CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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CLINICAL REVIEW(S)

CLINICAL MEMORANDUM

Application Type	BLA (resubmission)
Application Number	761148
Submit Date	March 11, 2022
Received Date	March 11, 2022
PDUFA Goal Date	September 9, 2022
Division/Office	Division of Nonmalignant Hematology (DNH)/ Office of Cardiology, Hematology, Endocrinology and Nephrology (OCHEN)
Reviewer Name	Hyon-Zu Lee, PharmD
Review Completion Date	See stamped date
Established/Proper Name	Eflapegrastim-xnst
(Proposed) Trade Name	Rolvedon
Applicant	Spectrum Pharmaceuticals, Inc.
Dosage Form	Solution for injection
Applicant Proposed Dosing Regimen	13.2 mg once as a subcutaneous injection per chemotherapy cycle (to be administered 24 hours after cytotoxic chemotherapy)
Applicant Proposed Indication	Decrease the incidence of infection, as manifested by febrile neutropenia, in adult patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs.
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	To decrease the incidence of infection, as manifested by febrile neutropenia, in adult patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs associated with clinically significant incidence of febrile neutropenia.

Background

Rolvedon (eflapegrastim-xnst) injection is a recombinant human granulocyte colony stimulating factor (rhG-CSF). Eflapegrastim-xnst is a new biological product presented as 13.2 mg/0.6 mL solution in a single-dose prefilled syringe. The proposed indication by the Applicant is to decrease the incidence of infection, as manifested by febrile neutropenia, in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs. The proposed dosing regimen of eflapegrastim-xnst in patients with cancer receiving myelosuppressive chemotherapy is 13.2 mg to be administered subcutaneously once per chemotherapy cycle approximately 24 hours after cytotoxic chemotherapy.

The original BLA was submitted on October 24, 2019. A Complete Response letter (CRL) was issued on August 3, 2021, due to product quality issues. No clinical deficiencies were identified (see review clinical review dated June 24, 2020). The Sponsor submitted a response to the CRL on March 11, 2022. This clinical memorandum provides review of the efficacy (no new updates), safety update and outstanding labeling issues that were not resolved during the first review cycle.

Efficacy Summary

The efficacy evaluation was based on two 1:1 randomized, open-label, active-controlled, non-inferiority clinical studies of similar design (Study SPI-GCF-301 [NCT02643420] and Study SPI-GCF-302 [NCT02953340]) that enrolled a total of 643 patients with early-stage breast cancer. Docetaxel 75 mg/m^2 and cyclophosphamide 600 mg/m^2 (TC) were administered intravenously every 21 days (on Day 1 of each cycle) for up to 4 cycles. A fixed dose of Rolvedon 13.2 mg/0.6 mL or pegfilgrastim (6 mg/0.6 mL) was administered subcutaneously on Day 2 of each cycle after TC chemotherapy. For pegfilgrastim, only Neulasta approved in the US (manufactured by Amgen) was used.

Overall, the median age of patients enrolled in the two randomized studies was 60 years (range: 24 to 88), the majority of patients were female (>99%), 77% were White and 12% were Black or African American. Eighty-one percent of patients were enrolled from the US clinical sites.

Table 1. SPI-GCF-301 and SPI-GCF-302: Patient Demographics (ITT Population)

	SPI-GCF-301			SPI-GCF-302		
	SPI-2012 (n=196)	Pegfilgrastim (n=210)	Total (n=406)	SPI-2012 (n=118)	Pegfilgrastim (n=119)	Total (n=237)
Gender						
Female	195 (99%)	209 (>99%)	404 (>99%)	118 (100%)	119 (100%)	237 (100%)
Male	1 (1%)	1 (<1%)	2 (<1%)	0	0	0
Age (years)						

Median	61	60	61	58	59	59
Range	28, 83	24, 84	24, 84	29, 80	34, 88	29, 88
Race						
White	156 (80%)	159 (76%)	315 (78%)	85 (72%)	96 (81%)	181 (76%)
Black/African American	26 (13%)	32 (15%)	58 (14%)	11 (9%)	7 (6%)	18 (5%)
Asian	9 (5%)	9 (4%)	18 (4%)	20 (17%)	16 (13%)	36 (15%)
Other	5 (3%)	10 (5%)	15 (4%)	2 (2%)	0	2 (<1%)
Ethnicity						
Hispanic/ Latino	34 (17%)	40 (19%)	74 (18%)	18 (15%)	15 (13%)	33 (14%)
Not Hispanic or Latino	162 (83%)	170 (81%)	332 (82%)	100 (85%)	104 (87%)	204 (86%)
Weight (kg)						
Median	79	79	79	75	74	74
Range	42, 145	42, 150	42, 150	40, 171	46, 153	40, 171

[Source: ADSL.xpt]

In Study SPI-GCF-301, the difference in duration of severe neutropenia (DSN) between the Rolvedon treatment arm and the pegfilgrastim treatment arm was -0.148 days and the corresponding 95% CI was (-0.265, -0.033). Non-inferiority to pegfilgrastim was demonstrated for the Rolvedon treatment arm (upper bound of 95% CI <0.62 days) for the mean DSN.

In Study SPI-GCF-302, the difference in DSN between the Rolvedon treatment arm and the pegfilgrastim treatment arm was -0.073 days and the corresponding 95% CI was (-0.292, 0.129). Non-inferiority to pegfilgrastim was demonstrated for the Rolvedon treatment arm (upper bound of 95% CI <0.62 days).

Table 1. Duration of Severe Neutropenia (DSN) in Cycle 1 (Study SPI-GCF-301 and Study SPI-GCF-302) (ITT Population)

	Study SPI-GCF-301		Study SPI-GCF-302	
	Rolvedon (n=196)	Pegfilgrastim (n=210)	Rolvedon (n=118)	Pegfilgrastim (n=119)
Mean DSN (SD) (Days)	0.20 (0.503)	0.35 (0.683)	0.31 (0.688)	0.39 (0.949)
Median DSN (Range) (Days)	0 (0, 3)	0 (0, 3)	0 (0, 3)	0 (0, 7)
Difference in DSN (Days)	-0.148		-0.073	

*95% Confidence Interval[a]	-0.265, -0.033	-0.292, 0.129

[a]Confidence intervals were obtained using 2.5 percentile and 97.5 percentile of the 100,000 bootstrap samples with treatment as stratification factor.
*The non-inferiority of Rolvedon to pegfilgrastim was to be declared if the upper bound of 95% CI of the difference in mean DSN between the treatment arms was <0.62 days.

Both pivotal studies, individually, met the non-inferiority criteria for the primary endpoint of DSN in Cycle 1 in the ITT population. The results in the Per Protocol population and additional sensitivity analyses were consistent with the results in the ITT population. There were no outliers in the subgroup analyses of DSN in Cycle 1 by age, gender, race, disease status, region, and body weight in both studies. The analyses of all secondary efficacy endpoints including time to ANC recovery, depth of ANC nadir, and incidence of febrile neutropenia also showed that there were no significant differences between eflapegrastim and pegfilgrastim (see clinical review dated June 24, 2020).

Safety Summary

The safety review of eflapegrastim-xnst was primarily based on a total of 640 patients (eflapegrastim-xnst: 314 patients, pegfilgrastim: 326 patients) who participated in the two phase 3 pivotal trials (SPI-GCF-301 and SPI-GCF-302). Patients randomized to the eflapegrastim-xnst arm received 13.2 mg/0.6 mL SQ injections on Day 2 of each cycle (24 hours after the last dose of TC chemotherapy). The median duration of treatment of eflapegrastim-xnst in both studies was 4 cycles (range: 1, 4).

The overall incidence of serious adverse reactions was similar in the two arms (eflapegrastim-xnst: 2%, pegfilgrastim: 3%). Serious adverse reactions reported in the eflapegrastim-xnst arm included chest pain and supraventricular tachycardia in addition to arthralgia, back pain, bone pain, white blood cell increased and pyrexia. The most frequently reported ≥ grade 3 AEs (>10%) were cytopenias; the incidences were also similar between the two arms (lymphopenia [eflapegrastim-xnst: 46%, pegfilgrastim: 47%], neutropenia [eflapegrastim-xnst: 46%, pegfilgrastim: 46%], leukopenia [eflapegrastim-xnst: 22%, pegfilgrastim: 25%]).

In the resubmission, the Applicant included new, unblinded safety information from ongoing Study SPI-GCF-104, an open-label, phase 1 dosing schedule trial (n=27) to evaluate the duration of Grade 4 neutropenia in patients with early-stage breast cancer when eflapegrastim-xnst is administered on the same day (with varying dose time schedules) as docetaxel and cyclophosphamide (TC) chemotherapy; and Study SPI-GCF-202, an open-label, phase 2 pediatric study (n=2) to evaluate the safety and PK of eflapegrastim-xnst in pediatric patients with solid tumors or lymphomas and treated with myelosuppressive chemotherapy. Datasets were not

provided, and these studies were not included in the original BLA. Per the Applicant, as of the interim analysis of October 11, 2021 cutoff date, data from the two studies were not mature.

Overall, safety results reported by the Applicant from the above two ongoing trials were generally consistent with those observed in the pivotal trials (SPI-GCF-301 and SPI-GCF-302) and other trials submitted in the original BLA. Based on the reported safety results, there were no new safety signals.

Labeling

Indication:
During the first review cycle, the indication was revised to add the phrase "associated with clinically significant incidence of febrile neutropenia" to the Sponsor's proposed indication of "decrease the incidence of infection, as manifested by febrile neutropenia, in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs."

During this review cycle, the applicability of Rolvedon efficacy and safety data to patient populations not evaluated in the phase 3 trials (i.e., cancer types other than breast and other chemotherapeutic regimens other than those used in two trials) was reviewed. The Applicant provided further justification for the proposed indication for eflapegrastim-xnst as follows:

> Granulocyte-colony stimulating factor (G-CSF) receptors are present throughout the body, specifically in progenitor cells in bone marrow in normal humans and are also retained in cancer or other form of malignancies. These G-CSF receptors are present in the bone marrow regardless of the type of cancer that a patient is being treated for, including lung cancer, invasive bladder cancer, gastric and colon cancer, etc. It has been well documented that use of G-CSF and other myeloid growth factors help to regulate the proliferation, differentiation, survival and activation of hematopoietic cells in the myeloid lineage.
>
> Eflapegrastim is taken up by the bone marrow, where it binds to G-CSF receptors stimulating progenitor cell differentiation, proliferation, and mobilization of granulocytes, including neutrophils. The efficacy of eflapegrastim was evaluated in two pivotal studies in patients with early-stage breast cancer (ESBC) who were treated with docetaxel and cyclophosphamide (TC). These chemotherapeutic agents are not specific for breast cancer treatment. Docetaxel is approved alone and in combination with other chemotherapeutic agents (e.g., gemcitabine, doxorubicin, cis-/carboplatin, trastuzumab, 5-fluorouracil) for the treatment of patients with breast cancer, non-small cell lung cancer, prostate cancer, gastric adenocarcinoma, and squamous cell carcinoma of the head and neck. Cyclophosphamide is approved in combination with other chemotherapeutic agents (e.g., doxorubicin, vincristine, dactinomycin) for the treatment of solid tumors, lymphomas, and leukemias.
>
> In conclusion, G-CSF receptors are abundant in the bone marrow irrespective of the type of

underlying cancer that a patient may have developed.

Based on the overall efficacy results of the two trials and the Applicant's justification, the indication as revised appear adequate for eflapegrastim-xnst. The proposed indication includes diverse tumor types treated with a wide array of chemotherapeutic agents and Division's requirement for a broad indication is to ensure the utility of the product for multiple tumor types and chemotherapies. The major mechanisms of actions of chemotherapeutic agents and the clinical trial data did not demonstrate an interaction with Rolvedon so additional study in other tumor types with different chemotherapeutic agents is not necessary. Based on the overall efficacy results of the pivotal trials and the Applicant's justification, the broad indication appears adequate for eflapegrastim-xnst.

Limitations of Use:
A limitations of use statement was included that Rolvedon is not indicated for the mobilization of peripheral blood progenitor cells for hematopoietic stem cell transplantation.

Similar to pegfilgastrim (Neulasta), Rolvedon has not been evaluated in patients undergoing stem cell mobilization.

Warnings and Precautions Section:
The Warnings and Precautions were revised to include class effects for the rhG-CSF products (i.e., splenic rupture, acute respiratory distress syndrome, serious allergic reactions, sickle cell crisis in patients with sickle cell disorders, glomerulonephritis, leukocytosis, thrombocytopenia, capillary leak syndrome, potential for tumor growth stimulatory effects on malignant cells, myelodysplastic syndrome and acute myeloid leukemia in patients with breast and lung cancer, aortitis and nuclear imaging were added).

Adverse Reactions Section:
During the resubmission cycle, the Agency revised the adverse reactions table in Section 6 as shown in the table below based on the safety findings observed in the pivotal Studies SPI-GCF-301 and SPI-GCF-302 and safety profile of G-CSF class products. The terms (b) (4), (b) (4) "pyrexia", (b) (4) were removed from the table.

The most common adverse reactions (≥20%) were fatigue, nausea, diarrhea, bone pain, headache, pyrexia, anemia, rash, myalgia, arthralgia, and back pain.

Serious adverse reactions were (b) (4) arthralgia, back pain, bone pain, white blood cell increased and pyrexia, which each occurred in one subject. During the resubmission cycle, these serious adverse reactions were removed from the label based on the known risks of G-CSF products (i.e., arthralgia, back pain, bone pain, leukocytosis

and pyrexia) [redacted] (b) (4)

Table 3 Pooled Analysis of Studies SPI-GCF-301 and SPI-GCF-302: Adverse Reactions in Patients with a Frequency of ≥ 10% (Safety Population)

Adverse Reaction	Rolvedon (N = 314) %	Pegfilgrastim (N=326) %
Fatigue*	181 (58%)	192 (59%)
Nausea	162 (52%)	166 (51%)
[redacted] (b) (4)		
Diarrhea	125 (40%)	126 (39%)
Bone pain	119 (38%)	121 (37%)
Headache	92 (29%)	90 (28%)
[redacted] (b) (4)		
Anemia *	77 (25%)	52 (16%)
~~Pyrexia*~~	~~87 (28%)~~	~~84 (26%)~~
Rash*	77 (25%)	99 (30%)
Myalgia	69 (22%)	49 (15%)
Arthralgia	66 (21%)	48 (15%)
Back pain*	63 (20%)	55 (17%)
Decreased appetite	61 (19%)	50 (15%)
[redacted] (b) (4)		
Edema peripheral*	57 (18%)	53 (16%)
[redacted] (b) (4)		
Abdominal pain	53 (17%)	67 (21%)
Dizziness *	50 (16%)	38 (12%)
[redacted] (b) (4)		
Dyspnea*	49 (16%)	44 (13%)
Cough*	48 (15%)	51 (16%)

Thrombocytopenia*	44 (14%)	17 (5%)
Pain	37 (12%)	42 (13%)
Pain in extremity	36 (11%)	42 (13%)
(b) (4)		
Local administration reactions*	34 (11%)	27 (8%)
(b) (4)		
Flushing	32 (10%)	27 (8%)
(b) (4)		

*Grouped Terms by FDA Medical Query (FMQ)
The highlighted terms were removed.
[Source: ADAE.xpt]

Conclusions:

Overall, substantial evidence of effectiveness of Rolvedon to decrease the incidence of infection, as manifested by febrile neutropenia, in adult patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs associated with clinically significant incidence of febrile neutropenia was established based on at least two adequate and well-controlled clinical investigations (i.e., Studies SPI-GCF-301 and SPI-GCF-302). The primary endpoint of both trials was duration of severe neutropenia (DSN) in Cycle 1. Studies SPI-GCF-301 and SPI-GCF-302 both demonstrated that Rolvedon is non-inferior to pegfilgrastim for the endpoint of DSN. In the two studies, the similar incidence of febrile neutropenia between patients who received Rolvedon and pegfilgrastim, support the benefit of the study drug.

The most common adverse reactions for Rolvedon treatment arms were (≥ 20%) were fatigue, nausea, diarrhea, bone pain, headache, pyrexia, anemia, rash, myalgia, arthralgia and back pain. No new safety signals were detected in patients treated with Rolvedon compared to pegfilgrastim in the pooled safety analysis of Studies SPI-GCF-301 and SPI-GCF-302. The benefit-risk is favorable.

The recommended action for this BLA is approval by traditional pathway.

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/s/

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FILE MEMORANDUM

Memo Date:	July 12, 2021
To BLA:	761148
Submission Date:	October 24, 2019
Received Date:	October 24, 2019
Division/Office:	DNH/OCHEN
EDR Location:	\\CDSESUB1\evsprod\BLA761148\0000
From:	Hyon-Zu Lee, PharmD, Clinical Reviewer; DNH
Subject:	Rolontis (eflapegrastim)
Via:	Tanya Wroblewski, MD, Clinical Team Leader, DNH

This is an addendum to the clinical and statistical review signed off in DARRTS on June 24, 2020. Table 59 on page 87 of the review should be replaced with the table below.

