicity results from the two Phase 3 studies are outlined in ***Table 5***. Cumulative incidence of ADAs was higher in patients treated with eflapegrastim compared to pegfilgrastim. Incidence of treatment-emergent anti-PEG antibodies was significantly higher in the pegfilgrastim arm than in the eflapegrastim arm.

Table 5 Immunogenicity results from Phase 3 studies

Assay	**Eflapegrastim**		**Pegfilgrastim**	
	n	%	n	%
Treatment-Induced or Treatment-Boosted Antibodies	28/297	9.4	10/306	3.3
Treatment-Emergent Anti-PEG Antibodies	126/268	47	167/263	63.5
Treatment-Induced Neutralizing ADA	1/297	0.3	0/306	0.0

[Source: Integrated Immunogenicity Summary Report]

The impact of anti-eflapegrastim antibodies and anti-PEG antibodies on the PK of eflapegrastim was studied as a part of a popPK analysis. Anti-eflapegrastim and anti-PEG antibodies were not found to impact the clearance of eflapegrastim following the forward addition and backward elimination procedure. The impact of anti-eflapegrastim antibodies on efficacy was evaluated in Cycles 1 and 3 with pooled data from both the Phase 3 studies as a part of a popPK analysis by chi-square test of independence. DSN was found to be independent of the presence of anti-eflapegrastim antibodies in both Cycles 1 and 3. The impact of anti-eflapegrastim antibodies on efficacy was also evaluated in the two Phase 3 studies by studying the temporal correlation between occurrence of severe neutropenia and incidence of anti-eflapegrastim antibodies for all patients positive for anti-eflapegrastim antibodies. There was no apparent temporal correlation for any of the patients suggesting that anti-eflapegrastim antibodies had no demonstrable effect on efficacy. The impact of ADA on safety was also evaluated by examining potential hypersensitivity or allergic reactions reported for each patient who was positive for ADA. The incidence of allergic reactions was found to be independent of the presence of anti-eflapegrastim antibodies.

4.3 Population PK Analysis

4.3.1 Review Summary

The applicant's population PK analysis is acceptable. Although the goodness-of-fit plots indicate bias and trends, visual predictive check indicates that the final population PK model is adequate in characterizing the PK profile of eflapegrastim in subjects with breast cancer undergoing chemotherapy with docetaxel and cyclophosphamide. The inter-individual variability (IIV) for CL/F (67%), Vc/F (118%), Ka (90%), and D1 (210%) were large. Eta shrinkage values for CL/F (9%), Vc/F (38%), Ka (22%) and D1 (27%) are reasonable and support evaluation of covariates. Consistent with target mediated drug disposition principles, time varying absolute neutrophil count (ANC) was a significant covariate on eflapegrastim clearance with an exponent value of less than 1. Clearance increased with increasing ANC values in a less than linear relationship. Body weight was also a covariate on CL and V, with exponents greater than 1 indicating greater than linear increase in clearance and volume with increasing body-weight. The estimated PK parameters, such as CL/F and Vc/F appear reasonable. The applicant's analyses were verified by the reviewer, with no significant discordance identified.

The developed model was NOT used to support labeling of eflapegrastim in the current submission as outlined in Table 6.

Table 6. Specific Comments on Applicant's Final Population PK model

Utility of the final model			**Reviewer's Comments**
Support applicant's proposed labeling statements about intrinsic and extrinsic factors	**Intrinsic factor**	Dosing not dependent on body weight nor ANC values despite these being significant CL and V covariates	No clinically meaningful exposure-efficacy relationship was identified. This could be attributed to apparent low eflapegrastim exposure in treatment responders due to neutrophil uptake and corresponding elimination of eflapegrastim. Furthermore, no clinically meaningful relationship between exposures and safety measures was identified. Based on these apparent relationships, the analyses cannot be used to support dose adjustment based on any intrinsic or extrinsic factors
	Extrinsic factor	No extrinsic factor was identified as a covariate on PK parameters	

Derive exposure metrics for Exposure-Response analyses		The use of predicted exposures in E-R analyses is acceptable since the model performance was reasonable as indicated by visual predictive checks (VPC)
Predict exposures at alternative dosing regimen		The model was not used to assess predicted exposures at other doses

4.3.2 Introduction

The primary objectives of the applicant's population PK analysis were to:

- Characterize the structural pharmacokinetic (PK) model and quantify the population variability in the PK parameters of eflapegrastim.
- Describe the effects of intrinsic and/or extrinsic factors on Eflapegrastim exposure.
- Generate post-hoc PK parameters through non-compartmental analyses of predicted concentrations for individual patients in phase studies that can be used for subsequent exposure-response analyses

4.3.3 Model development

Data

The analyses were based on PK data from 3 studies. The study design, study population, and timing of blood samples varied among the 3 clinical studies. Brief descriptions of the studies included are presented in ***Table 7***

Table 7. Summary of Studies with PK Sampling Included in Population PK Analysis

Study #	Patient Population	Study Design	Eflapegrastim Dosing Regimen	PK Sample Collection
SPI-GCF-301	Breast cancer patients treated with TC chemotherapy	Randomized, open-label, active-controlled, multicenter Phase 3 study	13.2 mg/0.6 mL fixed dose on Day 2 of every 21-day cycle; 4 cycles total TC therapy administered on Day 1	Cycle 1: Day 2 (1-4 hours after eflapegrastim administration) Days 4, 5 Cycle 3: Days 2 (1-4 h post-dose) Days 4, 7 (±1 day)
SPI-GCF-301-PK	Breast cancer patients treated with TC chemotherapy	Single-arm, multicenter Phase 1 study	13.2 mg/0.6 mL fixed dose on Day 2 of every 21-day cycle; 4-6 cycles total TC therapy administered on Day 1	Cycle 1: Day 2 (pre-dose, 1, 3, 6, 8, 10 h after eflapegrastim administration) Days 3, 4, 5, 8, 10, 15 (±2 h after eflapegrastim dose) Cycle 3: Pre-dose (within 15 min of dose) Days 3, 4, 5, 8, 10, 15 (±2 h after eflapegrastim dose) Pre-dose for all other cycles
SPI-GCF-302	Breast cancer patients treated with TC chemotherapy	Randomized, open-label, active-controlled, multicenter Phase 3 study	13.2 mg/0.6 mL fixed dose on Day 2 of every 21-day cycle; 4 cycles total TC therapy administered on Day 1	Cycle 1: Day 2 (1 to 4 hours after eflapegrastim administration) Day 4 (at the same time as CBC blood draw) Day 5 (at the same time as CBC blood draw) Cycle 3: Day 2 (1 to 4 hours post-dose) Day 4 (± 1 day, at the same time CBC blood draw); Day 7 ((± 1 day, at the same time CBC blood draw)

Abbreviations: CBC = complete blood count; TC = Taxotere (docetaxel) and cyclophosphamide

Source: Applicant's amended population pharmacokinetic report (page 55 of 153)

The final NONMEM data file for analysis contained 2147 PK observations from 329 subjects. ***Table 8*** provides summary statistics of the baseline demographic covariates in the analysis dataset.