Table 1 SPI-GCF-301 and SPI-GCF-302: TEAEs that Occurred ≥ 10% of Patients (Safety Population)

FMQ (Narrow)	Eflapegrastim (n=314)		Pegfilgrastim (n=326)	
	Any grade	Grade 3/4	Any grade	Grade 3/4
All	307 (98%)	233 (74%)	320 (98%)	235 (72%)
Fatigue*	181 (58%)	5 (2%)	192 (59%)	5 (2%)
Nausea	162 (52%)	1 (<1%)	166 (51%)	3 (1%)
Lymphopenia*	152 (48%)	146 (46%)	159 (49%)	153 (47%)
Neutropenia*	149 (47%)	145 (46%)	156 (48%)	150 (46%)
Alopecia	135 (43%)	2 (<1%)	136 (42%)	7 (2%)
Diarrhea	125 (40%)	4 (1%)	126 (39%)	2 (<1%)
Bone pain	119 (38%)	13 (4%)	121 (37%)	4 (1%)
Headache*	92 (29%)	1 (<1%)	90 (28%)	2 (<1%)
Constipation	88 (28%)	1 (<1%)	72 (22%)	3 (1%)
Leukopenia*	82 (26%)	69 (22%)	90 (28%)	83 (25%)
Anemia*	79 (25%)	22 (7%)	54 (17%)	10 (3%)
Pyrexia*	87 (28%)	5 (2%)	84 (26%)	2 (<1%)
Rash*	77 (25%)	6 (2%)	99 (30%)	6 (2%)
Myalgia	69 (22%)	2 (<1%)	49 (15%)	1 (<1%)
Arthralgia	66 (21%)	5 (2%)	48 (15%)	3 (1%)
Decreased appetite	61 (19%)	0	50 (15%)	0
Back pain*	63 (20%)	6 (2%)	55 (17%)	3 (1%)
Insomnia	57 (18%)	1 (<1%)	43 (13%)	0
Edema peripheral*	57 (18%)	0	53 (16%)	0
Vomiting	54 (17%)	1 (<1%)	55 (17%)	4 (1%)
Abdominal pain*	53 (17%)	2 (<1%)	67 (21%)	4 (1%)
Dizziness*	50 (16%)	0	38 (12%)	0
Dysgeusia*	49 (16%)	1 (<1%)	49 (15%)	0

Dyspnea*	49 (16%)	5 (2%)	44 (13%)	4 (1%)
Thrombocytopenia*	44 (14%)	14 (4%)	17 (5%)	4 (1%)
Cough*	48 (15%)	0	51 (16%)	0
Pain	37 (12%)	2 (<1%)	42 (13%)	3 (1%)
Pain in extremity	36 (11%)	1 (<1%)	42 (13%)	0
Stomatitis	36 (11%)	1 (<1%)	35 (11%)	0
Hemorrhage*	35 (11%)	2 (<1%)	51 (16%)	1 (<1%)
Pruritus*	35 (11%)	2 (<1%)	36 (11%)	1 (<1%)
Local administration reactions*	34 (11%)	0	27 (8%)	1 (<1%)
Dyspepsia	34 (11%)	0	34 (10%)	0
Flushing	32 (10%)	2 (<1%)	27 (8%)	0
Urinary tract infection*	26 (8%)	3 (<1%)	34 (10%)	7 (2%)

*Grouped Terms by FDA Medical Query (FMQ)
Fatigue includes fatigue, asthenia, lethargy, and malaise.
Lymphopenia includes lymphopenia and lymphocyte count decreased.
Neutropenia includes neutropenia and neutrophil count decreased.
Headache includes headache, migraine, and tension headache.
Leukopenia includes leukopenia and white blood cell count decreased.
Anemia includes anemia and hemoglobin decreased.
Pyrexia includes pyrexia, body temperature increased, and febrile neutropenia.
Rash includes rash, rash erythematous, rash generalized, rash macular, rash maculo-papular, rash papular, rash pruritic, rash pustular, rash vesicular, blister, catheter site rash, dermatitis, erythema multiforme, genital rash, skin exfoliation, skin reaction, urticaria, and vulvovaginal rash.
Back pain includes back pain, flank pain, and sciatica.
Edema peripheral includes edema peripheral and peripheral swelling.
Abdominal pain includes abdominal pain, abdominal pain lower, abdominal pain upper, abdominal discomfort, abdominal distension, and abdominal rigidity.
Dizziness includes dizziness, balance disorder, dizziness postural, presyncope and vertigo.
Dysgeusia includes dysgeusia, ageusia and hypogeusia.
Dyspnea includes dyspnea and dyspnea exertional
Thrombocytopenia includes thrombocytopenia, pancytopenia and platelet count decreased.
Cough includes cough, hemoptysis, productive cough and upper-airway cough syndrome.
Hemorrhage includes hemorrhage, anal hemorrhage, blood urine present, breast hemorrhage, catheter site hemorrhage, contusion, ecchymosis, epistaxis, gastrointestinal hemorrhage, gingival bleeding, hematemesis, hematochezia, hematoma, hematuria, hemoptysis, hemorrhagic diathesis, incision site hemorrhage, melaena, menorrhagia, petechiae, post procedural hemorrhage, rectal hemorrhage and vaginal hemorrhage.
Pruritis includes pruritis, anal pruritus, application site pruritus, catheter site pruritus, eye pruritus, infusion site pruritus, and pruritus generalized.
Local administration reactions include local administration reactions, administration site pain, catheter site pain, catheter site rash, incision site pain, infusion related reaction, infusion site discomfort, infusion site erythema, infusion site extravasation, infusion site pain, infusion site reaction, injection site pain, injection site reaction, medical device site pain, and vessel puncture site pain.
Urinary tract infection includes urinary tract infection, cystitis, pyelonephritis, and urosepsis
[Source: ADAE.xpt]

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/s/

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07/22/2021 02:24:15 PM

CLINICAL and STATISTICAL REVIEW

Application Type	Original BLA
Application Number	761148
Priority or Standard	Standard
Submit Date	October 24, 2019
Received Date	October 24, 2019
PDUFA Goal Date	October 24, 2020
Division/Office	DNH/OCHEN
Reviewer Names	Clinical: Hyon-Zu Lee, PharmD (Reviewer) Kathy Robie-Suh, MD, PhD (Team Leader) Statistical: Kate Li Dwyer, PhD (Reviewer) Yeh-Fong Chen, PhD (Team Leader) Thomas E. Gwise, PhD (Division Director)
Review Completion Date	See stamped date
Established/Proper Name	Eflapegrastim
(Proposed) Trade Name	Rolontis
Applicant	Spectrum Pharmaceuticals, Inc.
Dosage Form	Solution for injection
Applicant Proposed Dosing Regimen	13.2 mg once as a subcutaneous injection per chemotherapy cycle (to be administered 24 hours after cytotoxic chemotherapy)
Applicant Proposed Indication	Decrease the incidence of infection, as manifested by febrile neutropenia, in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs.
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	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.

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Glossary

AC	advisory committee
ADaM	Analysis Data Model
AE	adverse event
ANC	absolute neutrophil count
AR	adverse reaction
ARDS	acute respiratory distress syndrome
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CBC	complete blood count
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
CTCAE	Common Terminology Criteria for Adverse Event
DMC	data monitoring committee
DNH	Division of Nonmalignant Hematology
DSN	Duration of severe neutropenia
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCTD	electronic common technical document
ESBC	early-stage breast cancer
ETASU	elements to assure safe use
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	good clinical practice
G-CSF	granulocyte colony stimulating factor

GRMP	good review management practice
ICH	International Council for Harmonization
IND	Investigational New Drug Application
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
NCCN	National Comprehensive Cancer Network
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NME	new molecular entity
OCHEN	Office of Cardiology, Hematology, Endocrinology and Nephrology
OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PEG	polyethylene glycol
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PI	prescribing information or package insert
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
RDI	Relative Dose Intensity
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SDTM	Study Data Tabulation Model
SGE	special government employee
SOC	standard of care
TC	docetaxel and cyclophosphamide
TEAE	treatment emergent adverse event

1. Executive Summary

1.1. Product Introduction

Rolontis®(eflapegrastim, also referred to as SPI-2012, HM10460A or LAPS-G-CSF) injection, is a granulocyte colony stimulating factor (G-CSF). The proposed indication is to decrease the incidence of infection, as manifested by febrile neutropenia, in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs. Eflapegrastim is a new biological product presented as 13.2 mg/0.6 mL [redacted] (b) (4) solution in a single-dose prefilled syringe. The proposed dosing regimen in patients with cancer receiving myelosuppressive chemotherapy is 13.2 mg to be administered subcutaneously once per chemotherapy cycle approximately 24 hours after cytotoxic chemotherapy.

Eflapegrastim is produced by covalent coupling of a human G-CSF analog (HM10411) and human immunoglobulin G4 (IgG4) Fc fragment (HMC001), both derived from recombinant Escherichia coli (E. coli), via a 3.4 kDa polyethylene glycol (PEG) linker.

1.2. Conclusions on the Substantial Evidence of Effectiveness

The efficacy of eflapegrastim to decrease the incidence of infection, as manifested by febrile neutropenia, in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs was demonstrated in the two similarly designed, randomized (1:1), open-label, non-inferiority, clinical studies (SPI-GCF-301 [ADVANCE] and SPI-GCF-302 [RECOVER]) that compared eflapegrastim (13.2 mg/0.6 mL) with pegfilgrastim (6 mg/0.6 mL), both by SQ injections, in patients with early-stage breast cancer receiving docetaxel and cyclophosphamide (TC) chemotherapy. For pegfilgrastim, only Neulasta approved in the US (manufactured by Amgen) was to be used.

In both studies, patients received the study treatment on Day 2 of each cycle, 24 hours after the last dose of TC chemotherapy, for a median of 4 cycles total. Studies SPI-GCF-301 and SPI-GCF-302 randomized a total of 406 patients (eflapegrastim: 196 patients, pegfilgrastim: 210 patients) and 237 patients (eflapegrastim: 118 patients, pegfilgrastim: 119 patients), respectively. The primary efficacy endpoint in the two trials was the duration of severe neutropenia (DSN) in Cycle 1. The non-inferiority of eflapegrastim to pegfilgrastim was to be demonstrated if the upper bound of the 95% CI of the difference in the mean DNS of the two treatment arms was less than the non-inferiority margin of 0.62 days.

In both studies, the treatment of eflapegrastim was non-inferior to pegfilgrastim therapy for the mean DSN in Cycle 1. In studies SPI-GCF-301 and SPI-GCF-302, the difference in the mean DSN in Cycle 1 of eflapegrastim compared to pegfilgrastim was -0.148 days (95% CI: -0.265, -0.033) and -0.073 days (95% CI: -0.292, 0.129), respectively.

1.3. Benefit-Risk Assessment

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Benefit-Risk Integrated Assessment

The benefit-risk assessment supports regular approval of eflapegrastim to decrease the incidence of infection, as manifested by febrile neutropenia, in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs.

The efficacy of eflapegrastim for the proposed indication was demonstrated in the two randomized (1:1), open-label, non-inferiority, clinical studies as described in Section 1.2. Conclusions on the Substantial Evidence of Effectiveness above.

The safety review of eflapegrastim was primarily based on a total of 640 patients (eflapegrastim: 314 patients, pegfilgrastim: 326 patients) who participated in the two phase 3 pivotal trials (SPI-GCF-301 and SPI-GCF-302). Patients randomized to the eflapegrastim arm received 13.2 mg/0.6 mL SQ injections on Day 2 of each cycle (24 hours after the last dose of TC chemotherapy). The median duration of treatment of eflapegrastim in both studies was 4 cycles (range: 1, 4).

The most frequently reported SAEs (> 2 patients) in the eflapegrastim arm were pyrexia, sepsis, febrile neutropenia, diarrhea and chest pain; and the incidences of these SAEs were similar to those observed in the pegfilgrastim arm. The most frequently reported ≥ grade 3 AEs (>10%) were cytopenias; the incidences were also similar between the two arms (lymphopenia [eflapegrastim: 46%, pegfilgrastim: 47%], neutropenia [eflapegrastim: 46%, pegfilgrastim: 46%], leukopenia [eflapegrastim: 22%, pegfilgrastim: 25%]). The most frequently reported AEs (>10%) that were considered related to study treatment in both arms included musculoskeletal and connective tissue AEs and increased white blood cell counts consistent with the safety profile of myeloid growth factors. The most common study treatment-related AEs in the eflapegrastim arm (≥ 5%) with at least 5% higher incidence compared to the pegfilgrastim arm were arthralgia (15% vs. 10%), myalgia (15% vs. 9%), back pain (14% vs. 9%), leukocytosis (11% vs. 6%) and diarrhea (9% vs. 3%).

The benefit-risk assessment of eflapegrastim to decrease the incidence of infection, as manifested by febrile neutropenia, in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs is favorable.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs are at risk of developing neutropenia which may progress to febrile neutropenia. The development of febrile neutropenia in this patient population may require dose reductions or treatment delays of the chemotherapy, which may compromise treatment outcomes.	In patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs, the development of febrile neutropenia may impact the treatment course and clinical outcomes.
Current Treatment Options	• Neupogen • Neulasta • Granix • Biosimilars to filgrastim and pegfilgrastim (see Table 1)	Multiple G-CSF therapies exist for the management of neutropenia in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs. Eflapegrastim provides another alternative treatment option for this patient population.
Benefit	• The efficacy results of studies SPI-GCF-301 and SPI-GCF-302 showed that eflapegrastim is non-inferior to pegfilgrastim for the mean DSN in Cycle 1. The difference in the mean DSN was -0.148 days (95% CI: -0.265, -0.033) and -0.073 days (95% CI: -0.292, 0.129), respectively, in studies SPI-GCF-301 and SPI-GCF-302.	The non-inferiority of eflapegrastim to pegfilgrastim for the mean DSN was demonstrated in two adequate and well-controlled clinical trials.
Risk and Risk Management	• Major toxicities of eflapegrastim include serious allergic reactions, splenic rupture, leukocytosis, sickle cell crises and potential for tumor stimulatory effects on malignant cells. • Based on the safety profile, there is no need for Risk Evaluation and Mitigation Strategy (REMS).	The toxicity of eflapegrastim is manageable with adequate recommendations for monitoring and treatment modifications in the prescribing information.

1.4. Patient Experience Data

Patient experience data was not included in this application.

2. Therapeutic Context

2.1. Analysis of Condition

Patients with non-myeloid malignancies receiving myelosuppressive chemotherapy are at risk of developing neutropenia. The risk of fever (febrile neutropenia) and life-threatening infections increases in patients with low absolute neutrophil count (ANC). In patients with febrile neutropenia, administration of intravenous broad-spectrum antibiotics is required and chemotherapy often results in dose reductions or treatment delays, which may compromise treatment outcomes. The National Comprehensive Cancer Network (NCCN) clinical guidelines for prevention and management of chemotherapy-induced neutropenia recommends the use of supportive care with granulocyte colony stimulating factors (G-CSF) in patients with solid tumors and non-myeloid malignancies with intermediate (10%-20%) and high (>20%) risk factors which are based on the disease, chemotherapy regimen, patient risk factors and treatment intent (curative vs. palliative).

2.2. Analysis of Current Treatment Options

The table below summarizes currently available G-CSFs.

Table 1 Currently Available G-CSFs

Drug	Approval Date
Neupogen (filgrastim)	2/20/1991
Neulasta (pegfilgrastim)	1/31/2002
Granix (Tbo-filgrastim)	8/29/2012
Zarxio (filgrastim-sndz) (biosilimar)	3/6/2015
Fulphila (pegfilgrastim-jmdb (biosimilar)	6/4/2018
Nivestym (filgrastim-aafi) (biosimilar)	7/20/2018
Udencya (Pegfilgrastim-cbqv) (biosimilar)	11/2/2018
Ziextenzo (pegfilgrastim-bmez) (biosimilar)	11/4/2019
Nyvepria (pegfilgrastim-apgf) (biosimilar)	6/10/2020

[Source: FDA compilation]

The proposed indication for eflapegrastim is “To decrease the incidence of infection, as manifested by febrile neutropenia, in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drug.” The table below summarizes the study design and efficacy

results of the pivotal studies that resulted in approval of G-CSFs and approved per 351(a) of the Public Health Service Act (Neupogen, Neulasta and Granix). (All other approved G-CSF products are biosimilars approved under section 351(k) of the Public Health Service Act).

Table 2 Leukocyte Growth Factors Approved per 351(a)*

Drug	Indication	Study Design and Patient Population	Efficacy Results
Neupogen (filgrastim)	Decrease the incidence of infection, as manifested by febrile neutropenia, in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a significant incidence of severe neutropenia with fever	-One randomized, double-blind, placebo-controlled trial conducted in patients with small cell lung cancer -Patients received up to 6 cycles of iv chemotherapy including iv cyclophosphamide and doxorubicin on day 1; and etoposide on days 1, 2, and 3 of 21-day cycles. -Patients were randomized to receive Neupogen (n = 99) at a dose of 230mcg/m^2 (4 to 8 mcg/kg/day) or placebo (n = 111). -Study drug was administered SQ daily beginning on day 4, for a maximum of 14 days.	-Febrile neutropenia was defined as ANC < 1,000/mm^3 and temperature > 38.2°C. -The incidence of infection (manifested by febrile neutropenia) was 40% in Neupogen arm and 76% in placebo arm, ($p < 0.001$).
Neulasta (pegfilgrastim)	Decrease the incidence of infection, as manifested by febrile neutropenia, in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a clinically significant incidence of febrile neutropenia.	-Three randomized, double-blind, controlled studies. -Studies 1 and 2: Active-controlled studies of doxorubicin 60 mg/m^2 and docetaxel 75 mg/m^2 administered every 21 days for up to 4 cycles for the treatment of metastatic breast cancer. -Study 1 investigated the utility of a fixed dose of Neulasta. Study 2 employed a weight-adjusted dose. - Study 1: 157 patients were randomized to receive a single SQ injection of Neulasta (6 mg) on day 2 of each chemotherapy cycle or daily SQ filgrastim (5 mcg/kg/day) beginning on day 2 of each chemotherapy cycle. - Study 2: 310 patients were randomized to receive a single SQ injection of Neulasta (100 mcg/kg) on day 2 or daily SQ filgrastim (5 mcg/kg/day) beginning on day 2 of	- Study 1: Mean days of severe neutropenia in cycle 1 were 1.8 days in Neulasta arm and 1.6 days in filgrastim arm [difference in means 0.2 (95% CI: - 0.2, 0.6)] and in; Study 2 were 1.7 days in Neulasta arm and 1.6 days in filgrastim arm [difference in means 0.1 (95% CI: - 0.2, 0.4)]. -Study 3: febrile neutropenia was defined as temperature

		each chemotherapy cycle. - Study 3: Double-blind, placebo-controlled study that employed docetaxel 100 mg/m^2 administered every 21 days for up to 4 cycles for the treatment of metastatic or non-metastatic breast cancer. In this study, 928 patients were randomized to receive a single SQ injection of Neulasta (6 mg) or placebo on day 2 of each chemotherapy cycle.	≥38.2°C and ANC ≤ 0.5 x 10^9/L). -The incidence of febrile neutropenia was 1% in Neulasta arm and 17% in placebo arm ($p < 0.001$).
Granix (Tbo-filgrastim)	Indicated in adult and pediatric patients 1 month and older for reduction in the duration of severe neutropenia in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a clinically significant incidence of febrile neutropenia.	-One controlled Phase 3 study in 348 chemotherapy-naive patients with high-risk stage II, stage III, or stage IV breast cancer receiving doxorubicin (60 mg/m^2) and docetaxel (75 mg/m^2) comparing Granix to placebo and a non-US-approved filgrastim product as controls. - Granix, placebo, and the non-US-approved filgrastim product were administered at 5 mcg/kg SQ once daily beginning one day after chemotherapy for at least 5 days and continued to a maximum of 14 days or until an ANC of ≥10,000 x 10^6/L after nadir was reached.	- Duration of severe neutropenia was 1.1 days in Granix arm and 3.8 days in placebo arm, ($p < 0.0001$).

[Source: FDA compilation]

3. Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Eflapegrastim is a new molecular entity (NME) and is not licensed for marketing in the US.

3.2. Summary of Presubmission/Submission Regulatory Activity

The table below summarizes the key relevant regulatory history pertaining to this BLA.

Table 3 Regulatory History

December 12, 2014	End of Phase 2 meeting was held. Key communication points were as follows: -Regarding the pivotal phase 3 non-inferiority studies, the FDA stated that the

	trials should be designed using a non-inferiority margin of 0.6 day versus the US-licensed Neulasta. -The FDA stated that two protocols in breast cancer patients might be acceptable to support an application if the Sponsor could provide in the application justification for extrapolation to other diseases and across gender. -The FDA agreed with the primary endpoint of Duration of Severe Neutropenia (DSN) in the two planned Phase 3 studies.
December 15, 2015	The FDA issued a Special Protocol Agreement letter for the protocol, SPI-GCF-301, entitled, "Randomized Trial of SPI-2012 Versus Pegfilgrastim in the Management of Chemotherapy Induced Neutropenia in Breast Cancer Patients Receiving Docetaxel and Cyclophosphamide (TC) (ADVANCE-1)". The FDA commented that a single pivotal trial may not be sufficient evidence for approval of a marketing application of a supportive care drug. In addition, the planned analyses of Time to ANC Recovery and Depth of ANC Nadir would not support a labeling claim for these two outcomes, but they can be performed for descriptive purposes to support the claim based on the primary endpoint analysis.
December 20, 2016	The FDA stated in a written response only communication that for the currently ongoing Phase 3 study, SPI-GCF-301, the reduced sample size of 188 per treatment arm (resulting in a statistical power of 85%) appears to be adequate for detecting non-inferiority of eflapegrastim to Neulasta using a one-sided, two sample t-test at one-sided Type I error rate of 0.025.
March 16, 2017	The FDA issued a Special Protocol Agreement letter for modifications made in the protocol, SPI-GCF-301. The main modifications were as follows: The sample size of the SPI-GCF-301 study was changed from 290 per treatment arm to 200 per treatment arm. The level of significance for the SPI-GCF-301 study was revised from a 0.5% level of significance to a 2.5% level of significance for 87% power. In addition, the FDA stated that the single pivotal trial, SPI-GCF-301 as revised, will not be sufficient as the sole basis of a marketing application for a supportive care drug, since the reduced sample size will not provide for sufficiently robust results to stand on its own, nor will it provide for an adequate safety database.
August 21, 2018	A pre-BLA meeting was held. The FDA stated the following: -Include a discussion of the following potential adverse reactions in related to the product: capillary leak syndrome, severe allergic reactions, complications with sickle cell disease, acute respiratory distress syndrome (ARDS) and splenic rupture. - With the class of G-CSF growth factor drugs there is a potential for tumor growth stimulatory effects on malignant cells as malignant cell lines possess G-CSF receptors on their cell surface raising theoretical concern that the drug

	product may promote neoplastic cell growth. Provide a discussion of this theoretical risk and the agent in the application. - Final determination of the proposed indication will be made during the review of the application.
December 21, 2018	The Applicant submitted a BLA (b) (4) for eflapegrastim.
March 14, 2019	The BLA (b) (4) was withdrawn by the Applicant after discussion with the Agency due to CMC filing deficiencies (incomplete CMC information and inadequate organization of the CMC section of the application).
October 24, 2019	The Applicant resubmitted the BLA for eflapegrastim under BLA 761148

[Source: FDA compilation]

3.3. Foreign Regulatory Actions and Marketing History

Eflapegrastim (SPI-2012) is not currently marketed in any country.

4. Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

Studies SPI-GCF-301 and SPI-GCF-302 are the pivotal trials to support efficacy and safety of eflapegrastim for the proposed indication. During the previous BLA (b) (4) review cycle of eflapegrastim, clinical sites of studies SPI-GCF-301 and SPI-GCF-302 in Table 4 were chosen for inspection. The site selection was based on presumed risks based on the number of patient enrollment, safety and efficacy results.

Table 4 Requested OSI Clinical Site Audits for SPI-GCF-301 and SPI-GCF-302

Protocol ID	Site ID	Number of enrolled patients	Name of the Principal Investigator	Location
SPI-GCF-301	US047	34	Richy Agajanian	15111 E. Whittier Blvd. Whittier, CA 90603 United States
SPI-GCF-302	HU003	10	Istvan Lang	Orszagos Onkologiai Intezet, B Belgyogyaszati Onkologiai Osztaly Rath Gyorgy utca 7-9, Budapest 1122, Hungary Budapest, 1122
SPI-GCF-302	HU004	13	Klara Mezei	Szabolcs-Szatmar-Bereg

				Megyei Korhazak es Egyetemi Oktato Korhaz, Onkologiai Osztaly Szent Istvan u. 68., 4400 Nyiregyhaza, Hungary Nyiregyhaza, 4400

OSI's overall assessment of findings and general recommendations for these sites were as follows:

"Three clinical sites were selected for inspection in support of BLA (b) (4) Data from Dr. Richy Agajanian's site in California (Site # US047) in Study SPI-GCF-301, as reported by the sponsor to the BLA, are considered to be reliable in support of the requested indication. No inspectional observations were noted at Dr. Istvan Lang's site (Site # HU003) and Dr. Klara Mezei's site (Site # HU004) in Hungary for Study SPI-GCF-302. The study data generated from these sites are considered to be reliable in support of the requested indication."

With the current resubmission of the BLA for eflapegrastim, there were no changes in the clinical sites. Therefore, clinical site inspections were not requested by DNH for the current BLA (761148). However, the OSI inspected the Applicant with respect to studies SPI-GCF-301 and SPI-GCF-302 in support of the current BLA application. OSI's overall assessment was that "The inspection of the Sponsor found regulatory deficiencies with oversight and monitoring of the trials, but the findings are not considered significant. Based on the inspection, data from the two studies appear reliable in support of the proposed drug indication."

Therefore, the overall compliance with GCP appears acceptable.

Refer to the OSI reviews dated July 10, 2019 (under BLA (b) (4) and March 6, 2020 (under BLA 761148).

4.2. Product Quality

Refer to Chemistry, Manufacturing and Controls (CMC) review.

4.3. Clinical Microbiology

This section is not applicable.

4.4. Nonclinical Pharmacology/Toxicology

Refer to Nonclinical Pharmacology/Toxicology review.

4.5. Clinical Pharmacology

Refer to Clinical Pharmacology review.

4.6. Devices and Companion Diagnostic Issues

Refer to Center for Devices and Radiological Health (CDRH) review.

4.7. Consumer Study Reviews

This section is not applicable.

5. Sources of Clinical Data and Review Strategy

5.1. Table of Clinical Studies

The clinical trials that are pertinent to the review of efficacy and safety included in this BLA are summarized in the table below.

Table 5 Listing of Clinical Trials for Efficacy and Safety Relevant to BLA 761148

Trial ID	Design	Regimen	Primary Endpoint	Patients enrolled	No. of Centers and Countries/ Status
Controlled Studies to Support Efficacy and Safety					
SPI-GCF-301	Randomized, open-label, active-controlled, multicenter study in the management of chemo-therapy induced neutropenia in breast cancer patients receiving docetaxel and cyclophos-phamide (TC) (ADVANCE)	-Eflapegrastim: 13.2 mg (3.6mg G-CSF equiv.) -Pegfilgrastim: 6 mg (as G-CSF) Each drug was given SC on Day 2 of each 21-day cycle, 24 to 26 hours after TC, for a total of 4 cycles	Duration of Severe Neutropenia (DSN) in Cycle 1	406 patients (eflapegrastim: 196, pegfil-grastim: 210)	-82 sites in 3 countries (US, Canada and Korea -Completed
SPI-GCF-	Randomized,	-Eflapegrastim:	DSN in Cycle 1	237 patients	-74 sites in 6

302	open-label, active-controlled, multicenter study in the management of chemo-therapy-induced neutropenia in early-stage breast cancer patients receiving TC (RECOVER)	13.2 mg (3.6mg G-CSF equiv.) -Pegfilgrastim 6 mg (as G-CSF) Each drug was given SC on Day 2 of each 21-day cycle, 24 to 26 hours after TC, for a total of 4 cycles		(eflapegrastim: 118, pegfil-grastim: 119)	countries (US, Korea, Poland, Hungary, Canada and India) -Completed
Other studies pertinent to the review of efficacy or safety					
SPI-GCF-12-201	Phase 2, open-label, dose-ranging study, sequentially enrolled by study dose, with a noninferiority design in patients with breast cancer who are candidates for adjuvant and neo-adjuvant chemotherapy with the TC regimen	-Eflapegrastim: 45, 135, and 270 mcg/kg -Pegfilgrastim: 6 mg Each drug: single SQ administration on Day 2 of each 21-day cycle for a total of 4 cycles	DSN in Cycle 1	148 patients (eflapegrastim: 45 mcg/kg: 39 135 mcg/kg: 37 270 mcg/kg: 36 pegfilgrastim: 36 patients)	-27 sites in 6 countries (US, Australia, Georgia, Hungary, Israel and Poland) -Completed
SPI-GCF-301-PK	Phase 1, single-arm, multicenter study to evaluate the PK and safety of SPI-2012 in early-stage breast cancer	Eflapegrastim: 13.2 mg SC on Day 2 of each 21-day cycle, approximately 24 to 26 hours after TC, for a total of 4 cycles	PK	26 patients (includes 6 patients enrolled in both SPI-GCF-301 and SPI-GCF-301-PK).	-4 sites in US -Completed

	patients treated with TC therapy.				
08-HM10460A-101	Randomized, double-blind, placebo-and active-controlled, escalating single-dose study of SC HM10460A to healthy adult Japanese and Caucasian subjects	Single SC doses. -Eflapegrastim: 1.1, 3.3, 10, 45, 135, 270 mcg/kg -Pegfilgrastim: 6 mg -Matching placebo (for eflapegrastim)	Safety/tolerability	84 patients -Eflapegrastim: 1.1 mcg/kg: 6 3.3 mcg/kg: 6 10 mcg/kg: 12 45 mcg/kg: 12 135 mcg/kg: 12 270 mcg/kg: 12 -Pegfilgrastim: 12 -Placebo: 12	-1 site in US -Completed
09-HM10460A-102	Randomized, double-blind, placebo-controlled, dose-escalation study of HM10460A SC single-dose in healthy adult Korean subjects	Single SC doses. -Eflapegrastim: 5, 15, 45, 135, 350 mcg/kg -Matching placebo	Safety/tolerability	41 patients -Eflapegrastim: 5 mcg/kg: 6 15 mcg/kg: 6 45 mcg/kg: 6 135 mcg/kg: 6 350 mcg/kg: 7 -Placebo:10	-1 site in Korea -Completed

[Source: FDA compilation from Sponsor's submission]

5.2. Review Strategy

The clinical review was primarily based on the two randomized clinical trials (SPI-GCF-301 and SPI-GCF-302) to support efficacy and safety of the proposed indication and included the following:

- Electronic submission of the clinical study reports and other relevant portions of the BLA (EDR link to submission: \\CDSESUB1\evsprod\BLA761148\0000)
- Efficacy and safety data were audited or reproduced using ADaM and STDM;
- The efficacy data of the phase 2 non-inferiority study, SPI-GCF-12-201, were reviewed (as supportive);
- The safety data of the phase 1 single-arm study, SPI-GCF-301-PK, were reviewed (as supportive);

- Data from other studies;
- Regulatory history;
- Applicant's responses to FDA information requests; and
- Relevant published literature.

Clinical data was provided in the Clinical Data Interchange Standards Consortium (CDISC) Foundational Standards SDTM (Study Data Tabulation Model) and ADaM (Analysis Data Model Implementation). Also submitted were the define files for the variables and the corresponding SAS programs for the primary ADaM data derivation to document the analysis results. The clinical and statistical reviewers were able to duplicate the analysis results based on the Applicant's submitted datasets.

The evaluation presented in Sections 6 and 7 of this review were performed jointly by clinical reviewer Dr. Hyon-Zu Lee and statistical reviewer Dr. Kate Li Dwyer. Analyses by Dr. Dwyer were performed using SAS 9.4 (SAS Institute, Inc.).

All tables and figures in this review are those of the reviewers unless noted otherwise. Studies SPI-GCF-301 and SPI-GCF-302 will also be referred to as studies 301 and 302, respectively, and eflapegrastim as SPI-2012 throughout the review.

6. Review of Relevant Individual Trials Used to Support Efficacy

6.1. Studies SPI-GCF-301 and SPI-GCF-302

6.1.1. Study Design

Trial Design

Trial IDs and Titles:
SPI-GCF-301: Randomized trial of SPI-2012 versus pegfilgrastim in the management of chemotherapy induced neutropenia in breast cancer patients receiving docetaxel and cyclophosphamide (TC) (ADVANCE).

SPI-GCF-302: Randomized, open-Label, active-control trial of SPI-2012 (eflapegrastim) versus pegfilgrastim in the management of chemotherapy-induced neutropenia in early-stage breast cancer patients receiving docetaxel and cyclophosphamide (TC) (RECOVER).

Review comment: According to the American Cancer Society (https://www.cancer.org/research/cancer-facts-statistics/all-cancer-facts-figures/cancer-facts-figures-2020.html), besides skin cancers, breast cancer is the most common cancer in American women. In 2020, it is estimated that about 276,480 new cases of invasive breast cancer will be

diagnosed in women. Breast cancer is the second leading cause of cancer death in women (lung cancer is the leading cause). In men, about 2,620 new cases of invasive breast cancer are expected to be diagnosed in 2020. Docetaxel and cyclophosphamide (TC) chemotherapy is considered a standard regimen for adjuvant therapy for node-negative or low-risk node-positive breast cancer. However, according to the NCCN guidelines, TC regimen is associated with high risk for febrile neutropenia (>20%) which necessitates the use of G-CSF. The approval of Neulasta was based on three double-blind studies in patients with breast cancer. Therefore, the proposed patient population and chemotherapy are adequate to evaluate the safety and efficacy of eflapegrastim.

Both studies (SPI-GCF-301 and SPI-GCF-302) were phase 3, randomized, open-label, active-controlled, multicenter trials to compare the efficacy and safety of eflapegrastim with pegfilgrastim in breast cancer patients treated with TC chemotherapy. Both studies had identical endpoints, statistical hypotheses and methods. The differences, however, were the planned numbers of patient enrollment (SPI-GCF-301: 400 patients, SPI-GCF-302: 218 patients) and statistical power. In both studies, patients were to be randomized (1:1) to receive SQ injections of eflapegrastim (13.2 mg/0.6 mL, equivalent to [redacted] (b) (4) or pegfilgrastim (6 mg/0.6 mL) in prefilled single-use syringes. For pegfilgrastim, only Neulasta (pegfilgrastim), manufactured by Amgen in the US (NDC 55513-190-01) was to be used; no other G-CSFs including biosimilars, could be used. Pegfilgrastim was to be supplied by Spectrum to all sites (US and ex-US) in 6 mg/0.6 mL prefilled single-use syringes.

Prior to the TC chemotherapy administration, patients could receive pre-medications per standard of care. TC chemotherapy was to be administered IV on Day 1 of each 21-day treatment cycle as follows:

- Docetaxel 75 mg/m^2 IV infusion per institute's standard of care
- Cyclophosphamide 600 mg/m^2 IV infusion per institute's standard of care

For these studies, a total of 4 cycles were to be evaluated.