Table 8. Summary of Baseline Demographic Covariates for Analysis

Characteristic	Statistic	Study 1	Study 2	Study 3	All Subjects
AGE (years)	N	188	26	115	329
	Mean (SD)	60.2 (11.0)	55.1 (12.5)	57.9 (11.3)	59.0 (11.3)
	Median (Min, Max)	61.0 (28.0, 83.0)	56.0 (29.0, 77.0)	58.0 (29.0, 80.0)	60.0 (28.0, 83.0)
ALT (U/L)	N	187	25	115	327
	Mean (SD)	19.5 (10.2)	20.6 (10.9)	20.7 (10.8)	20.0 (10.4)
	Median (Min, Max)	18.0 (6.00, 71.0)	16.0 (10.0, 49.0)	18.0 (6.00, 61.0)	18.0 (6.00, 71.0)
ANC (10^3/uL)	N	188	26	115	329
	Mean (SD)	7.69 (4.82)	8.73 (2.95)	7.09 (5.06)	7.56 (4.80)
	Median (Min, Max)	6.16 (1.74, 28.6)	8.14 (3.63, 16.8)	5.12 (1.29, 33.9)	6.18 (1.29, 33.9)
ANTBASE (10^3/uL)	N	188	26	115	329
	Mean (SD)	7.31 (4.48)	7.92 (4.02)	6.58 (4.16)	7.10 (4.34)
	Median (Min, Max)	5.84 (1.74, 28.6)	7.02 (3.10, 16.7)	5.02 (1.29, 24.6)	5.59 (1.29, 28.6)
ANTEFLAP (Titer Units/mL)	N	188	0	115	303
	Mean (SD)	42.6 (338)	NaN (NA)	19.1 (154)	33.7 (283)
	Median (Min, Max)	0 (0, 3200)	NA (Inf, -Inf)	0 (0, 1600)	0 (0, 3200)
ANTEOT (10^3/uL)	N	188	26	115	329
	Mean (SD)	6.24 (5.51)	5.36 (3.96)	5.35 (4.26)	5.86 (5.00)
	Median (Min, Max)	4.77 (0.260, 36.7)	4.18 (1.74, 22.7)	4.33 (0.680, 31.3)	4.53 (0.260, 36.7)
ANTPEG (Titer Units/mL)	N	188	0	115	303
	Mean (SD)	285 (936)	NaN (NA)	134 (618)	227 (832)
	Median (Min, Max)	0 (0, 6400)	NA (Inf, -Inf)	0 (0, 6400)	0 (0, 6400)
AST (U/L)	N	187	25	115	327
	Mean (SD)	19.6 (7.02)	20.4 (7.38)	19.8 (7.43)	19.7 (7.17)
	Median (Min, Max)	17.0 (10.0, 50.0)	17.0 (13.0, 41.0)	18.0 (7.00, 48.0)	17.0 (7.00, 50.0)
BILI (mg/dL)	N	163	22	102	287
	Mean (SD)	0.353 (0.161)	0.373 (0.155)	0.481 (0.285)	0.400 (0.221)
	Median (Min, Max)	0.300 (0.200, 1.00)	0.300 (0.200, 0.800)	0.400 (0.200, 1.80)	0.300 (0.200, 1.80)
BMI (kg/m^2)	N	188	26	115	329
	Mean (SD)	30.8 (6.58)	32.3 (7.94)	29.6 (7.22)	30.5 (6.94)
	Median (Min, Max)	29.8 (16.2, 54.7)	31.4 (19.9, 61.4)	28.7 (16.1, 63.0)	29.6 (16.1, 63.0)
BSA (m^2)	N	188	26	115	329
	Mean (SD)	1.84 (0.190)	1.86 (0.225)	1.80 (0.223)	1.83 (0.206)
	Median (Min, Max)	1.83 (1.39, 2.48)	1.84 (1.29, 2.51)	1.78 (1.35, 2.59)	1.82 (1.29, 2.59)
CRCL (mL/min)	N	187	26	115	328
	Mean (SD)	102 (33.6)	122 (43.8)	107 (34.5)	105 (35.1)
	Median (Min, Max)	98.6 (37.3, 251)	121 (60.8, 247)	98.1 (51.0, 199)	99.6 (37.3, 251)
CREAT (mg/dL)	N	187	26	115	328
	Mean (SD)	0.781 (0.203)	0.719 (0.177)	0.723 (0.157)	0.755 (0.188)