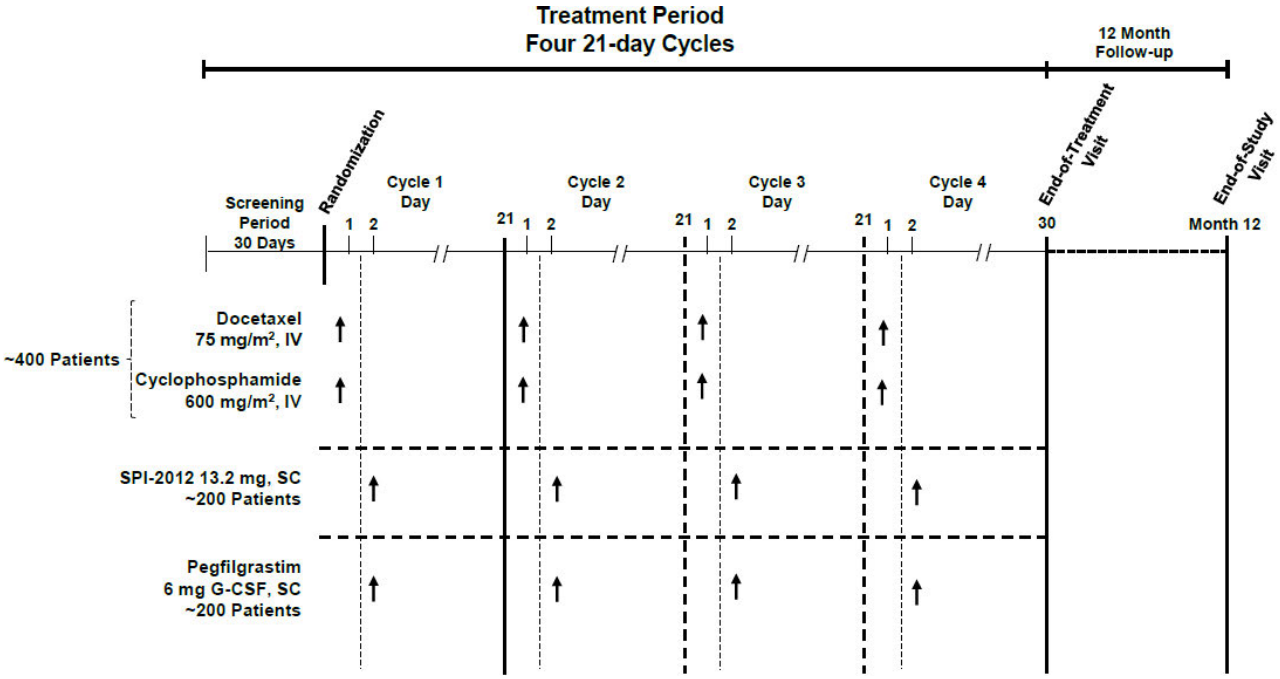
Review comment: The duration of chemotherapy for breast cancer usually depends on the stage of breast cancer. For early-stage it is typically 3-6 months. For advanced breast cancer, it may extend beyond 6 months. For other non-myeloid malignancies, it depends on the chemotherapy regimen. Duration of a total of 4 cycles is acceptable for assessment for the proposed indication.

To receive chemotherapy after Cycle 1, patients were to have ANC ≥1.5 × 10^9/L and platelet count ≥100 × 10^9/L. The study treatment (eflapegrastim or pegfilgrastim) was to be administered on Day 2 of each cycle, 24 to 26 hours after the last dose of TC chemotherapy. Dose modifications were not allowed.

Patients were to be monitored on Day 1 and Days 4 to 15 in Cycle 1. If the ANC was ≤1.0 × 10^9/L at any time during Cycle 1, then daily CBCs were to be required until ANC ≥1.5 × 10^9/L, after

reaching nadir. In Cycles 2 to 4, all patients were to have blood samples drawn on Day 1 (prior to chemotherapy administration), on Days 4, 7, 10, and 15 (±1 day for each collection), and at the End-of-Treatment Visit. If the ANC was ≤1.0 × 10^9/L at any time during Cycles 2 to 4, then daily CBCs were to be required until the ANC ≥1.5 × 10^9/L, after reaching nadir, but blood samples were still to be drawn on Days 4, 7, 10, and 15. As applicable, patients who have received at least one dose of study drug were to be followed for approximately 12 months after the last dose of study treatment for safety follow-up.

Figure 1 SPI-GCF-301 and SPI-GCF-302: Study Design



[Source: SPI-GCF-301 protocol]

Trial Objectives:

The primary objective was to compare the efficacy of eflapegrastim with pegfilgrastim in patients with early-stage breast cancer receiving docetaxel and cyclophosphamide (TC), as measured by the duration of severe neutropenia (DSN) in Cycle 1.

The key secondary objectives were to compare eflapegrastim with pegfilgrastim in:

- Time to ANC Recovery in Cycle 1
- Depth of ANC Nadir, defined as the patient's lowest ANC in Cycle 1
- Incidence of febrile neutropenia in patients during Cycle 1

Other secondary objectives included comparisons of the following:

- DSN in Cycles 2, 3, and 4
- Incidence of neutropenic complications, including anti-infective use and hospitalizations

in patients during Cycle 1
- Incidence of febrile neutropenia in Cycles 2, 3, and 4
- Relative Dose Intensity (RDI) of TC in Cycles 1 to 4
- Safety

Eligibility Criteria:

Key Inclusion Criteria:

1. A new diagnosis of histologically confirmed early-stage breast cancer (ESBC), defined as operable Stage I to Stage IIIA breast cancer.
2. Candidate to receive adjuvant or neoadjuvant TC chemotherapy.
3. Male or female ≥ 18 years of age.
4. Adequate hematological, renal and hepatic function as defined by:
    1. ANC $\geq 1.5 \times 10^9$/L
    2. Platelet count $\geq 100 \times 10^9$/L
    3. Hemoglobin >9 g/dL
    4. Calculated creatinine clearance > 50 mL/min
    5. Total bilirubin ≤1.5 mg/dL
    6. AST and ALT ≤2.5 × ULN, and ALP ≤2.0 × ULN
5. Eastern Cooperative Oncology Group (ECOG) performance status ≤2.
6. Willing to practice two forms of contraception, one of which must be a barrier method, from study entry through 30 days after the last dose of study drug administration or 30 days after date of patient early discontinuation.
7. Females of childbearing potential must have a negative urine pregnancy test within 30 days prior to randomization. Females who are postmenopausal for at least 1 year (defined as more than 12 months since last menses) or are surgically sterilized do not require this test.

Key Exclusion Criteria:

1. Active concurrent malignancy (except non melanoma skin cancer or carcinoma in situ of the cervix) or life-threatening disease. If there is a history of prior malignancies or contralateral breast cancer, the patient must be disease free for at least 5 years.
2. Known sensitivity or previous reaction to Escherichia coli (E. coli) derived products (e.g., filgrastim, recombinant insulin [Humulin®], L-asparaginase, somatropin [Humatrop®] growth hormone, recombinant interferon alfa-2b [Intron® A]), or any of the products to be administered during study participation.
3. Concurrent adjuvant cancer therapy (chemotherapy, radiation therapy, immunotherapy, biologic therapy other than the trial specified therapies).
4. Has locally recurrent/metastatic breast cancer.
5. Previous exposure to filgrastim, pegfilgrastim, or other G-CSF products in clinical development within 12 months prior to the administration of study drug (eflapegrastim or pegfilgrastim).

6. Active infection or on anti-infectives, an underlying medical condition or another serious illness that would impair the ability of the patient to receive protocol-specified treatment.
7. Has used any investigational drugs, biologics, or devices within 30 days prior to study treatment or plans to use any of these during the course of the study.
8. Has had prior bone marrow or hematopoietic stem cell transplant.
9. Has had prior radiation therapy within 30 days prior to enrollment.
10. Has had major surgery within 30 days prior to enrollment. Patients who have breast surgery related to the breast cancer diagnosis or have had a port-a-cath placement may be enrolled prior to 30 days once they have fully recovered from the procedure.
11. Patient is pregnant or breast-feeding.

Schedule of Events:

Table 6 SPI-GCF-301 and SPI-GCF-302: Schedule of Assessments and Procedure - Cycle 1

Procedure	Screening (≤30 days)	Cycle 1						Go To Schedule of Assessments and Procedures - Cycles 2 to 4 [a]
		Baseline Day 1 Pre-dose	Day 1 Dose	Day 1 Post-Dose	Day 2	Days 4-15	Days 16-21	
Informed Consent	x							
Medical History and Demographics	x							
Physical Exam	x	x						
Weight	x	x						
Height	x							
ECOG Performance Status	x	x						
Vital Signs	x	x		x	x [b]			
Body Temperature [c]		x			x	x	x	
CBC w/5-part Differential [d]	x [e]	x				x		
Chemistry	x [e]	x						
Urine (β-hCG) Pregnancy Testing	x							
Hormone Receptor Status (ER, PR, HER2) and Stage	x							
Assess Number of Nodes	x							
Immunogenicity Sample Collection		x						
Concomitant Medications		x			x	x	x	
Adverse Event Assessment	x [f]	x		x	x	x	x	
Docetaxel/Cyclophosphamide (TC) Chemotherapy			x					
SPI-2012/Pegfilgrastim Administration [g]					x			
PK Samples [h]					x	x		

b) Vital signs were to be recorded prior to treatment as well as approximately 30 and 60 minutes after drug administration on Day 2 of each cycle.
c) Temperature was to be checked twice daily throughout the study. All randomized patients were to receive a thermometer provided by Spectrum. If a patient has a fever, defined as an oral temperature >38.0°C (100.4°F), a CBC was to be obtained within 1 calendar day.
d) A CBC with 5-part differential were to be performed in each cycle on Day 1 before chemotherapy administration on Days 4 to 15 in Cycle 1. If the patient continued to be neutropenic, the investigator was to consult with the Sponsor to determine whether study treatment should be discontinued. If the participating site was notified that the ANC is $\leq 1.0\times10^9$/L on Day 15, then daily CBCs were to be required until their ANC is $\geq 1.5\times10^9$/L post-nadir.
e) If blood samples were drawn within 3 days before Cycle 1, Day 1, the collection did not need to be repeated on Day 1.

f) Prior to the first TC administration on Cycle 1, Day 1, only SAEs related to a study procedure were to be recorded.
g) Study drug (eflapegrastim or pegfilgrastim) was to be administered approximately 24 to 26 hours after chemotherapy administration in each cycle.
[Source: Protocol]

Table 7 SPI-GCF-301 and SPI-GCF-302: Schedule of Assessments and Procedure – Cycles 2 to 4

Procedure	Cycle 2 through Cycle 4						End-of-Treatment Visit [a]	Safety Follow-up [b]				
	Day 1 Pre-Dose	Day 1 Dose	Day 1 Post-Dose	Day 2	Days 4-15	Days 16-20	Cycle 4 Only Day 35 (±5)	3 Months	6 Months	9 Months	12 Months [c]	End of Study Visit [c]
Physical Exam	x						x					
Weight	x						x					
ECOG Performance Status	x						x					
Vital Signs	x		x	x [d]			x					
Body temperature [e]	x			x	x	x	x					
CBC w/5-Part Differential [f]	x				x		x					
Chemistry	x						x					
Immunogenicity Sample Collection [g]	x						x		x		x	x
Concomitant Medications	x			x	x	x	x	x [g]	x [g]	x [g]	x [g]	x [g]
Adverse Event Assessment	x		x	x	x	x	x	x	x	x	x	x
Docetaxel/ Cyclophosphamide (TC) Chemotherapy		x										
SPI-2012/Pegfilgrastim Administration [h]				x								
PK Samples [i]				x	x							

a) The End-of-Treatment Visit was to occur approximately 35 (±5) days after the last dose of study treatment in Cycle 4 or 35 (±5) days after the date of patient early discontinuation.
b) Time to telephone contact or visit was to be from the date of the last study treatment (eflapegrastim or pegfilgrastim), up to Cycle 4 or from the date of early discontinuation. Patients will be contacted by telephone and 3 and 9 months (±2 weeks) and will visit the clinic at 6 and 12 months (±2 weeks).
c) Patients who completed the 12 Month Safety Follow-up Period did not require a separate End-of-Study Visit.
d) Vital signs were to be recorded prior to treatment as well as approximately 30 and 60 minutes after drug administration on Day 2 of each cycle.
e) Temperature was to be checked twice daily. All randomized patients were to receive a thermometer provided by Spectrum. If a patient had a fever, defined as an oral temperature >38.0°C (100.4°F), a CBC was to be obtained within 1 calendar day.
f) In Cycles 2 to 4, all patients were to have blood samples drawn on Day 1 (prior to chemotherapy administration), on Days 4, 7, 10, and 15 (±1 day for each collection), and at the End-of-Treatment Visit. If the participating site was notified that the ANC is $\leq 1.0\times10^9$/L at any time during Cycles 2 to 4, then daily CBCs were to be required until ANC $\geq 1.5\times10^9$/L, after reaching nadir, but blood samples were to still be drawn on Days 4, 7, 10, and 15. If the patient continued to have ANC values <1.5×109/L, the investigator was to consult with the Sponsor to determine whether study treatment should be discontinued.
g) Concomitant medications only included additional myeloid growth factors, including filgrastim, pegfilgrastim or biosimilars, and additional cancer therapy. Patients who received additional myeloid growth factors or subsequent breast cancer chemotherapy were to be discontinued from the study.
h) Study drug (eflapegrastim or pegfilgrastim) was to be administered approximately 24 to 26 hours after chemotherapy administration in each cycle.
[Source: Protocol]

Patients were to be withdrawn from the study with delay of TC administration for >42 days

since last study drug administration.

During the study treatment period and the subsequent 12-Month Safety Follow-up Period, additional, concomitant treatment with myeloid growth factors, including filgrastim, pegfilgrastim or its biosimilars, and other anti-cancer therapy were prohibited with the exception of hormonal therapy and HER-2 targeted therapy for the patients who need such a targeted therapy. Premedications used for supportive care were allowed as per institutional standards. Corticosteroids as premedication for docetaxel were allowed during study treatment. Other uses of systemic steroids were to be approved by the Medical Monitor.

Other anti-cancer therapy including chemotherapy, radiation therapy, immunotherapy, or experimental medications were not permitted during the study, except that radiation therapy was allowed during the 12-Month Safety Follow-up Period. Any patients with disease progression that required antitumor therapy, other than TC, had to discontinue from the trial. No other myeloid growth factors other than study drugs (eflapegrastim or pegfilgrastim) were to be administered to patients at any time during the treatment phase or follow-up. No white blood cell or whole blood transfusions were allowed.

Study Endpoints

Primary efficacy endpoint:
The primary efficacy endpoint was the comparison of the DSN in Cycle 1 between the eflapegrastim arm and the pegfilgrastim arm (using the ITT Population).

Review comment: According to study by Crawford et al., in patients with breast, lung, colorectal, lymphoma, and ovarian cancers initiating a new chemotherapy regimen, the incidence of febrile neutropenia was 11% in the first 3 cycles of treatment with most of these events (59%) occurring in the first cycle. This first-cycle pattern was consistently observed despite variations in event rates by tumor type, disease stage, chemotherapy regimen and dose, and patient characteristics. Therefore, the proposed primary endpoint to assess DSN is Cycle 1 is adequate.

DSN in Cycle 1 was defined as the number of days of severe neutropenia (ANC $<0.5\times10^9$/L) from the first occurrence of an ANC below the threshold. The assessment of ANC was to be performed on Day 1 and Days 4-15 in Cycle 1. For patients who do not meet severe neutropenia criteria, the endpoint measurement was to be defined as DSN=0.

Secondary Endpoints:
The key secondary endpoints were the following:

1. Time to ANC Recovery in Cycle 1, defined as the time from chemotherapy administration until the patient's ANC increases to $\geq1.5\times10^9$/L after the expected nadir. For patients with ANC value $\geq1.5\times10^9$/L at all times, Time to ANC Recovery was to be assigned to a value of 0.

2. Depth of ANC Nadir, defined as the patient's lowest ANC in Cycle 1
3. Incidence of febrile neutropenia in patients during Cycle 1, in which febrile neutropenia was defined as an oral temperature >38.3°C (101.0°F) or two consecutive readings of >38.0°C (100.4°F) for 2 hours and ANC $<1.0\times10^9$/L

Additional secondary endpoints were the following:

1. DSN in Cycles 2, 3, and 4
2. Incidence of neutropenic complications, including use of anti-infectives and hospitalizations, in patients during Cycle 1
3. Incidence of febrile neutropenia in Cycles 2, 3, and 4
4. RDI of TC in Cycles 1 to 4
5. Safety

Statistical Analysis Plan

Randomization Scheme:

Patients who met all eligibility criteria, and after review and approval by the Sponsor's Medical Monitor, were randomized 1:1 using an interactive web response system (IWRS) to receive either eflapegrastim or pegfilgrastim.

For study SPI-GCF-301, randomization was only stratified by study site. For study SPI-GCF-302, the randomization scheme using a permuted block design was determined by IWRS, and a block size of 4 patients was used in each country of enrollment. This randomization was not controlled by either study sites, patients, or the Sponsor team.

Statistical Hypothesis:

Let Y be the Test group (eflapegrastim), X be the Control group (pegfilgrastim), μ be the mean DSN in Cycle 1.

$$H_0: \mu_X = \mu_Y \text{ versus } H_A: \mu_X \neq \mu_Y$$

The non-inferiority of eflapegrastim to pegfilgrastim would be declared if the upper bound of 95% CI of the difference in mean DSN between the test groups (i.e., eflapegrastim minus pegfilgrastim) was less than the non-inferiority margin of 0.62 day.