	Median (Min, Max)	0.700 (0.500, 2.00)	0.700 (0.500, 1.30)	0.700 (0.400, 1.30)	0.700 (0.400, 2.00)
EGFR (mL/min/(1.73m)^2)	N	187	26	115	328
	Mean (SD)	82.8 (20.6)	90.5 (21.5)	89.2 (20.3)	85.7 (20.8)
	Median (Min, Max)	83.0 (24.6, 140)	87.4 (40.0, 133)	87.5 (45.1, 160)	84.6 (24.6, 160)
HEIGHT (cm)	N	188	26	115	329
	Mean (SD)	162 (6.84)	161 (6.43)	161 (7.51)	161 (7.04)
	Median (Min, Max)	161 (145, 183)	161 (145, 173)	160 (142, 196)	161 (142, 196)
WEIGHT (kg)	N	188	26	115	329
	Mean (SD)	80.4 (17.4)	83.7 (22.2)	76.9 (20.2)	79.4 (18.9)
	Median (Min, Max)	78.6 (41.5, 145)	80.7 (41.8, 163)	74.5 (40.3, 171)	78.0 (40.3, 171)
SEX: Female	N (%)	187 (99.5%)	26 (100%)	115 (100%)	328 (99.7%)
SEX: Male	N (%)	1 (0.532%)	0 (0%)	0 (0%)	1 (0.304%)
RACE: White/Caucasian	N (%)	151 (80.3%)	20 (76.9%)	82 (71.3%)	253 (76.9%)
RACE: Black/African American	N (%)	24 (12.8%)	1 (3.85%)	11 (9.57%)	36 (10.9%)
RACE: Asian	N (%)	8 (4.26%)	1 (3.85%)	20 (17.4%)	29 (8.81%)
RACE: Native American	N (%)	1 (0.532%)	0 (0%)	1 (0.870%)	2 (0.608%)
RACE: Other	N (%)	4 (2.13%)	4 (15.4%)	1 (0.870%)	9 (2.74%)
ETHNIC: Non-Hispanic or Latino	N (%)	156 (83.0%)	12 (46.2%)	98 (85.2%)	266 (80.9%)
ETHNIC: Hispanic or Latino	N (%)	32 (17.0%)	14 (53.8%)	17 (14.8%)	63 (19.1%)
DS: Adjuvant	N (%)	159 (84.6%)	15 (57.7%)	97 (84.3%)	271 (82.4%)
DS: Neoadjuvant	N (%)	29 (15.4%)	11 (42.3%)	18 (15.7%)	58 (17.6%)

Study 1 = SPI-GCF-301; Study 2 = SPI-GCF-301-PK; Study 3 = SPI-GCF-302

Source: Applicant's amended population pharmacokinetic report (page 70-71 of 153)

Base Model

The final base model was a one-compartment PK model with sequential zero order and first-order absorption. The effect of absolute neutrophil count was included as a time varying covariate on CL using a power model with exponent estimated. The effect of weight was included as a covariate on both CL/F and Vc/F using a power model with exponents estimated. The effects of ANC and body-weight on PK parameters were parameterized as shown in ***Figure 3*** below. Data below limit of quantification (BLQ) were handled using Beal's M3 method which estimates probability of a record being BLQ at given values of model parameter.

Figure 3. Parameterization of the covariate effects on CL/F and V/F

$$CL = \left(ANC^{\theta_8}\right) * ANCEFF$$

where

$$ANCEFF = \theta_9 * \left(\frac{weight}{medianweight}\right)^{\theta_{10}}$$

$$V = \theta_2 * \left(\frac{weight}{medianweight}\right)^{\theta_{12}}$$

Inter-individual variability (IIV) was modelled assuming a log-normal distribution for patient level random effects. Residual variability was tested as additive, proportional or both on the dependent variable. Model evaluation and selection of the base model were based on standard statistical criteria of goodness-of-fit such as a decrease in the minimum objective function value (OFV), accuracy of parameter estimation (i.e., 95% confidence interval excluding 0), successful model convergence, and diagnostic plots.

Covariate Analysis

Covariate effects on PK parameters, including anti-drug antibodies, cycle number, disease status, subject demographics (age, sex, race, and ethinicity), baseline body size (height, body surface area and BMI) and serum chemistry (creatinine, estimated glomerular filtration rate (eGFR), total bilirubin, alanine aminotransferase (ALT), aspertate aminotransferase (AST)) were assessed using stepwise covariate model building procedure. Clinical judgment, physiologic relevance, and mechanistic plausibility were used to determine which covariates should be tested with the various PK parameters. Continuous covariates were evaluated using a power function and categorical covariates were parameterized as a fractional change. In a foward step, covariate-parameter relationship was to be included into the model if OFV decreased by more than 3.84 ($p<0.05$). In a backward step, covariate-parameter relationship was to be excluded from the model if doing this would result is less than 10.828 increase in OFV.

4.3.4 Final Model

Covariate analysis did not identify any other additional covariates than ANC and body-weight. The parameter estimates for the final covariate model are listed in ***Table 9***. The goodness-of-fit plots for the final covariate model for all data are shown in ***Figure 4***. The Visual Predictive Check (VPC) plot for the final covariate model with all data is shown in ***Figure 5***.

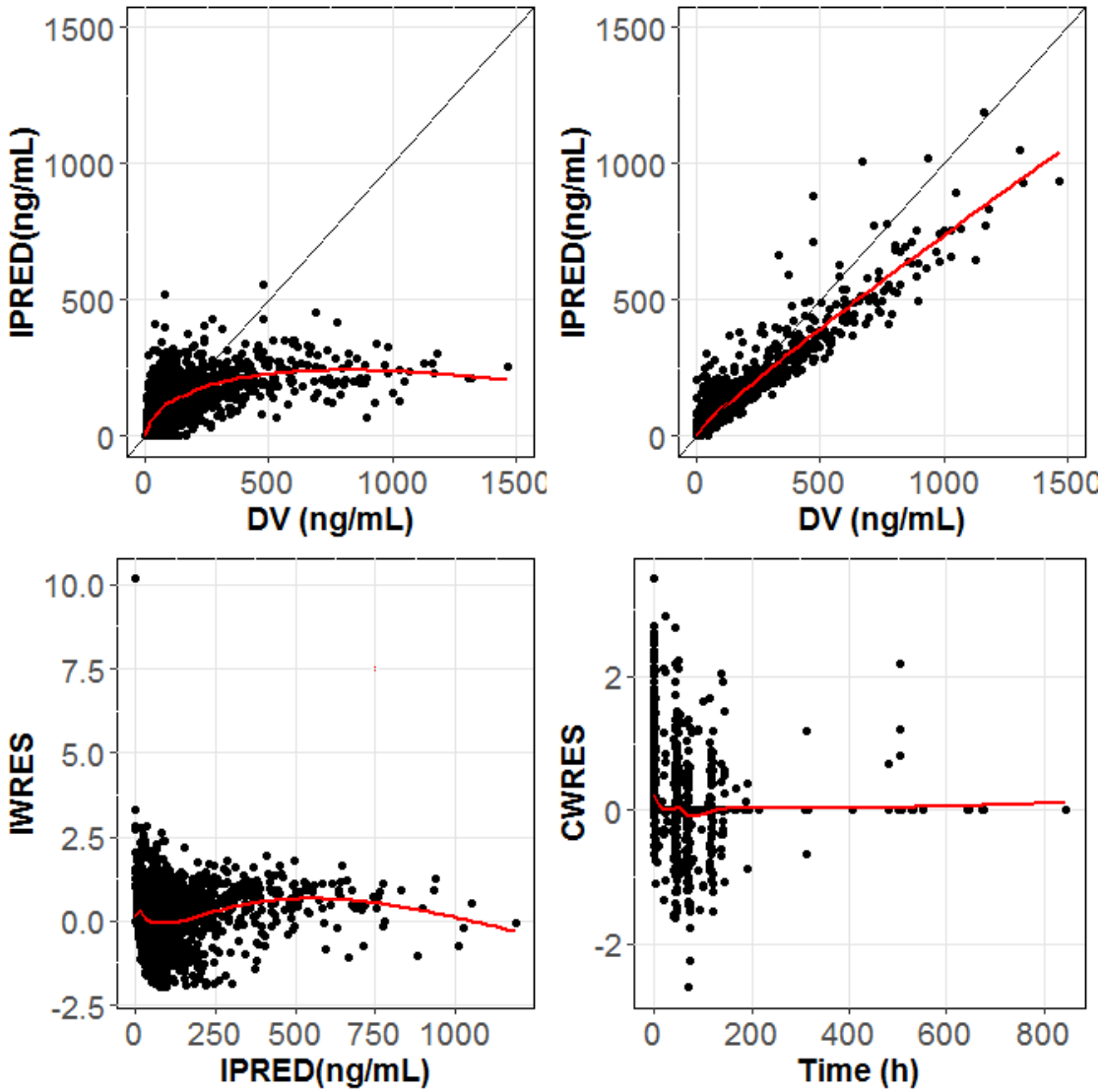
Table 9. Parameter Estimates and Objective Function Values of Applicant's Final Model

Parameters	Descriptions	Estimates (RSE)
OFV	Objective function value	14849.831
CL	Clearance (L/hr/78Kg)	0.2003(17%)
Vc	Volume of central compartment (L/78Kg)	2.072(22%)
KA	First order Absorption rate constant (/h)	0.008684(44%)
D1	Duration of zero order absorption (h)	7.848(12%)

Delay	Time delay to start of zero order absorption (h)	0(NA%)
ADD	Additive residual error	4.933(9%)
PROP	Proportional residual error	0.4548(3%)
ANC ~ CL	power term for effect of ANC on CL	0.3289(17%)
WT ~ CL	Power term for effect of Weight on CL	1.311(19%)
ANC ~ VOL	Power term for effect of ANC on Vc	1.819(34%)
CYCLE~F1	fractional effect of CYCLE3 on F1	0.3499(6%)
BSC_CL	Between subject variability for CL	0.6006(5%)
BSC_CL_cor_BSC_V	variance correlation between CL and V	0.4756(51%)
BSC_V	Between subject variability for V	1.053(17%)
BSC_KA	Between subject variability for KA	0.7823(10%)
BSC_KA_cor_BSC_D1	variance correlation between KA and D1	0.6444(13%)
BSC_D1	Between subject variability for AD1	1.314(25%)

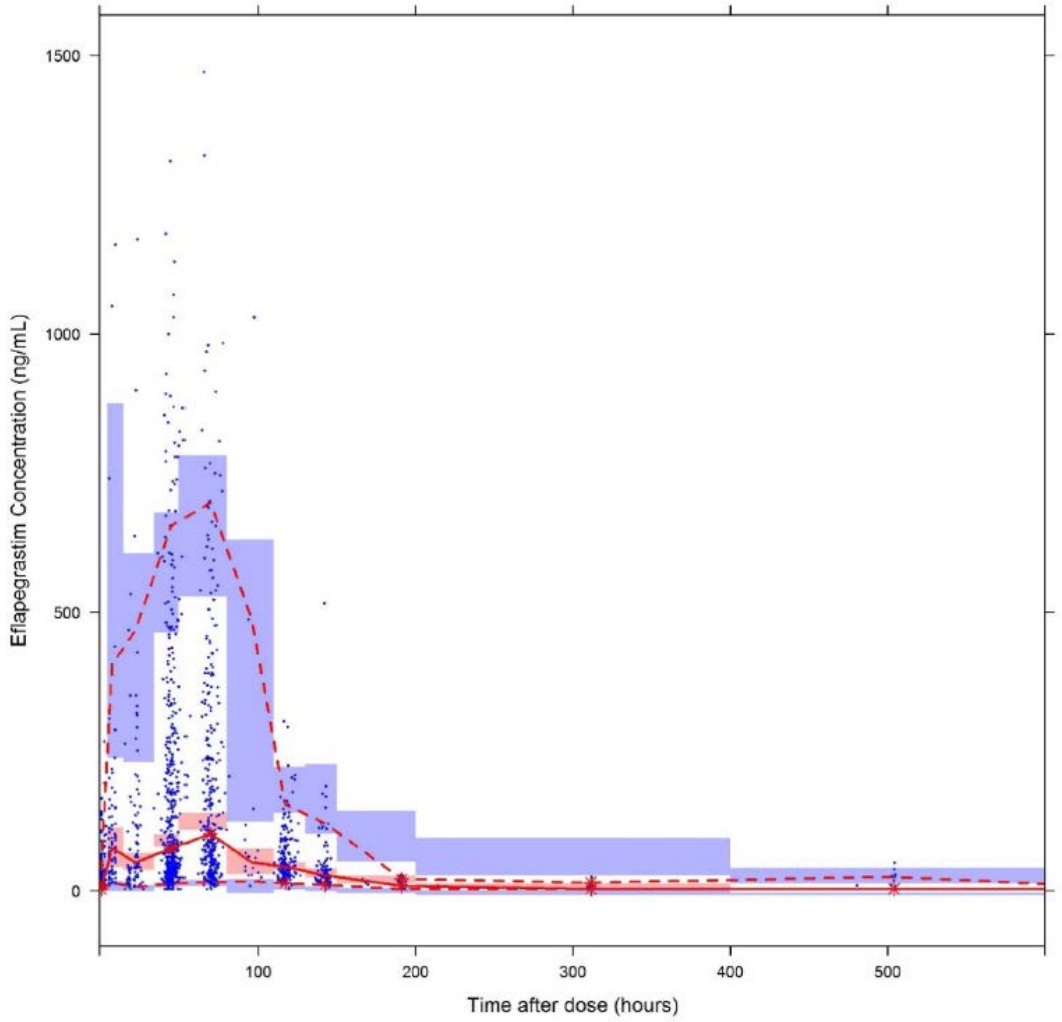
Source: Reviewer's re-analysis of the applicant's final model