Reviewer's Comment:

- *The control treatment pegfilgrastim (Neulasta) was approved based on the comparison with filgrastim (Neupogen) using the non-inferiority margin of 1 day in mean DSN. The Applicant originally proposed using the same margin of 1 day. However, Agency recommended that a 0.6 day non-inferiority margin should be used in order to maintain the results of the randomized trials comparing DSN of pegfilgrastim (Neulasta) to Neupogen which led to the approval of Neulasta. Thereafter, the Applicant adopted the non-inferiority margin of 0.62 day.*

Sample Size Determination:

Sample size estimates for both studies were based on a non-inferiority design comparing eflapegrastim-treated patients to pegfilgrastim-treated patients. The primary endpoint of DSN in Cycle 1 was used to assess non-inferiority. The non-inferiority margin used in both studies is 0.62 days. The non-inferiority of eflapegrastim to pegfilgrastim would be declared if the upper bound of 95% CI of the difference in mean DSN between the treatment arms is <0.62 days.

For study SPI-GCF-301, the pooled standard deviation (SD) of the DSN was assumed to be 2.0 days and the true difference between the two treatments' means of the DSN was assumed to be 0.0 days, a sample size of 400 (200 per treatment arm) would provide 87% power to detect non-inferiority using a one-sided, two-sample t-test at 2.5% level of significance.

For study SPI-GCF-302, the pooled standard deviation of the DSN was assumed to be 1.5 days and the true difference between the two treatments' means of the DSN was assumed to be 0.0 days, a sample size of 218 (109 per treatment arm) would provide 86% power to detect non-inferiority using a one-sided, two-sample t-test at 2.5% level of significance.

Reviewer's Comment:

- *Study SPI-GCF-302 was designed one year later after study SPI-GCF-301. A different assumption of the pooled SD of the DSN was used to calculate the sample size for Study SPI-GCF-302. Per Applicant, the pooled SD was monitored in the ongoing sister study SPI-GCF-301. If the pooled SD in the sister study was estimated to be greater than 1.4 days, the sample size may have been increased to reflect the potential extra variability for study.*

Analysis Population:

Intent-to-Treat (ITT) Population included all patients who are randomized. Patients were analyzed in the treatment arm as randomized if the actual treatment assignments deviated from the randomization schema.

Per Protocol (PP) Population included all patients in the ITT Population with no important protocol deviations that affected the analysis of the primary efficacy endpoint. Patients were analyzed as treated if the actual treatment assignments deviated from the randomization scheme.

Patients with the following important protocol deviations were excluded from the PP Population and the analysis:

1. Failure to meet inclusion/exclusion criteria
2. Any dose modifications of the study drug (eflapegrastim or pegfilgrastim) during Cycle 1
3. Relative dose intensity (RDI) of TC chemotherapy <80% or >120% in Cycle 1
4. Prohibited concomitant medication (prednisone or steroid) used in Cycle 1

5. Any additional myeloid growth factors other than the protocol-specified study drug (eflapegrastim or pegfilgrastim) given during Cycle 1
6. Study drug (eflapegrastim or pegfilgrastim) administered less than 12 hours or more than 48 hours after the end of TC chemotherapy administration in Cycle 1

Primary efficacy analysis was based on the ITT Population. Analysis based on the PP Population was performed as a sensitivity analysis.

Handling of Missing Data:

Missing data were not imputed except for the calculation of DSN. For all days in Cycle 1, if a patient had a missing ANC value(s) and the two adjacent ANC values (i.e., the last available value before the missing value and the first available value after the missing value) were both $\geq 0.5\times10^9$/L, the missing ANC value(s) was considered as $\geq 0.5\times10^9$/L and the day(s) with the missing value(s) was not counted to calculate DSN.

If either of the two adjacent ANC values were $<0.5\times10^9$/L, the missing ANC value(s) was considered as $<0.5\times10^9$/L and the day(s) with the missing value(s) was counted in the calculation of DSN. If an ANC value was missing in Cycle 1 but the corresponding WBC value was present and was $\leq 0.5\times10^9$/L, the ANC value was imputed as the WBC value for that timepoint.

The missing ANC values in Cycles 2 to 4 were handled differently from that in Cycle 1 as blood samples were only to be evaluated on nominal Days 4, 7, 10, and 15 in Cycle 2 to 4. The missing data were handled as below:

- If there were multiple ANC values on a nominal visit day, the latest value was used.
- If a patient had a missing ANC value and the two adjacent ANC values (i.e., the last available value before the missing value and the first available value after the missing value) were both $\geq 0.5\times10^9$/L, the missing ANC value(s) was considered as $\geq 0.5\times10^9$/L and the day(s) with the missing value(s) were not counted to calculate DSN.
- If the two adjacent ANC values were both $<0.5\times10^9$/L, the missing ANC values were considered as $<0.5\times10^9$/L to calculate DSN.
- If either of the two adjacent ANC values was $<0.5\times10^9$/L, only the timepoint with ANC value $<0.5\times10^9$/L was used to calculate DSN
- If a patient in either treatment arm had no blood draws (missing ANC values) because of the discontinuation from Days 4 to 15, or for any part of this duration, the DSN was imputed as 0 days for that patient.

A sensitivity analysis using a worst case scenario was performed to examine the impact of missing data. When ANC data were missing on or after Day 5, and before patients' ANC increase to $\geq 1.5\times10^9$/L after the expected nadir in Cycle 1, missing ANC values were imputed as $<0.5\times10^9$/L for eflapegrastim and $\geq 0.5\times10^9$/L for pegfilgrastim to maximize the impact of missing data, to calculate DSN in this sensitivity analysis.

Efficacy Analyses:

Primary Endpoint - Duration of Severe Neutropenia in Cycle 1

The primary efficacy endpoint of the study was DSN in Cycle 1, defined as the number of days in which the patient had an ANC $<0.5\times10^9$/L in Cycle 1, after administration of study drug (eflapegrastim or pegfilgrastim). The ANC measurements were performed on Day 1 and on Days 4 to 15 in Cycle 1. DSN was calculated for all patients in the ITT Population. Patients who did not present with severe neutropenia were given a DSN value of 0. If a patient had multiple ANC values within the same day, the last ANC value recorded was used for that day.

For the primary efficacy analysis, the mean DSN in Cycle 1 was compared between the Eflapegrastim Arm and the Pegfilgrastim Arm using a bootstrap resampling method with a non-inferiority hypothesis in the ITT population. A 2-sided 95% confidence interval (CI) of the difference between the mean DSN for the Eflapegrastim Arm and the mean DSN for the Pegfilgrastim Arm (i.e., eflapegrastim minus pegfilgrastim) was calculated based upon 10,000 bootstrap samples with treatment as the only stratification factor. For each sample, the difference between treatment arms was calculated. The percentile confidence interval was obtained from the resampling. The study was to use non-inferiority margin of 0.62 days for the above comparison. The non-inferiority of eflapegrastim to pegfilgrastim was to be declared if the upper bound of 95% CI of the difference in mean DSN between the treatment arms (i.e., Eflapegrastim minus Pegfilgrastim) was <0.62 days. An analysis based on the PP Population was to be performed as a sensitivity analysis.

Additional Sensitivity Analyses

1. The test of the difference in mean DSN between treatment arms was conducted using Poisson distribution and negative binomial regression.
   For the Poisson and negative binomial regression, the corresponding identical link function was used, and treatment was the only covariate in the model. The difference in mean DSN between the eflapegrastim and pegfilgrastim Arms was calculated along with 2-sided 95% CI, based on Poisson or negative binomial regression.
2. Study site was used as an additional stratification factor in the resampling.
3. Disease status was used as an additional stratification factor in the resampling.
4. Worst-case scenario was used to examine the impact of missing data.
   When ANC data were missing on or after Day 5, and before that patients' ANC increased to $\geq1.5\times10^9$/L after the expected nadir in Cycle 1, missing ANC values were imputed as $<0.5\times10^9$/L for eflapegrastim and $\geq 0.5\times10^9$/L for pegfilgrastim, for the purpose of DSN calculation.

Subgroup Analyses

The following subgroups were examined for DSN in Cycle 1:

- Age (<65 years, ≥65 years)
- Gender (Male, Female)
- Race (White, non-White)
- Disease Status (Adjuvant, Neoadjuvant) at randomization
- Geographic region (US, non-US)
- Weight (<65 kg, 65 to 75 kg, or >75 kg)

Key Secondary Endpoints

Time to ANC Recovery in Cycle 1

Time to ANC Recovery was defined as the time from chemotherapy administration until the patient's ANC increased to $\geq 1.5\times10^9$/L after the expected nadir. For patients with ANC value $\geq 1.5\times10^9$/L at all times, Time to ANC Recovery was assigned to a value of 0.

The mean Time to ANC Recovery in Cycle 1 with two-sided 95% CI was estimated for each treatment arm using negative binomial regression. The corresponding identical link function was used, and treatment was the only covariate in the model. The difference in the mean of the time to ANC Recovery in Cycle 1 between eflapegrastim and pegfilgrastim was calculated based on negative binomial regression, along with 2-sided 95% CI.

In addition to the above analysis, alternate analysis of the time to ANC recovery was also performed. In this analysis, time to ANC recovery was defined as the time from ANC nadir to ANC increased to $\geq 1.5\times10^9$/L after the expected nadir in the subgroup of patients who experienced severe neutropenia ($<0.5\times10^9$/L). Since this was a small subgroup in both treatment arms, only summary statistics were provided.

Depth of ANC Nadir in Cycle 1

Depth of ANC Nadir was defined as the lowest ANC value after administration of study drug (eflapegrastim or pegfilgrastim) for each cycle.

To assess treatment differences, $\log_{10}$ transformation was used on the nadirs to satisfy the normality assumption, due to the skewness of the data. The ANC nadir ratio between the treatment arms, associated 2-sided 95% CI, assuming asymptotic normality on the log transformed data, was provided.

Incidence of Febrile Neutropenia (FN) in Cycle 1

FN was defined as an oral temperature >38.3°C (101.0°F) or two consecutive readings of >38.0°C (100.4°F) for 2 hours and ANC $<1.0\times10^9$/L.

Incidence of FN after administration of study drug (eflapegrastim or pegfilgrastim) in Cycle 1 was summarized by treatment arm. Patients who experienced more than one event were counted only once in each cycle. An exact 2-sided 95% CI was provided.

Testing Procedure for Key Secondary Efficacy Endpoints

A hierarchical closed testing procedure was used to test the key secondary endpoints where the endpoints were ranked with the primary endpoint first and then the Key Secondary Endpoints in the order listed below:

1. DSN in Cycle 1
2. Time to ANC Recovery in Cycle 1
3. Depth of ANC Nadir in Cycle 1
4. Incidences of FN in Cycle 1

For the secondary efficacy analyses, the results were each summarized by Treatment Arm and Cycle in the ITT population. Two-sided 95% CI for the difference between the two treatment arms were calculated. Per Applicant, no adjustment to alpha was needed once the preceding endpoint comparison was significant for the subsequent endpoints in the above order, with each tested at the same significance level of α=0.05.

Reviewer's Comment:
Although a hierarchical closed testing procedure was planned for the key secondary efficacy endpoints, no clear statistical hypotheses were pre-specified and stated in the statistical analysis plan. Because the studies were not powered to test non-inferiority for any of the key secondary endpoints, failing on the superiority tests would not lead to any labeling claim.

Additional Secondary Endpoints

DSN in Cycles 2, 3, and 4

These endpoints were defined and analyzed similarly to the primary endpoint of DSN in Cycle 1. Two-sided 95% CI comparing eflapegrastim to pegfilgrastim based on bootstrap resampling method was provided. The analyses were performed based on the ITT Population.

Incidence of neutropenic complications, including use of anti-infectives and hospitalizations, in patients during Cycle 1

Incidence of neutropenic complications after administration of study drug (eflapegrastim or pegfilgrastim) in Cycle 1 was summarized by treatment arm. Patients who experience more than one event were counted only once for each cycle. An exact 2-sided 95% CI was provided based on the ITT Population.

Protocol Amendments

The clinical trial landmarks and protocol amendments are summarized below.

Table 8 SPI-GCF-301 and SPI-GCF-302: Landmarks and Key Protocol Amendments

Date	Landmarks
November 4, 2015	SPI-GCF-301: Original protocol
January 19, 2016	SPI-GCF-301: Study initiation (first patient, first visit)
September 27, 2016	SPI-GCF-302: Original protocol
January 26, 2017	SPI-GCF-301: Amendment 1 -Revised the exclusion criteria that patients with previous exposure to filgrastim, pegfilgrastim, or other G-CSF products in clinical development within 12 months should be excluded.
May 10, 2017	SPI-GCF-302: Study initiation (first patient, first visit)
July 28, 2017	SPI-GCF-302: Amendment 1 - Revised to make the eligibility criteria and procedures for SPI-GCF-302 consistent with the other Phase 3 trial, SPI-GCF-301.
October 31, 2018	SPI-GCF-301: Study completion (last patient, last visit)
May 6, 2019	SPI-GCF-302: Study completion (last patient, last visit)

[Source: FDA compilation]

Statistical Analysis Plan (SAP) Amendments

The original SAP dated 22 Nov 2016 was amended three times.

SAP Version 1.1 (26 Jan 2017):

- Analysis of the key secondary endpoint, "Time to ANC Recovery in Cycle 1" was added as following. "The analysis will be performed based on the ITT Population. For patients with ANC value $\geq 1.5\times10^9$/L at all times in Cycle 1, Time to ANC Recovery will be assigned to a value of 0. The analysis of this endpoint will be based on negative binomial regression with the corresponding identical link function, and treatment was the only covariate."
- Two sensitivity analyses for primary endpoint were added: sensitivity analysis adjusting for disease status at randomization (adjuvant or neoadjuvant) and sensitivity analyses using worst case scenario.
- Subgroup analyses for primary endpoint were added: gender, race and disease status at randomization.
- Superiority test for the primary endpoint was removed from the SAP, according to the protocol.

SAP Version 1.2 (17 Apr 2017):

The primary purpose of this amendment was to change the number of patients from 580 patients to 400 patients:

- Sample size was changed, and the level of significance was updated since superiority was removed as a statistical test.
- Simulation results are presented in Table 2 with revised sample size.

SAP Version 1.3 (31 Jul 2018):
The primary purpose of SAP Amendment 3 was to provide clarity and details for the handling of missing data for ANC and efficacy analyses listed below:

- The contents of the SAP were reordered to reflect the updates of SOP of Spectrum Pharmaceuticals, Inc.
- Clarification of missing data handling.
- Updated the method of sensitivity analysis using worst case scenario.

6.1.2. Study Results

Compliance with Good Clinical Practices

Both studies SPI-GCF-301 and SPI-GCF-302 were reviewed and approved by the Independent Ethics Committees or Institutional Review Boards and conducted in accordance with Good Clinical Practice (GCP) and the Declaration of Helsinki. Written informed consent was obtained from each subject prior to performance of study-specific procedures.

Financial Disclosure

The BLA submission contained FDA financial certification form 3454 signed by Kurt Gustafson, the Executive Vice President and CFO of Spectrum Pharmaceuticals, dated October 23, 2019. The Applicant certified to the following statement:

"As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f)."

The submission contained a list of clinical investigators that participated in the SPI-GCF-301 (approximately 650 principal/sub-investigators) and SPI-GCF-302 (approximately 450 principal/sub-investigators) trials.

One sub-investigator (b) (6) who participated in studies SPI-GCF-301 and SPI-GCF-302 at sites (b) (6) was reported to have disclosed equity interest, as defined by 21 CFR 54.2(b). This sub-investigator disclosed the purchase of 25,000 shares of Spectrum's stock at $7.43 per share (total $185,750) in (b) (6) Sites (b) (6) enrolled (b) (6) patients (SPI-GCF- (b) (6) patients, SPI-GCF (b) (6) (b) (6)) and 10 patients (all (b) (6) in study SPI-GCF-301), respectively. The percentages of patient enrollment at these affected sites were (b) (6) and (b) (6), respectively. Since relatively small percentages of patients were enrolled at the affected sites, it is not likely that this financial conflict of interest affected the overall efficacy and safety results.

None of the clinical investigators were full or part-time employees of the Sponsor for the covered clinical studies.

Patient Disposition

SPI-GCF-301:
Study 301 randomized a total of 406 patients (eflapegrastim: 196, pegfilgrastim: 210) from 82 sites in 3 countries. Most of the patients (99%) were enrolled from North America (See Table 10). The PP population was comprised of patients in the ITT population who had no major protocol deviation in Cycle 1 (eflapegrastim: 187, pegfilgrastim: 196).

SPI-GCF-302:
A total of 237 patients (eflapegrastim: 118, pegfilgrastim: 119) were randomized from 74 sites in 6 countries (mostly North American or European [87%]). The PP population was comprised of a total of 221 patients (eflapegrastim: 100, pegfilgrastim: 111).

Table 9 SPI-GCF-301 and SPI-GCF-302: Analysis Populations

	SPI-GCF-301			SPI-GCF-302		
	eflapegrastim	pegfilgrastim	Total	eflapegrastim	pegfilgrastim	Total
ITT population	196	210	406	118	119	237
PP population	187	196	383	100	111	221
Safety population	197*	208*	405*	117**	118**	235**

*One patient (b) (6) was randomized to the pegfilgrastim arm, but did not receive any study treatment or TC therapy: this patient is included in ITT population but not in the safety population. Another patient (b) (6) was randomized to the pegfilgrastim arm but was inadvertently administered eflapegrastim on Cycle 1, Day 2 and is included in the pegfilgrastim arm for the ITT population; however, this patient is included in the eflapegrastim Arm for the safety population.
**There were a total of 2 patients (b) (6) randomized to the eflapegrastim arm and pegfilgrastim arm, respectively, who did not receive any treatment with study drug or TC therapy. Both patients are included in the ITT population, but not in the safety population.
[Source: ADSL.xpt]

Table 10 SPI-GCF-301 and SPI-GCF-302: Patient Enrollment by Country (ITT Population)

	SPI-GCF-301			SPI-GCF-302		
	SPI-2012 (n=196)	Pegfilgrastim (n=210)	Total (n=406)	SPI-2012 (n=118)	Pegfilgrastim (n=119)	Total (n=237)
USA	189 (96%)	204 (97%)	393 (97%)	63 (53%)	68 (57%)	131 (55%)
Canada	4 (2%)	3 (1%)	7 (2%)	5 (4%)	0	5 (2%)
Korea	3 (2%)	3 (1%)	6 (1%)	11 (9%)	11 (9%)	22 (9%)
Hungary	-	-	-	23 (19%)	24 (20%)	47 (20%)
Poland	-	-	-	12 (10%)	12 (10%)	24 (10%)
India	-	-	-	4 (3%)	4 (3%)	8 (3%)

[Source: ADSL.xpt]

In both studies, the proportion of patients who discontinued study treatment was similar in the two arms (301: 15% [eflapegrastim: 14%, pegfilgrastim: 15%], 302: 13% [eflapegrastim:12%, pegfilgrastim: 14%]). Primary reasons for discontinuing study treatment in both studies were mostly due to consent withdrawal by patient (301: 6%, 302: 4%) and adverse event (301: 5%, 302: 5%).

Table 11 SPI-GCF-301 and SPI-GCF-302: Patient Disposition (ITT Population)

	SPI-GCF-301			SPI-GCF-302		
	SPI-2012 (n=196)	Pegfilgrastim (n=210)	Total (n=406)	SPI-2012 (n=118)	Pegfilgrastim (n=119)	Total (n=237)
Completed Treatment Cycles						
Cycle 1	194 (99%)	208 (99%)	402 (99%)	115 (97%)	118 (99%)	233 (98%)
Cycle 2	181 (92%)	190 (90%)	371 (91%)	111 (94%)	111 (93%)	222 (94%)
Cycle 3	176 (90%)	182 (87%)	358 (88%)	105 (89%)	106 (89%)	211 (89%)
Cycle 4	168 (86%)	179 (86%)	347 (85%)	104 (88%)	102 (86%)	206 (87%)
Discontinued from treatment	28 (14%)	31 (15%)	59 (15%)	14 (12%)	17 (14%)	31 (13%)
Primary reason for discontinuation						
Patient withdrew consent	12 (6%)	11 (5%)	23 (6%)	5 (4%)	5 (4%)	10 (4%)
Adverse event	9 (5%)	10 (5%)	19 (5%)	4 (3%)	9 (8%)	13 (5%)
Investigator decision	2 (1%)	6 (3%)	8 (2%)	1 (<1%)	1 (<1%)	2 (<1%)
Study drug discontinuation	3 (2%)	0	3 (<1%)	2 (2%)	0	2 (<1%)
Delay of TC administration for >42 Days since last study drug	0	1 (<1%)	1 (<1%)	0	0	0

administration						
Sponsor Decision	0	1 (<1%)	1 (<1%)	0	1 (<1%)	1 (<1%)
Death	0	1 (<1%)	1 (<1%)	0	0	0
Other	2 (1%)*	1 (<1%)*	3 (<1%)*	2 (2%)**	1 (<1%)**	3 (1%)**

* Eflapegrastim arm: One patient received filgrastim in Cycle 3 and another patient had treatment noncompliance. Pegfilgrastim arm: Reason was not provided.
**SPI-2012 arm: One patient did not want to continue in the study and one patient did not attend due to a death in the family. Pegfilgrastim arm: Reason was not provided.
[Source: ADSL.xpt]

In study 301, similar proportion of patients in both arm (eflapegrastim: 72%, pegfilgrastim: 69%) completed the 12-month follow-up period while in study 302, a higher proportion of patients in the eflapegrastim arm compared to pegfilgrastim arm (eflapegrastim: 81%, pegfilgrastim: 71%) completed the 12-month follow-up period. Reasons for study withdrawal were mostly due to withdrawal by patient (301: 11%, 302: 8%) and initiation of non-protocol therapy for breast cancer (301: 4%, 302: 8%).

Table 12 SPI-GCF-301 and SPI-GCF-302: Patient Disposition Through the 12-Month Follow-up (ITT Population)

	SPI-GCF-301			SPI-GCF-302		
	SPI-2012 (n=196)	Pegfilgrastim (n=210)	Total (n=406)	SPI-2012 (n=118)	Pegfilgrastim (n=119)	Total (n=237)
Patients who completed the study	142 (72%)	145 (69%)	287 (71%)	96 (81%)	85 (71%)	181 (76%)
Withdrew from the study	54 (28%)	65 (31%)	119 (29%)	22 (19%)	34 (29%)	56 (24%)
Primary reason for study withdrawal						
Withdrawal by patient	25 (13%)	19 (9%)	44 (11%)	9 (8%)	9 (8%)	18 (8%)
Initiation of non-protocol therapy for breast cancer	6 (3%)	12 (6%)	18 (4%)	5 (4%)	14 (12%)	19 (8%)
Lost to follow up	6 (3%)	10 (5%)	16 (4%)	3 (3%)	2 (2%)	5 (2%)
Treatment with additional myeloid growth factors during follow-Up	6 (3%)	10 (5%)	16 (4%)	0	1 (<1%)	1 (<1%)

Investigator decision	2 (1%)	4 (2%)	6 (1%)	3 (3%)	3 (3%)	6 (3%)
Sponsor Decision	1 (<1%)	1 (<1%)	2 (<1%)	0	2 (2%)	2 (1%)
Death	0	2 (1%)	2 (<1%)	0	1 (<1%)	1 (<1%)
Other	8 (4%)*	7 (3%)*	15 (4%)*	2 (2%)**	2 (2%)**	4 (2%)**

* Other reasons included: four patients relocated, three patients had adverse events, three patients had additional chemotherapy cycles, two patients started new trials, two patients were lost to follow-up, and one patient started new job,
** Other reasons included: One research site closed, one patient was transferred to hospice, one patient missed 12-month follow-up visit, and one patient was diagnosed with colon cancer.
[Source: ADSL.xpt]

Protocol Violations/Deviations

Overall, the proportion of patients that had protocol violations was quite high in both trials (301: 78% [eflapegrastim: 81%, pegfilgrastim: 76%], 302: 84% [eflapegrastim: 91%, pegfilgrastim: 78%). In studies 301 and 302, 67% and 75% of patients, respectively, had minor violations. With respect to protocol violations that were considered major, the incidences were similar in the two arms in both studies (301: 45% [eflapegrastim: 46%, pegfilgrastim: 44%], 302: 52% [eflapegrastim: 55%, pegfilgrastim: 49%). Most of the major protocol violations were related to laboratory procedures in both studies (301: 36%, 302: 44%).

The table below summarizes the protocol violations that were reported in studies 301 and 302.

Table 13 SPI-GCF-301 and SPI-GCF-302: Protocol Violations (ITT Population)

	SPI-GCF-301			SPI-GCF-302		
	SPI-2012 (n=196)	Pegfilgrastim (n=210)	Total (n=406)	SPI-2012 (n=118)	Pegfilgrastim (n=119)	Total (n=237)
All patients	158 (81%)	160 (76%)	318 (78%)	107 (91%)	93 (78%)	200 (84%)
Minor violation	139 (71%)	132 (63%)	271 (67%)	101 (86%)	76 (64%)	177 (75%)
Major violation	90 (46%)	93 (44%)	183 (45%)	65 (55%)	58 (49%)	123 (52%)
Laboratory procedures	73 (37%)	74 (35%)	147 (36%)	56 (47%)	49 (41%)	105 (44%)
Prohibited/concomitant medications	11 (6%)	18 (9%)	29 (7%)	9 (8%)	10 (8%)	19 (8%)
Informed consent Procedures	14 (7%)	13 (6%)	27 (7%)	2 (2%)	4 (3%)	6 (3%)
Study medication /dosing	5 (3%)	8 (4%)	13 (3%)	6 (5%)	4 (3%)	10 (4%)
Inclusion/ exclusion criteria	2 (1%)[a]	2 (1%)[a]	4 (1%)	2 (2%)[b]	0	2 (1%)
Safety[c]	1 (<1%)	1 (<1%)	2 (<1%)	1 (<1%)	5 (4%)	6 (3%)
Others	2 (1%)	1 (<1%)	3 (<1%)	0	1 (<1%)	1 (<1%)

a. A total of 3 patients had locally recurrent/metastatic breast cancer and 1 patient completed radiation treatment 29 days before being randomized and completed C1D1 treatment.
b. One patient had prior radiation therapy within 30 days and 1 patient had active concurrent malignancy.
c. Included: "SAE was not submitted within 24 hours" and "Site reported SAE follow-up more than 24 hours after PI acknowledgement of follow-up".
A patient may appear in more than one category.
[Source: DV.xpt]

The proportions of patients that had important protocol violations (that were also major protocol violations) and excluded from the PP population were similar between the two arms and in the two studies (301: 5% [eflapegrastim: 4%, pegfilgrastim: 6%], 302: 5% [eflapegrastim: 3%, pegfilgrastim: 6%]). These important protocol violations did not affect the overall efficacy analysis of the primary endpoint (see Table 25 and Table 26, Analysis of Duration of Severe Neutropenia in Cycle 1 in the PP population for studies 301 and 302, respectively).

Table 14 SPI-GCF-301 and SPI-GCF-302: Important Protocol Violations (ITT Population)

	SPI-GCF-301			SPI-GCF-302		
	SPI-2012 (n=196)	Pegfilgrastim (n=210)	Total (n=406)	SPI-2012 (n=118)	Pegfilgrastim (n=119)	Total (n=237)
All patients	7 (4%)	13 (6%)	20 (5%)	4 (3%)	7 (6%)	11 (5%)
Prohibited med (steroids) was used in Cycle 1	2 (1%)	7 (3%)	9 (2%)	0	5 (4%)	5 (2%)
RDI of TC chemotherapy <80% or >120% in Cycle 1	3 (2%)	4 (2%)	7 (2%)	3 (3%)	2 (2%)	5 (2%)
Eligibility criteria	2 (1%)	2 (1%)	4 (1%)	2 (2%)	0	2 (<1%)
Dose modifications to study drug in Cycle 1	0	1 (<1%)	1 (<1%)	0	0	0
Prohibited concomitant medication (prednisone) was used	1 (1%)	0	1 (<1%)	0	0	0
Study drug administered <12 hours or >48 hours After the End of TC in Cycle 1	0	1 (<1%)	1 (<1%)	0	0	0

RDI=relative dose intensity; TC=docetaxel plus cyclophosphamide
[Source: DV.xpt]

Table of Demographic Characteristics

In both studies, patient demographics were largely balanced between the treatment arms. All patients except 2 patients in study 301 (>99%) and all patients in study 302 were females, the median age was 61 years (range 24-84) in study 301 and 59 years (range 29-88) in study 302. Approximately three quarters of patients were White in both studies.

Table 15 SPI-GCF-301 and SPI-GCF-302: Patient Demographics (ITT Population)

	SPI-GCF-301			SPI-GCF-302		
	SPI-2012 (n=196)	Pegfilgrastim (n=210)	Total (n=406)	SPI-2012 (n=118)	Pegfilgrastim (n=119)	Total (n=237)
Gender						
Female	195 (99%)	209 (>99%)	404 (>99%)	118 (100%)	119 (100%)	237 (100%)
Male	1 (1%)	1 (<1%)	2 (<1%)	0	0	0
Age (years)						
Median	61	60	61	58	59	59
Range	28, 83	24, 84	24, 84	29, 80	34, 88	29, 88
Age (by category, years)						
< 65	118 (60%)	129 (61%)	247 (61%)	74 (63%)	79 (66%)	153 (65%)
≥ 65	78 (40%)	81 (39%)	159 (39%)	44 (37%)	40 (34%)	84 (35%)
≥ 75	13 (7%)	15 (7%)	28 (7%)	5 (4%)	14 (12%)	19 (8%)
Race						
White	156 (80%)	159 (76%)	315 (78%)	85 (72%)	96 (81%)	181 (76%)
Black/African American	26 (13%)	32 (15%)	58 (14%)	11 (9%)	7 (6%)	18 (5%)
Asian	9 (5%)	9 (4%)	18 (4%)	20 (17%)	16 (13%)	36 (15%)
Other	5 (3%)	10 (5%)	15 (4%)	2 (2%)	0	2 (<1%)
Ethnicity						
Hispanic/ Latino	34 (17%)	40 (19%)	74 (18%)	18 (15%)	15 (13%)	33 (14%)
Not Hispanic or Latino	162 (83%)	170 (81%)	332 (82%)	100 (85%)	104 (87%)	204 (86%)
Weight (kg)						
Median	79	79	79	75	74	74
Range	42, 145	42, 150	42, 150	40, 171	46, 153	40, 171
ECOG score						
0	140 (71%)	147 (70%)	287 (71%)	99 (84%)	90 (76%)	189 (80%)
1	56 (29%)	59 (28%)	115 (28%)	19 (16%)	27 (23%)	46 (19%)

2	0	4 (2%)	4 (1%)	0	2 (2%)	2 (<1%)

[Source: ADSL.xpt]

The results of the pooled patient demographics of studies 301 and 302 were similar. The median age was 60 years (range 24-88), almost all patients were female (>99%) and 77% of patients were White.

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

Baseline disease characteristics were also generally balanced between the treatment arms in both studies. To be eligible for the studies patients had to have a new diagnosis of histologically confirmed early-stage breast cancer, defined as operable Stage I to Stage IIIA breast cancer. Most of the patients in studies 301 and 302 had Stage I or IIA breast cancer (301: 74%, 302: 66%). The median ANC at baseline was 5.9 x10^9/L (range 1 x10^9/L, 29 x10^9/L) and 4.9 x10^9/L (range 1 x10^9/L, 25 x10^9/L) in studies 301 and 302, respectively. The WHO classification was ductal invasive carcinoma in most patients (301: 88%, 302: 80%), and most patients (301: 83%, 302: 81%) were candidates to receive adjuvant TC chemotherapy. Approximately 91% and 90% of patients in studies 301 and 302, respectively, were HER2 negative.

Table 16 SPI-GCF-301 and SPI-GCF-302: Baseline Disease Characteristics (ITT Population)

	SPI-GCF-301			SPI-GCF-302		
	SPI-2012 (n=196)	Pegfilgrastim (n=210)	Total (n=406)	SPI-2012 (n=118)	Pegfilgrastim (n=119)	Total (n=237)
Baseline ANC (x10^9/L)						
Median	5.8	5.9	5.9	5.0	4.8	4.9
Range	2, 29	1, 23	1, 29	1, 25	2, 15	1, 25
Stage						
I	68 (35%)	74 (35%)	142 (35%)	36 (31%)	36 (30%)	72 (30%)
IIA	83 (42%)	77 (37%)	160 (39%)	40 (34%)	46 (39%)	86 (36%)
IIB	27 (14%)	38 (18%)	65 (16%)	28 (24%)	29 (24%)	57 (24%)
IIIA	18 (9%)	21 (10%)	39 (10%)	14 (12%)	8 (7%)	22 (9%)
Histology type						
Ductal invasive	174 (89%)	182 (87%)	356 (88%)	91 (77%)	98 (82%)	189 (80%)
Ductal other	6 (3%)	6 (3%)	12 (3%)	0	2 (2%)	2 (<1%)
Lobular invasive	9 (5%)	12 (6%)	21 (5%)	17 (14%)	6 (5%)	23 (10%)
Mixed	3 (2%)	6 (3%)	9 (2%)	1 (<1%)	3 (3%)	4 (2%)
Other	4 (2%)	4 (2%)	8 (2%)	9 (8%)	10 (8%)	19 (8%)
Type of TC						
Adjuvant	162 (83%)	174 (83%)	336 (83%)	99 (84%)	92 (77%)	191 (81%)
Neo-adjuvant	34 (17%)	36 (17%)	70 (17%)	19 (16%)	27 (23%)	46 (19%)
Hormone receptor status						
ER+/PR+/HER2-	106 (54%)	124 (59%)	230 (57%)	71 (60%)	67 (56%)	138 (58%)

ER-/PR-/HER2-	41 (21%)	41 (20%)	82 (20%)	19 (16%)	25 (21%)	44 (19%)
ER+/PR-/HER2-	29 (15%)	28 (13%)	57 (14%)	13 (11%)	13 (11%)	26 (11%)
ER+/PR+/HER2+	7 (4%)	7 (3%)	14 (3%)	8 (7%)	8 (7%)	16 (7%)
ER+/PR-/HER2+	10 (5%)	4 (2%)	14 (3%)	2 (2%)	1 (<1%)	3 (1%)
ER-/PR-/HER2+	3 (2%)	5 (2%)	8 (2%)	3 (3%)	3 (3%)	6 (3%)
ER-/PR+/HER2-	0	1 (<1%)	1 (<1%)	2 (2%)	2 (2%)	4 (2%)
ER-/PR+/HER2+	0	0	0	0	0	0

[Source: ADSL.xpt]

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Treatment Compliance:
In studies 301 and 302, treatment compliance to study treatment in Cycle 1 was high in both arms (301 [eflapegrastim: 99%, pegfilgrastim: 99%], 302 [eflapegrastim: 98%, pegfilgrastim: 100%]). Most patients received study treatment for all 4 cycles (301 [eflapegrastim: 85%, pegfilgrastim: 86%], 302 [eflapegrastim: 89%, pegfilgrastim: 86%]). Table 17 summarizes overall compliance with the study treatment.