Figure 4. Goodness-of-fit plots for final covariate model



Source: Reviewer's re-analysis of the applicant's final model

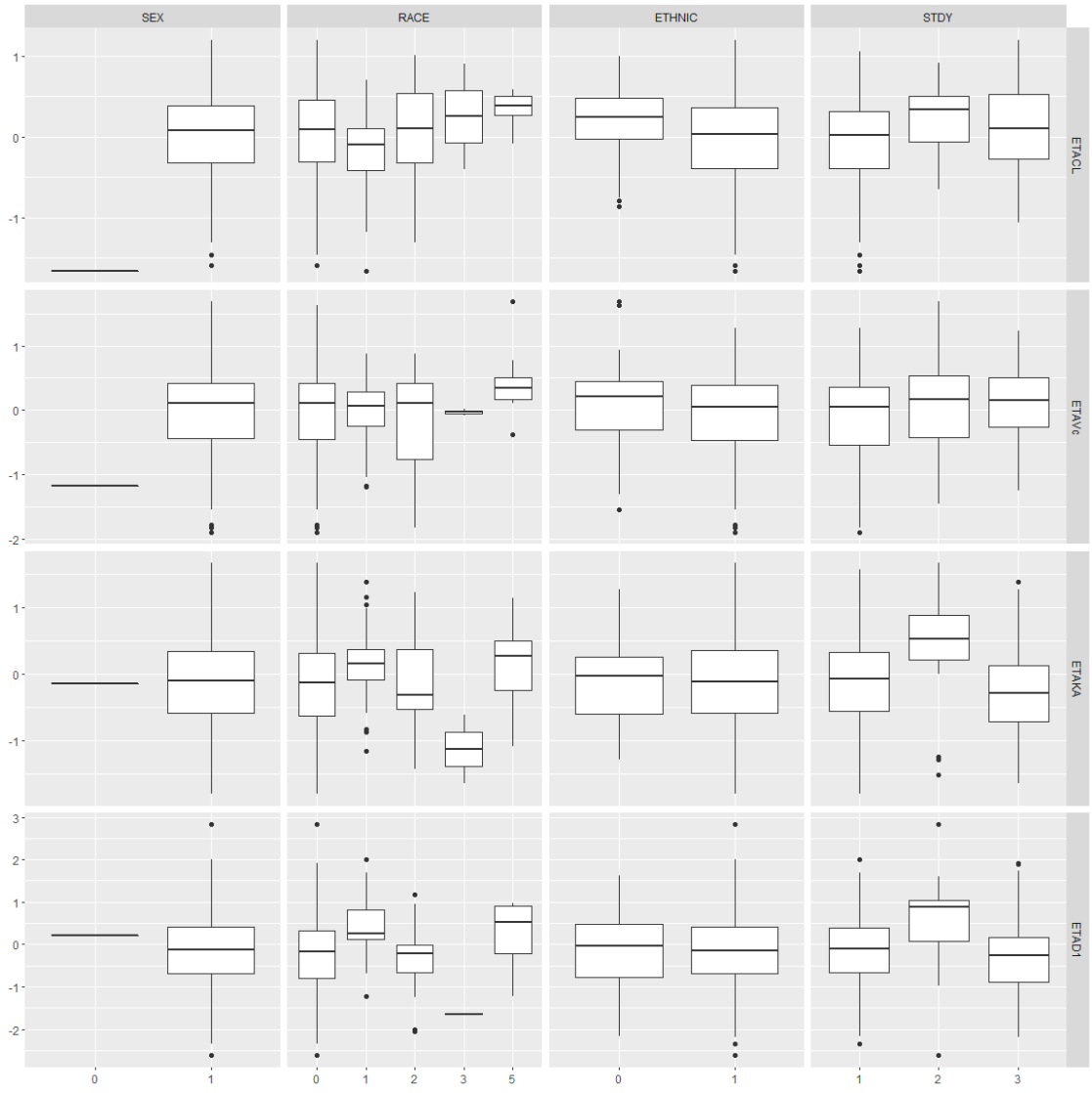
Figure 5. Visual predictive check of the final model: All cycles and all time points



Source: Applicant's amended population pharmacokinetics report (page 29 of 153)