In study 301, a total of 2 patients (1%) in the eflapegrastim arm and 1 patient (<1%) in the pegfilgrastim arm received TC but did not receive study treatment due to AEs associated with the TC treatment. In addition, there were 2 patients in the pegfilgrastim arm who received eflapegrastim instead of pegfilgrastim (one patient on Cycle 1, Day 2 [patient (b) (6) and one patient on Cycle 2, Day 2 [patient (b) (6)

In study 302, a total of 2 patients (2%) in the eflapegrastim arm received TC on Cycle 1, Day 1, but were not administered eflapegrastim on Day 2 due to reactions to docetaxel in Cycle 1. Throughout the study, a total of 3 (3%) patients in each arm received TC on Day 1 of a cycle and did not receive study drug on Day 2.

Table 17 SPI-GCF-301 and SPI-GCF-302: Treatment Compliance with Study Treatment (Safety Population)

	SPI-GCF-301		SPI-GCF-302	
	Eflapegrastim (n=197)	Pegfilgrastim (n=208)	Eflapegrastim (n=117)	Pegfilgrastim (n=118)
Cycle 1	194 (99%)	206 (99%)	115 (98%)	118 (100%)
Cycle 2	181 (92%)	188 (90%)	111 (95%)	111 (94%)
Cycle 3	176 (89%)	181 (87%)	105 (90%)	106 (90%)
Cycle 4	168 (85%)	178 (86%)	104 (89%)	102 (86%)
Received only 1 cycle of study treatment	13 (7%)	18 (9%)	4 (3%)	7 (6%)

Received TC but did not receive eflapegrastim or pegfilgrastim	2 (1%)	1 (<1%)	2 (2%)*	0

*Patients discontinued treatment due to reactions to docetaxel in Cycle 1, prior to eflapegrastim administration.
[Source: CSR and confirmed by FDA]

Dose compliance with docetaxel and cyclophosphamide was also high in the two treatment arms in studies 301 and 302. For both docetaxel and cyclophosphamide, the median numbers of cycles (and range) administered in both treatment arms were all 4 (range 1, 4) in both studies. The incidence of dose adjustments of docetaxel and cyclophosphamide were generally similar between the two arms in both studies. The proportion of patients who had docetaxel dose reduction was small throughout the 4 cycles in both studies except in the eflapegrastim arm in study 302 (301 [eflapegrastim: 5%, pegfilgrastim: 8%], 302 [eflapegrastim: 18%, pegfilgrastim: 5%]). The proportion of patients who had cyclophosphamide dose reduction was also small throughout the 4 cycles in both studies (301 [eflapegrastim: 3%, pegfilgrastim: 4%], 302 [eflapegrastim: 8%, pegfilgrastim: 5%]).

Table 18 SPI-GCF-301 and SPI-GCF-302: Dose Adjustment (Safety Population)

	SPI-GCF-301				SPI-GCF-302			
	Eflapegrastim (n=197)		Pegfilgrastim (n=208)		Eflapegrastim (n=117)		Pegfilgrastim (n=118)	
	Cycle 1	All cycles	Cycle 1	All cycles	Cycle 1	All cycles	Cycle 1	All cycles
Docetaxel								
Dose reduced	2 (1%)	10 (5%)	2 (1%)	16 (8%)	3 (3%)	21 (18%)	1 (<1%)	6 (5%)
Drug interrupted	8 (4%)	26 (13%)	9 (4%)	23 (11%)	3 (3%)	6 (5%)	3 (3%)	5 (4%)
Discontinued	0	1 (<1%)	1 (<1%)	1 (<1%)	0	0	0	2 (2%)
Cyclophosphamide								
Dose Reduced	0	5 (3%)	0	8 (4%)	1 (<1%)	9 (8%)	2 (2%)	6 (5%)
Drug interrupted	2 (1%)	2 (1%)	3 (1%)	4 (2%)	1 (<1%)	2 (2%)	0	1 (<1%)
Discontinued	0	0	0	0	0	0	0	0
Eflapegrastim or pegfilgrastim								
Discontinued	0	0	0	0	0	1 (<1%)	0	0
Drug delayed	1 (<1%)*	0*	0	0	0	1 (<1%)	0	2 (2%)

*Patient (b) (6) was randomized to the pegfilgrastim arm but received eflapegrastim in Cycle 1. Dose compliance could not be calculated for this patient in all cycles and the patient is excluded from this analysis.
[Source: CSR]

Concomitant Medications:

The use of concomitant medications was generally balanced between the two arms in both studies. The most frequently administered concomitant medications during the treatment period included systemic glucocorticosteroids (mainly as pre-medication for chemotherapy and for AE management), gastric acid suppressants, antihistamines, anti-nausea medications, and nonsteroidal anti-inflammatory drugs or pain medications.

Table 19 SPI-GCF-301 and SPI-GCF-302: Use of Concomitant Medication in > 20% of Patients (ITT Population)

Medication	SPI-GCF-301				SPI-GCF-302			
	Eflapegrastim (n=196)		Pegfilgrastim (n=210)		Eflapegrastim (n=118)		Pegfilgrastim (n=119)	
	Cycle 1	All cycles	Cycle 1	All cycles	Cycle 1	All cycles	Cycle 1	All cycles
Dexamethasone	71%	88%	71%	87%	67%	75%	69%	73%
Ondansetron	47%	68%	47%	62%	63%	64%	53%	63%
Diphenhydramine	44%	56%	40%	51%	27%	30%	31%	34%
Paracetamol	30%	51%	24%	40%	24%	33%	23%	39%
Famotidine	20%	27%	21%	24%	25%	30%	25%	29%
Ibuprofen	18%	29%	11%	20%	7%	14%	10%	20%

[Source: CSR]

In studies 301 and 302, additional concomitant treatment with myeloid growth factors, including filgrastim, pegfilgrastim or its biosimilars, and other anti-cancer therapy were prohibited with the exception of hormonal therapy and HER-2 targeted therapy for the patients who need such a targeted therapy. Premedications used for supportive care were allowed. Corticosteroids as premedication for docetaxel were allowed during study treatment. Other uses of systemic steroids were to be approved by the Medical Monitor.

Other anti-cancer therapy including chemotherapy, radiation therapy, immunotherapy, or experimental medications were not permitted during the study, except that radiation therapy was allowed during the 12-Month Safety Follow-up Period. Any patients with disease progression that required antitumor therapy, other than TC, had to discontinue from the trial. No white blood cell or whole blood transfusions were allowed.

In study 301, a total of 5 patients (eflapegrastim: 3 patients, pegfilgrastim: 2 patients) received filgrastim or pegfilgrastim during Cycles 2-4 and were discontinued from the study. In study 302, one patient in the pegfilgrastim arm received filgrastim in Cycle 2 for decreased ANC and was discontinued from the study.

During the follow-up period, a total of 16 patients in study 301 (eflapegrastim: 6, pegfilgrastim: 10) and 1 patient in study 302 (eflapegrastim: 0, pegfilgrastim: 1) had treatment with additional myeloid growth factors and withdrew from the study (as described in Table 12 above).

In addition, a total of 18 patients in study 301 (eflapegrastim: 6, pegfilgrastim: 12) and 19 patients in study 302 (eflapegrastim: 5, pegfilgrastim: 14) withdrew from the study due to initiation of non-protocol therapy for breast cancer (see Table 12).

In studies 301 and 302, no white blood cell or whole blood transfusions were given and use of systemic steroids was balanced between the two arms.

Table 20 SPI-GCF-301 and SPI-GCF-302: Use of Prohibited Concomitant Medication (ITT Population)

	SPI-GCF-301				SPI-GCF-302			
	Eflapegrastim (n=196)		Pegfilgrastim (n=210)		Eflapegrastim (n=118)		Pegfilgrastim (n=119)	
	Cycle 1	All cycles	Cycle 1	All cycles	Cycle 1	All cycles	Cycle 1	All cycles
Concomitant treatment with myeloid growth factors								
Filgrastim	0	3 (2%)	0	0	0	0	0	1 (<1%)
Pegfilgrastim	0	0	0	2 (1%)	0	0	0	0
Systemic Hormonal Preparations, Excluding Sex Hormones								
Cortisone	0	1 (<1%)	0	1 (<1%)	0	0	0	0
Dexamethasone	139 (71%)	172 (88%)	150 (71%)	183 (87%)	79 (67%)	88 (75%)	82 (69%)	87 (73%)
Hydrocortisone	12 (6%)	19 (10%)	7 (3%)	19 (9%)	5 (4%)	17 (14%)	7 (6%)	9 (8%)
Methylpred-nisolone	6 (3%)	24 (12%)	7 (3%)	25 (12%)	22 (19%)	26 (22%)	24 (20%)	31 (26%)
Prednisolone	0	1 (<1%)	0	1 (<1%)	0	2 (2%)	1 (<1%)	1 (<1%)
Prednisone	5 (3%)	15 (8%)	2 (1%)	12 (6%)	0	6 (5%)	1 (<1%)	6 (5%)

[Source: CSR]

Efficacy Results – Primary Endpoint

The primary efficacy endpoint was DSN in Cycle 1 and the primary analysis was based on the treatment differences between the eflapegrastim and the pegfilgrastim for the ITT Population in both studies.

For Study 301 (Table 21), the difference in mean DSN between the eflapegrastim Arm and the pegfilgrastim Arm was -0.148 days (95% CI: -0.265, -0.033) using bootstrap sampling method with repetitions of 100,000 and seed of 201502 in Cycle 1. The results showed that eflapegrastim was non-inferior (NI) to pegfilgrastim in Cycle 1 (upper bound of 95% CI <0.62 days; NI p<0.0001). Although superiority test was not planned in the SAP, eflapegrastim showed statistical superiority to pegfilgrastim in Cycle 1 (upper bound of 95% CI <0; p=0.013).

Table 21 SPI-GCF-301: Analysis of Duration of Severe Neutropenia in Cycle 1 (ITT Population)

	Eflapegrastim (N=196)	Pegfilgrastim (N=210)
DSN (Days), n (%)		
0	165 (84)	159 (76)
1	24 (12)	32 (15)
2	6 (3)	16 (8)
3	1 (1)	3 (1)
Statistics		
Mean (SD)	0.20 (0.503)	0.35 (0.683)
95% Confidence Interval	0.13, 0.27	0.25, 0.44
Difference with Pegfilgrastim		

	Eflapegrastim (N=196)	Pegfilgrastim (N=210)
Difference with Pegfilgrastim	-0.148	
Percentile Method: Confidence Interval [a]	-0.265, -0.033	
95% Confidence Interval [b]	-0.266, -0.031	
Non-inferiority p-value [b]	<0.0001	
Superiority p-value [b, c]	0.013	

[a] Confidence intervals are obtained using 2.5 percentile and 97.5 percentile of the 100,000 bootstrap samples with treatment as stratification factor.

[b] Obtained using T-test with treatment as stratification factor.

[c] Nominal p-value.

Source: FDA Analysis

For Study 302, the difference in DSN between the eflapegrastim Arm and the pegfilgrastim Arm was -0.073 days (95% CI: -0.292, 0.129) using bootstrap sampling method with repetitions of 100,000 and seed of 201502 in Cycle 1. The difference showed that eflapegrastim was non-inferior (NI) to pegfilgrastim in Cycle 1 (upper bound of 95% CI <0.62 days; NI p<0.0001). However, superiority of eflapegrastim to pegfilgrastim did not show (upper bound of 95% CI > 0; p=0.499) in Study 302. Note that the study was not powered to test superiority.

Table 22 SPI-GCF-302: Analysis of Duration of Severe Neutropenia in Cycle 1 (ITT Population)

	Eflapegrastim (N=118)	Pegfilgrastim (N=119)
DSN (Days), n (%)		
0	94 (80)	91 (76)
1	13 (11)	20 (17)
2	9 (8)	3 (3)
3 +	2 (2)	5 (5)
Statistics		
Mean (SD)	0.31 (0.688)	0.35 (0.683)
95% Confidence Interval	0.19, 0.44	0.21, 0.56
Difference with Pegfilgrastim		
Difference with Pegfilgrastim	-0.073	
Percentile Method: Confidence Interval [a]	-0.292, 0.129	
95% Confidence Interval [b]	-0.285, 0.139	
Non-inferiority p-value [b]	<0.0001	
Superiority p-value [b, c]	0.499	

[a] Confidence intervals are obtained using 2.5 percentile and 97.5 percentile of the 100,000 bootstrap samples with treatment as stratification factor.

[b] Obtained using T-test with treatment as stratification factor.

[c] Nominal p-value.
Source: FDA Analysis

Reviewer's Comment:

- *The FDA's analysis was conducted using the 100,000 bootstrap sampling to replace the 10,000 sampling reported by the sponsor.*
- *As stated in the Table 16 of CSR, the sponsor claimed that results under the footnote b were from bootstrap sampling. We confirmed that these results were from T-test.*

In order to assess the impact of starting seed and repetition times with the bootstrap sampling approach, we conducted additional simulations. As showed in Table 23 and Table 76 (Appendix), different starting seeds and sampling times resulted in slightly different results. Further, larger sampling time seems to make the results more stable. Therefore, we reported results with 100,000 sampling times instead of 10,000 in this review.

Table 23 SPI-GCF-301: Simulation Results of DSN in Cycle 1 (ITT Population)

Starting Seed	Trt Difference	Confidence Interval[a]	Repetitions
201502	-0.148	-0.264, -0.032[b]	10,000
	-0.148	-0.265, -0.033	100,000
202002	-0.148	-0.265, -0.035	10,000
	-0.148	-0.265, -0.034	100,000
2262020	-0.149	-0.265, -0.034	10,000
	-0.149	-0.266, -0.034	100,000
1111964	-0.150	-0.269, -0.034	10,000
	-0.149	-0.266, -0.033	100,000
2292020	-0.148	-0.266, -0.033	10,000
	-0.149	-0.265, -0.033	100,000
12345	-0.148	-0.264, -0.034	10,000
	-0.149	-0.264, -0.033	100,000

[a] Confidence intervals are obtained using 2.5 percentile and 97.5 percentile of bootstrap samples with treatment as stratification factor.
[b] Same as those reported in Table 16, CSR.
Source: FDA Analysis

Handling of Dropouts or Missing Data

As stated in the statistical analysis plan, missing data were not imputed in the study except for the ANC values for the primary endpoint. Assessment of ANC was performed daily from Days 4 to 15 in Cycle 1. During this time window, patients were expected to have severe neutropenia, and missing ANC values could affect the calculation of the primary efficacy endpoint.

The frequency of missing data at the sample level in Cycle 1 was presented in Table 24. The number of total samples was calculated based on 5 days (Days 5-9) multiplied by the number of patients in each treatment arm. For Study 301, the proportion of missing samples during Days 5 to 9 in Cycle 1 was 10% and 13% in the eflapegrastim Arm and 12% and 10% in the pegfilgrastim Arm for Study 301 and Study 302, respectively. The frequency of missing samples was comparable between the two treatment arms in both studies.

Table 24 SPI-GCF-301 and SPI-GCF-302: Frequency of Missing ANC Samples in Cycle 1 by Study Day (ITT Population)

	Study 301		Study 302	
	Eflapegrastim (N=196)	Pegfilgrastim (N=210)	Eflapegrastim (N=118)	Pegfilgrastim (N=119)
# of Planned Sample [a]	980	1050	590	595
Day of Missing Sample				
Day 5	17 (9)	27 (13)	13 (11)	12 (10)
Day 6	14 (7)	24 (11)	13 (11)	11 (9)
Day 7	17 (9)	26 (12)	16 (14)	13 (11)
Day 8	20 (10)	22 (10)	17 (14)	11 (9)
Day 9	26 (13)	26 (12)	15 (13)	13 (11)
All Missing Samples	94 (10)	125 (12)	74 (13)	60 (10)
Missing one sample	27 (3)	16 (2)	32 (5)	22 (4)
Missing ≥2 samples	67 (7)	109 (10)	42 (7)	38 (6)

Source: Table 26 in CSR

Sensitivity Analyses of the Primary Endpoint

Sensitivity analyses of the primary endpoint of DSN in Cycle 1 in PP population were performed. For Study 301, the mean DSN in Cycle 1 for the eflapegrastim Arm was 0.21 (±0.513) days compared with the mean DSN of 0.36 (±0.699) days in the pegfilgrastim Arm. The difference in DSN between the eflapegrastim Arm and the pegfilgrastim Arm was - 0.153 days (95% CI: -0.274, -0.030); the 95% CI was calculated using bootstrap sampling and percentile method. Using the same criterion for the primary endpoint, eflapegrastim was non-inferior to pegfilgrastim (upper bound of 95% CI <0.62 days; NI p<0.0001).

Table 25 SPI-GCF-301: Analysis of Duration of Severe Neutropenia in Cycle 1 (PP Population)

	Eflapegrastim (N=187)	Pegfilgrastim (N=196)
DSN (Days), n (%)		
0	156 (83)	147 (75)
1	24 (13)	30 (15)
2	6 (3)	16 (8)

	Eflapegrastim (N=187)	Pegfilgrastim (N=196)
3	1 (1)	3 (2)
Statistics		
Mean (SD)	0.21 (0.513)	0.36 (0.699)
95% Confidence Interval	0.13, 0.28	0.25, 0.46
Difference with Pegfilgrastim		
Difference with Pegfilgrastim	-0.153	
Percentile Method: Confidence Interval [a]	-0.276, -0.033	
95% Confidence Interval [c]	-0.277, -0.030	
Non-inferiority p-value [b]	<0.0001	
Superiority p-value [b, c]	0.015	

[a] Confidence interval is obtained using 2.5 percentile and 97.5 percentile of the 100,000 bootstrap samples with treatment as stratification factor.