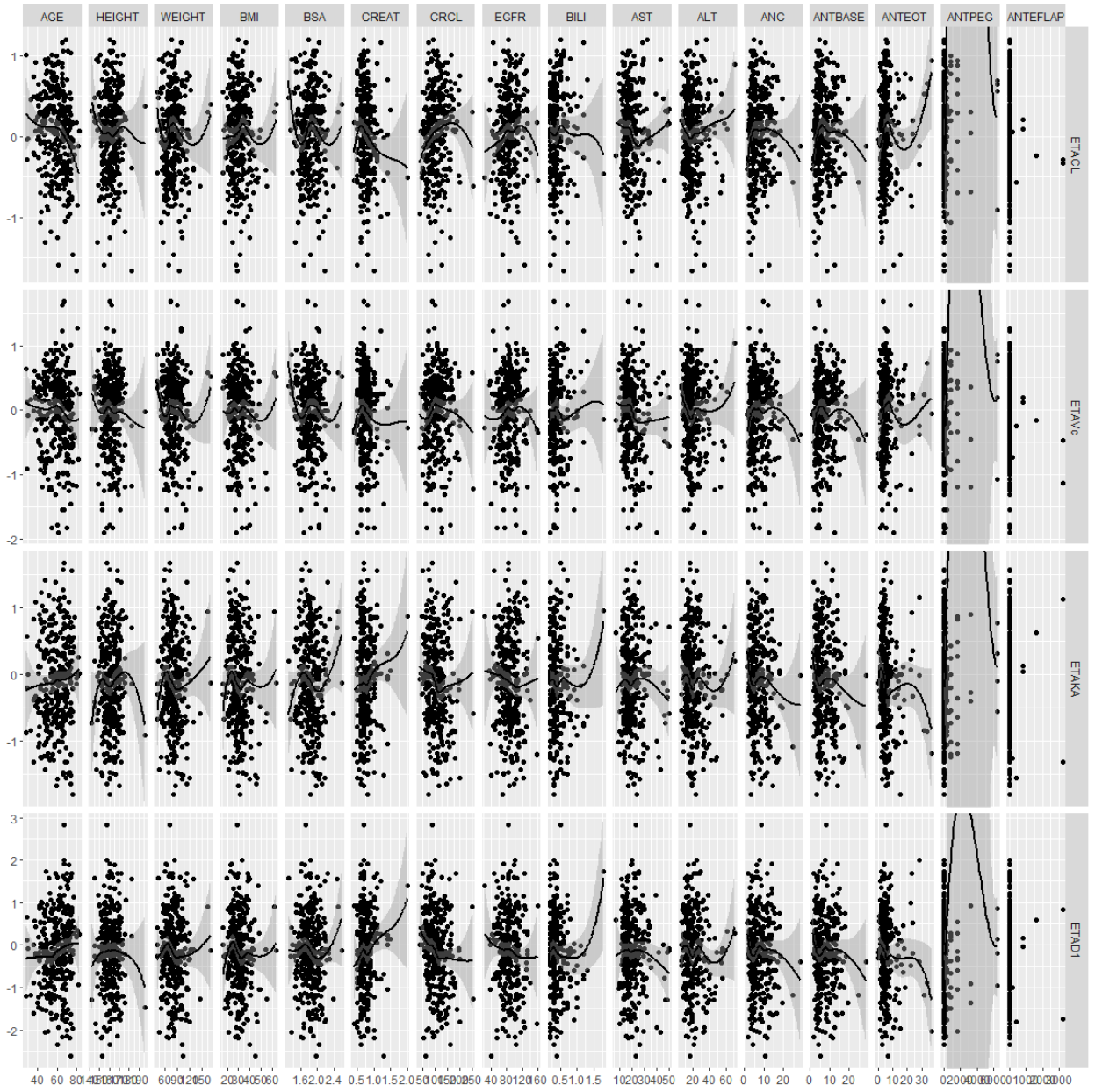
The reviewer's analysis of covariates effect on PK was like that of the applicant. The effects of *anti-drug antibodies, cycle number, disease status, subject demographics (age, sex, race, and ethinicity), baseline body size (height, body surface area and BMI) and serum chemistry (creatinine, estimated glomerular filtration rate (eGFR), total bilirubin, alanine aminotransferase (ALT), aspertate aminotransferase (AST))* are explored in ***Figure 6*** and ***Figure 7***.

Figure 6. ETA versus Categorical covariates



Source: Reviewer's re-analysis of the applicant's final model

Figure 7. ETA versus Continuous covariates



Source: Reviewer's re-analysis of the applicant's final model

4.4 Exposure-vs-efficacy Analysis

4.4.1 Review Summary

The applicant's exposure-response (E-R) analyses for efficacy have limitations and do not represent the expected (E-R) relationships. This is largely due to the CL of eflapegrastim being directly related to the PD (absolute neutrophil count) – response appears better in patients with lower eflapegrastim because of the available neutrophils and precursor cells in these patients. The applicant used post-hoc PK parameters (AUC, C_{max}, and C_{min}) from their population PK model to

assess linear or non-linear relationships between exposure and efficacy endpoints. The evaluated efficacy endpoints included neutrophil nadir (cells/uL), duration of severe neutropenia, and time to ANC recovery (time from ANC<1×10^3cells/uL to ANC>1×10^3cells/uL). Neutrophil nadir was found to be correlated with C_{max}, but the relationship is confounded as C_{max} is also a function of ANC -- subjects with lower C_{max} had higher neutrophil nadir than subjects with high C_{max}. Similarly, although AUC was positively related to both DSN and time to ANC recovery, the relationships were not clinically meaningful as they indicated better outcomes in patients with lower exposure than those with higher exposures. The identified relationships can be considered spurious owing to the neutrophil dependent clearance of eflapegrastim and visual inspection of plots of exposure versus efficacy indicated no obvious trends.

4.4.2 Results from the applicant's analyses

Table 10 shows results from the applicant's exposure-response modeling. Linear models estimated intercepts and slopes while E_{max} models estimated EC50 and E_{max} parameters. The estimated EC50 for C_{max} vs neutrophil nadir relationship was a negative value, which is implausible and is an indication that this relationship is spurious. ***Figure 8*** shows no obvious trends between C_{max} and neutrophil nadir. Similarly, although ***Table 10*** shows significant linear relationships between AUC vs DSN, and AUC vs time to ANC recovery, ***Figure 9*** and ***Figure 10*** shows no linear trends between AUC and these efficacy endpoints. However, these analyses are confounded based on the neutrophil-PK relationship for eflapegrastim.

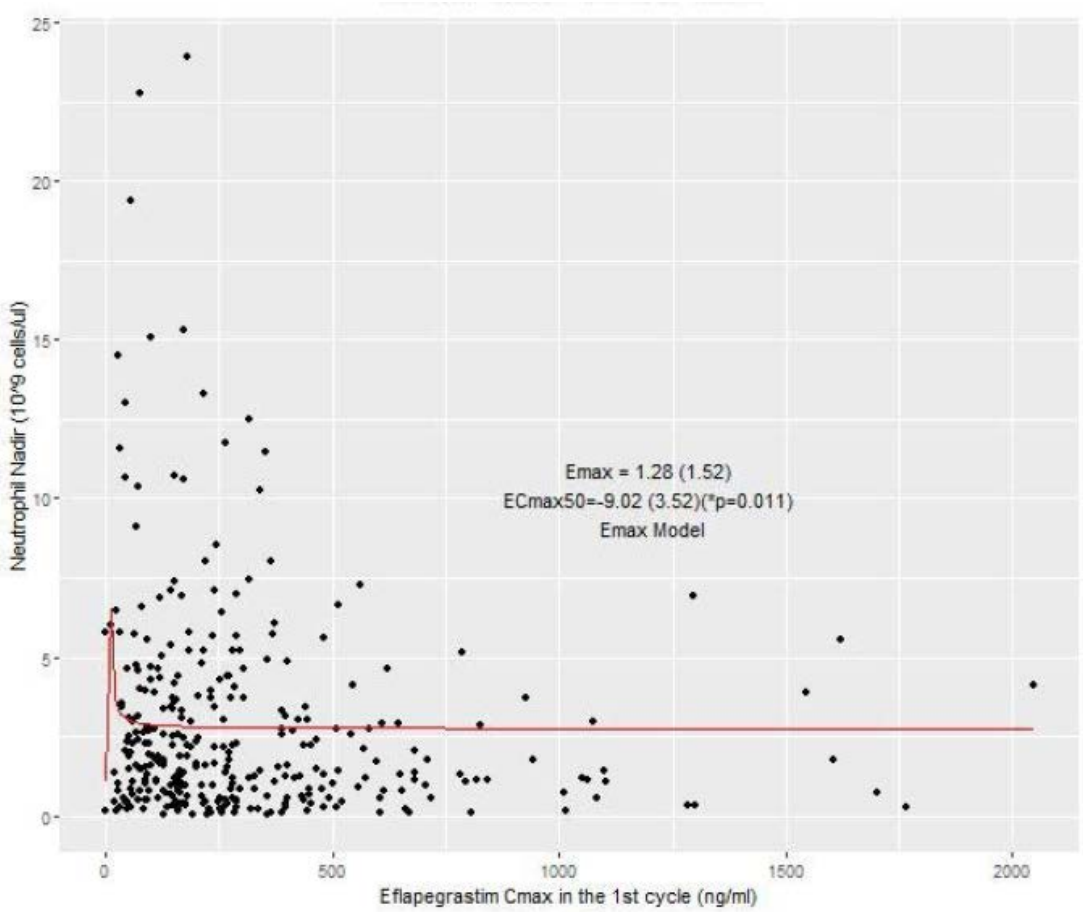
Table 10. Parameter Estimates (RSE) of the Exposure-vs-efficacy models

	Model	Emax or intercept (standard error of estimate)	EC50 or slope (standard error of estimate)
Neutrophil Nadir ~ AUC	Nonlinear	1.56 (22.9)*	1.22 (31.8)
Neutrophil Nadir~ Cmin	Linear	2.86 (0.22)	-0.001 (0.026)*
Neutrophil Nadir~ Cmax	Nonlinear	1.28 (1.52)	-9.02 (3.52)[a]
DSN~AUC	Linear	0.12 (0.05)	0.0000027 (0.0000011)[b]
DSN~Cmin	Linear	0.221 (0.033)	-0.0009 (0.004)*
DSN~Cmax	Linear	0.18 (0.04)	0.00012 (0.000091)*
TANC~AUC	Linear	2.265 (0.32)	0.000027 (0.0000074)[c]
TANC~Cmin	Linear	3.34 (0.23)	-0.036 (0.0275)*
TANC~Cmax	Nonlinear	-1 (0.647)*	415 (855) *

*Not significant
a; p=0.011
b; p=0.012
c; p=0.00034

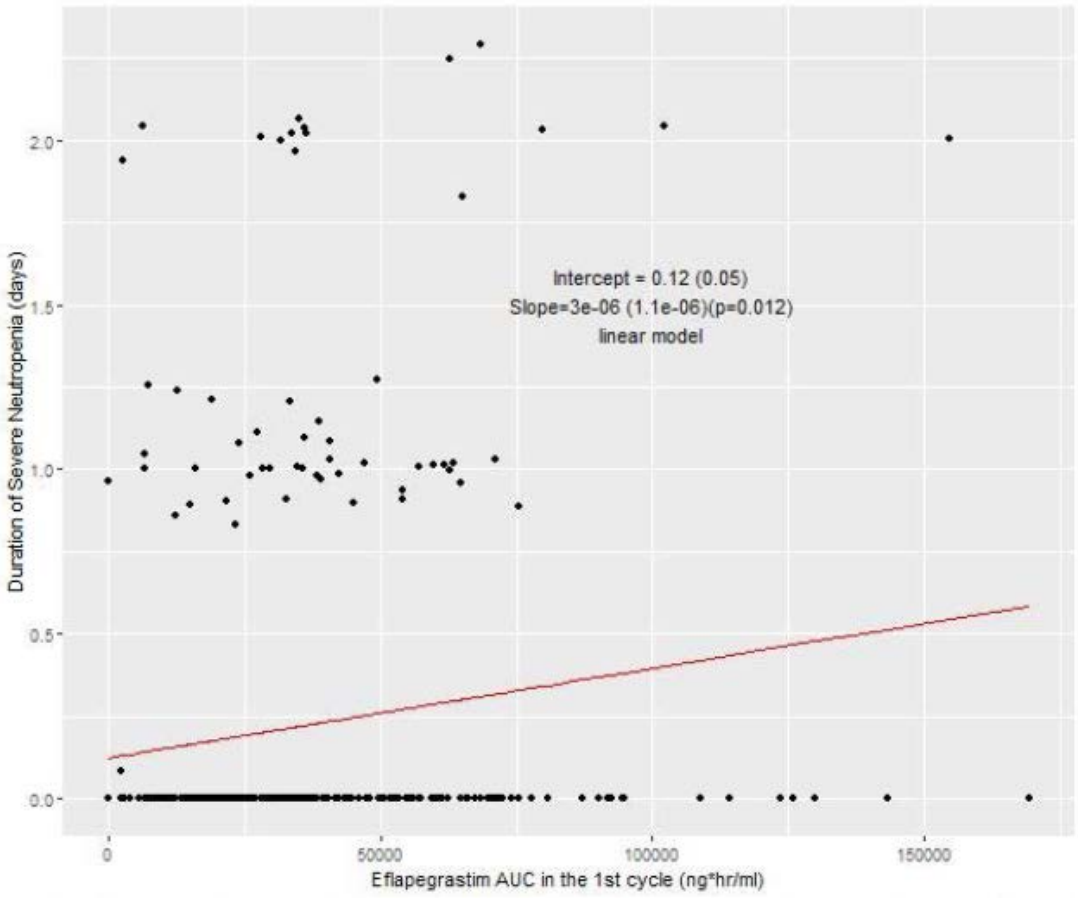
Source: Applicant's amended population pharmacokinetic report (page 34 of 153)

Figure 8. Eflapegrastim C_{max} versus neutrophil nadir



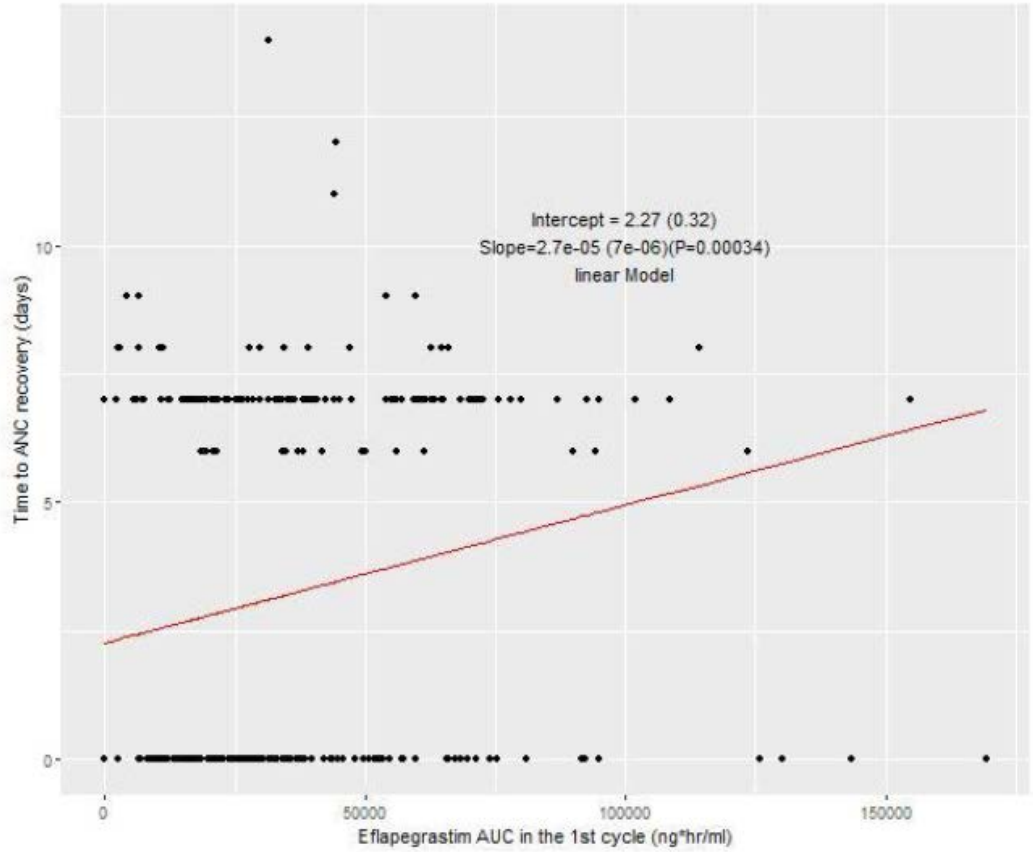
Source: Applicant's amended population pharmacokinetic report (page 35 of 153)

Figure 9. Eflapegrastim AUC versus Duration of severe neutropenia



Source: Applicant's amended population pharmacokinetic report (page 37 of 153)

Figure 10. Eflapegrastim AUC versus time to ANC recovery



Source: Applicant's amended population pharmacokinetic report (page 39 of 153)

4.5 Exposure-vs-Safety Analysis

4.5.1 Review Summary

The applicant's exposure -vs - safety analyses are acceptable when evaluating "off-target" adverse events. Using post-hoc PK parameters, the applicant assessed the relationship between eflapegrastim exposure and the following safety end points: Bone pain, immunogenicity and allergic reactions. Both, graphical and statistical analyses did not identify statistically significant (p-value<0.05) relationship.

4.5.2 Results from the applicant's analyses

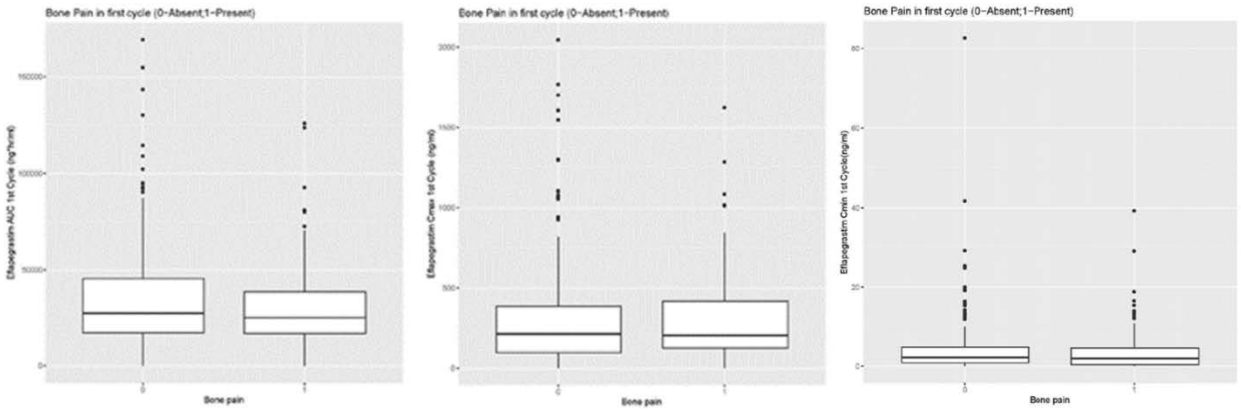
Table 11 shows parameter estimates for the logistic regression analyses of exposure -vs- allergic reactions. Allergic reactions were found to be unrelated to all three measures of exposure in the first cycle (AUC, C_{max}, and C_{min}). ***Figure 11*** compares the distribution of eflapegrastim exposures between subjects with and without bone pain. There were no differences in AUC, C_{max} or C_{min} in subjects with or without bone pain.

Table 11. Parameter estimates for logistic regression analysis of exposure-vs-allergic reactions

Evaluation	Slope	OR	95% CI of OR	p-value
Allergic reactions ~AUC (1st Cycle)	1.00E-05	1.011	0.984-1.031	0.334
Allergic reactions ~Cmax (1st Cycle)	0.00054	1.056	0.82-1.242	0.586
Allergic reactions ~Cmin (1st Cycle)	0.00785	1.082	0.25-1.944	0.862

Source: Applicant's amended population pharmacokinetic report (page 47 of 153)

Figure 11. Exploratory Analysis of Eflapegrastim Exposure vs. Bone Pain in 1st Cycle



Source: Applicant's amended population pharmacokinetic report (page 143-144 of 153)

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