[b] Obtained using T-test with treatment as stratification factor.

[c] Nominal p-value.

Source: FDA Analysis

For Study 302, the difference in DSN between the eflapegrastim Arm and the pegfilgrastim Arm was -0.073 days (95% CI: -0.306, 0.144); the 95% CI was calculated using bootstrap sampling and percentile method. Eflapegrastim was non-inferior to pegfilgrastim (upper bound of 95% CI <0.62 days).

Table 26 SPI-GCF-302: Analysis of Duration of Severe Neutropenia in Cycle 1 (PP Population)

	Eflapegrastim (N=110)	Pegfilgrastim (N=111)
DSN (Days), n (%)		
0	86 (78)	84 (76)
1	13 (12)	19 (17)
2	9 (8)	3 (3)
3+	2 (2)	5 (5)
Statistics		
Mean (SD)	0.34 (0.707)	0.41 (0.976)
95% Confidence Interval	0.20, 0.47	0.22, 0.59
Difference with Pegfilgrastim		
Difference with Pegfilgrastim	-0.069	
Percentile Method: Confidence Interval [a]	-0.304, 0.148	
95% Confidence Interval [b]	-0.295, 0.157	
Non-inferiority p-value [b]	<0.0001	
Superiority p-value [b, c]	0.548	

[a] Confidence interval is obtained using 2.5 percentile and 97.5 percentile of the 100,000 bootstrap samples with treatment as stratification factor.
[b] Obtained using T-test with treatment as stratification factor.
[c] Nominal p-value.
Source: FDA Analysis

Additional sensitivity analyses were conducted for Study 301 and 302 (refer to Table 77 and Table 78 in Appendix). These results support the primary analysis result because all the upper bound of 95% CIs were less than the non-inferiority margin of 0.62 days including the worst-case scenario. Therefore, the treatment effect of eflapegrastim compared to pegfilgrastim seems to be robust in both studies.

Subgroup Analyses of the Primary Endpoint

For Study 301, because only two patients were male and 13 out of 406 patients were from Non-US region, only subgroups by age group, race, disease status and weight are analyzed for the primary endpoint. Although there are some variations among these subgroups in the analyses of DSN in Cycle 1, no outliers were found by age, gender, race, disease status, region, and body weight in both studies. Note that, the DSN reduction in disease status of adjuvant patients treated with eflapegrastim was statistically superior to pegfilgrastim in patients (difference -0.182 days; 95% CI -0.315, -0.048) and patients weighing more than 75 kg (difference -0.245 days; 95% CI -0.406 to -0.084). The superiority was not seen in patients with neoadjuvant patients and patients weighing less than 75 kg. These differences were not seen in Study 302. The results from the subgroup analyses, in general, support the findings from the primary analysis.

Table 27 SPI-GCF-301: Subgroup Analysis of DSN in Cycle 1 (ITT Population)

	Difference with Pegfilgrastim	95% CI
Primary Analysis (n=406 [100%])	-0.148	-0.266, -0.031
Age (years)		
< 65 (n=247 [60.8%])	-0.112	-0.253, 0.029
≥ 65 (n=159 [39.2%])	-0.212	-0.415, -0.009
Race		
White (n=315 [77.6%])	-0.128	-0.255, -0.002
Non-White (n=91 [22.4%])	-0.212	-0.509, 0.086
Disease Status		
Adjuvant (n=336 [77.6%])	-0.182	-0.315, -0.048
Neoadjuvant (n=91 [22.4%])	0.011	0.229, 0.251
Weight (kg)		
< 65 (n=81 [20.0%])	-0.071	-0.340, 0.199
65 to 75 (n=93 [22.9%])	0.026	0.198, 0.249

	Difference with Pegfilgrastim	95% CI
> 75 (n=232 [57.1%])	-0.245	-0.406, -0.084

Source: FDA Analysis

Table 28 SPI-GCF-302: Subgroup Analysis of DSN in Cycle 1 (ITT Population)

	Difference with Pegfilgrastim	95% CI
Primary Analysis (n=237 [100%])	-0.073	-0.285, 0.139
Age (years)		
< 65 (n=153 [64.6%])	-0.113	-0.370, 0.145
≥ 65 (n=84 [35.4%])	-0.023	-0.397, 0.352
Race		
White (n=181 [76.4%])	-0.047	-0.296, 0.202
Non-White (n=56 [23.6%])	-0.175	-0.599, 0.249
Disease Status		
Adjuvant (n=191 [80.6%])	-0.100	-0.345, 0.146
Neoadjuvant (n=46 [19.4%])	0.019	-0.405, 0.444
Weight (kg)		
< 65 (n=68 [28.7%])	0.069	-0.304, 0.443
65 to 75 (n=55 [23.2%])	0.102	-0.141, 0.344
> 75 (n=114 [48.1%])	-0.243	-0.608, 0.122
Geographic Region		
US (n=131 [55.3%])	-0.056	-0.396, 0.284
Non-US (n=106 [44.7%])	-0.072	-0.288, 0.145

Source: FDA Analysis

Efficacy Results – Key Secondary endpoint Analyses

The key secondary endpoints for both studies were

1. Time to ANC Recovery in Cycle 1
2. Depth of ANC Nadir in Cycle 1
3. Incidences of FN in Cycle 1

A hierarchical testing procedure was planned to test the primary endpoint first then the key secondary endpoints in the order listed above. Because none of tests for the above key secondary endpoints was statistically significant, these efficacy results would be considered exploratory and the p-values reported were nominal.

1. Time to ANC Recovery in Cycles 1 to 4

A summary of Time to ANC Recovery is presented in Table 29 and Table 30 for Study 301 and 302, respectively. There were no statistically significant differences in time to ANC recovery between the eflapegrastim arm and the pegfilgrastim arm in any cycle for both studies.

Table 29 SPI-GCF-301: Analysis of Time to ANC Recovery in Cycles 1 to 4 (ITT Population)

	Eflapegrastim (N=196)	Pegfilgrastim (N=210)
Cycle 1		
Mean (SD) (days)	3.24 (3.565)	3.49 (3.589)
Difference with Pegfilgrastim (95% CI)	-0.25 (-1.43, 0.94)	
p-value	0.685	
Cycle 2		
Mean (SD)	2.28 (3.822)	2.10 (3.735)
Difference with Pegfilgrastim (95% CI)	0.18 (-1.18, 1.54)	
Cycle 3		
Mean (SD)	2.65 (4.035)	1.91 (3.641)
Difference with Pegfilgrastim (95% CI)	0.74 (-0.67, 2.15)	
Cycle 4		
Mean (SD)	2.80 (4.114)	2.51 (4.167)
Difference with Pegfilgrastim (95% CI)	0.28 (-1.20, 1.76)	

Time to ANC recovery was normally distributed and the test of comparison and the 95% CI of the difference between treatment arms used normal distribution.
Source: FDA Analysis

Table 30 SPI-GCF-302: Analysis of Time to ANC Recovery in Cycles 1 to 4 (ITT Population)

	Eflapegrastim (N=118)	Pegfilgrastim (N=119)
Cycle 1		
Mean (SD) (days)	3.49 (3.723)	3.35 (3.745)
Difference with Pegfilgrastim (95% CI)	0.14 (-1.47, 1.74)	
p-value	0.866	
Cycle 2		
Mean (SD)	2.19 (3.856)	1.96 (3.891)
Difference with Pegfilgrastim (95% CI)	0.23 (-1.60, 2.06)	
Cycle 3		
Mean (SD)	1.96 (3.999)	2.08 (3.804)
Difference with Pegfilgrastim (95% CI)	-0.13 (-1.96, 1.70)	
Cycle 4		

	Eflapegrastim (N=118)	Pegfilgrastim (N=119)
Mean (SD)	1.93 (3.660)	1.67 (3.589)
Difference with Pegfilgrastim (95% CI)	0.26 (-1.45, 1.97)	

Time to ANC recovery was normally distributed and the test of comparison and the 95% CI of the difference between treatment arms used normal distribution.
Source: FDA Analysis

2. Depth of ANC Nadir in Cycle 1

Depth of ANC Nadir is defined as the patient's lowest ANC value in Cycle 1. For Study 301 (Table 31), 191 patients in the eflapegrastim Arm and 196 patients in the pegfilgrastim Arm were evaluable for Depth of ANC Nadir in Cycle 1. Both the mean and median depth of the ANC nadir in the two arms were similar (Mean [eflapegrastim: $2.56x10^9$/L, pegfilgrastim: $2.53x10^9$/L]; Median [eflapegrastim: $1.57x10^9$/L, pegfilgrastim: $1.61x10^9$/L]) and were not statistically different in Cycle 1 (p-value = 0.155). There were no statistically significant differences in the Depth of ANC Nadir in Cycles 2 and 4 between the two treatment arms, however, the mean depth of ANC nadir in the eflapegrastim Arm ($3.96x10^9$/L) was lower than the ANC nadir in the pegfilgrastim Arm ($5.18x10^9$/L) in Cycle 3 (p-value = 0.011).

Table 31 SPI-GCF-301: Analysis of Depth of ANC Nadir in Cycles 1 to 4 (ITT Population)

	Eflapegrastim (N=196)	Pegfilgrastim (N=210)
Cycle 1		
N	191	196
Mean (SD) ($X10^9$/L)	2.56 (3.086)	2.53 (3.317)
Median (Min, Max) ($X10^9$/L)	1.57 (0.04, 23.92)	1.31 (0.01, 22.31)
Ratio with Pegfilgrastim (95% CI)*	1.2 (0.93, 1.56)	
p-value	0.155	
Cycle 2		
N	180	188
Mean (SD)	4.42 (6.464)	4.55 (4.987)
Median (Min, Max)	2.45 (0.05, 45.11)	3.26 (0.18, 42.96)
Ratio with Pegfilgrastim (95% CI)*	0.8 (0.64, 1.04)	
p-value	0.102	
Cycle 3		
N	172	177
Mean (SD)	3.96 (4.553)	5.18 (5.349)
Median (Min, Max)	2.29 (0.07, 30.33)	3.67 (0.01, 37.34)
Ratio with Pegfilgrastim (95% CI)*	0.7 (0.56, 0.93)	
p-value	0.011	

	Eflapegrastim (N=196)	Pegfilgrastim (N=210)
Cycle 4		
N	165	174
Mean (SD)	3.48 (4.054)	4.19 (4.221)
Median (Min, Max)	2.00 (0.08, 24.98)	2.84 (0.04, 26.20)
Ratio with Pegfilgrastim (95% CI)*	0.8 (0.64, 1.04)	
p-value	0.107	

Source: FDA Analysis

In Study 302, there were no statistically significant differences in both the mean and median depth of the ANC nadir in Cycle 1; the median depth in the Eflapegrastim Arm was $1.60X10^9$/L and in the Pegfilgrastim Arm it was $1.57X10^9$/L. There were no statistically differences between the two treatment arms in the Depth of ANC Nadir from Cycles 2 to 4 were also similar.

Table 32 SPI-GCF-302: Analysis of Depth of ANC Nadir in Cycles 1 to 4 (ITT Population)

	Eflapegrastim (N=118)	Pegfilgrastim (N=119)
Cycle 1		
N	115	116
Mean (SD) ($X10^9$/L)	2.67 (3.504)	2.06 (2.034)
Median (Min, Max) ($X10^9$/L)	1.60 (0.06, 22.78)	1.57 (0.05, 10.55)
Ratio with Pegfilgrastim (95% CI)*	1.2 (0.85, 1.56)	
p-value	0.363	
Cycle 2		
N	109	108
Mean (SD)	7.32 (9.327)	4.25 (3.890)
Median (Min, Max)	3.97 (0.15, 38.71)	2.84 (0.07, 17.74)
Ratio with Pegfilgrastim (95% CI)*	1.3 (0.92, 1.77)	
p-value	0.138	
Cycle 3		
N	104	105
Mean (SD)	5.80 (6.679)	4.74 (6.212)
Median (Min, Max)	3.48 (0.05, 39.49)	3.07 (0.11, 54.91)
Ratio with Pegfilgrastim (95% CI)*	1.1 (0.83, 1.58)	
p-value	0.416	
Cycle 4		

	Eflapegrastim (N=118)	Pegfilgrastim (N=119)
N	102	111
Mean (SD)	4.85 (4.757)	4.46 (4.815)
Median (Min, Max)	3.72 (0.02, 27.84)	2.86 (0.04, 27.35)
Ratio with Pegfilgrastim (95% CI)*	1.1 (0.80, 1.55)	
p-value	0.522	

Source: FDA Analysis

3. Incidence of Febrile Neutropenia in Cycle 1

A summary for the Incidence of Febrile Neutropenia in Cycle 1 is presented in Table 33. In Study 301, there were 4 (2.0%) patients in the eflapegrastim Arm and 2 (1.0%) patients in the pegfilgrastim Arm who experienced FN in Cycle 1. In Study 302, there was 1 (0.8%) patient in the eflapegrastim Arm and 4 (3.4%) patients in the pegfilgrastim Arm who experienced FN. No significant difference between the two arms were identified in both studies.

Table 33 SPI-GCF-301 and SPI-GCF-302: Incidence of Febrile Neutropenia in Cycles 1 (ITT)

	Study 301		Study 302	
	Eflapegrastim (N=196)	Pegfilgrastim (N=210)	Eflapegrastim (N=118)	Pegfilgrastim (N=119)
Incidence, n (%)	4 (2.0)	2 (1.0)	1 (0.8)	4 (3.4)
Diff. with Pegfilgrastim	1.1		-2.5	
95% CI, %	-8.6, 10.8		-15.2, 10.2	
p-value	0.435		0.370	

[a] Fisher's exact test
Source: FDA Analysis

Efficacy Results – Other Secondary Endpoint Analyses

Duration of Severe Neutropenia in Cycles 2 to 4

A summary of the DSN in Cycles 2 to 4 is presented in Table 34. The DSN in the eflapegrastim Arm was non-inferior to the pegfilgrastim Arm in all three cycles because all the upper bound of 95% CI were less than the pre-specified non-inferior margin of 0.62 days.

Table 34 SPI-GCF-301 and SPI-GCF-302: Analysis of Duration of Severe Neutropenia in Cycles 2 to 4 (ITT Population)

	Study 301		Study 302	
	Eflapegrastim (N=196)	Pegfilgrastim (N=210)	Eflapegrastim (N=118)	Pegfilgrastim (N=119)
Cycle 2				
Mean (SD)	0.13 (0.38)	0.09 (0.37)	0.08 (0.27)	0.09 (0.43)
Median (Range)	0 (0, 3)	0 (0, 4)	0 (0, 1)	0 (0, 4)
ΔDSN (Eflap – Peg) Percentile Method: CI [a]	0.042 (-0.032, 0.116)		-0.016 (-0.117, 0.068)	
Cycle 3				
Mean (SD)	0.11 (0.33)	0.08 (0.27)	0.07 (0.25)	0.07 (0.28)
Median (Range)	0 (0, 2)	0 (0, 1)	0 (0, 1)	0 (0, 2)
ΔDSN (Eflap – Peg) Percentile Method: CI [a]	0.026 (-0.032, 0.086)		0.001 (-0.067, 0.068)	
Cycle 4				
Mean (SD)	0.11 (0.36)	0.09 (0.28)	0.07 (0.25)	0.08 (0.27)
Median (Range)	0 (0, 3)	0 (0, 1)	0 (0, 1)	0 (0, 1)
ΔDSN (Eflap – Peg) Percentile Method: CI [a]	0.027 (-0.034, 0.091)		-0.008 (-0.075, 0.060)	

[a] Confidence intervals are obtained using 2.5 percentile and 97.5 percentile of the 100,000 bootstrap samples with treatment as stratification factor.
Source: FDA Analysis

Incidence of Severe Neutropenia in Cycle 1

The incidence of severe neutropenia in Cycle 1 was reported in Table 35. In Study 301, the incidence of severe neutropenia was lower in the eflapegrastim Arm (31 [15.8%]) than that of in the pegfilgrastim Arm (51 [24.3%]) during Cycle 1. Both the absolute risk and relative risk of reduction in severe neutropenia were nominally significant lower in the eflapegrastim Arm compared to the pegfilgrastim Arm (p=0.036 and p=0.034, respectively).

In the Study 302, the incidences of severe neutropenia were similar between eflapegrastim Arm (24 [20.3%]) and the pegfilgrastim Arm (28 [23.5%]). There were no statistical differences in both the absolute risk reduction and the relative risk between the two treatment arms (p=0.553 and p=0.554, respectively).

Table 35 SPI-GCF-301 and SPI-GCF-302: Analysis of Incidence of Severe Neutropenia in Cycle 1 (ITT Population)

	Study 301		Study 302	
	Eflapegrastim (N=196)	Pegfilgrastim (N=210)	Eflapegrastim (N=118)	Pegfilgrastim (N=119)
Incidence, n (%)	31 (15.8)	51 (24.3)	24 (20.3)	28 (23.5)
Absolute Risk Reduction				
Risk Reduction (%)	8.5		3.2	
95% CI, %	0.6, 16.1		-7.4, 13.7	
Nominal p-value	0.036		0.553	
Relative Risk Reduction				
Risk Reduction (%)	34.9		13.6	
95% CI, %	2.7, 56.4		-40.0, 46.6	
Nominal p-value	0.034		0.554	

Source: FDA Analysis

Data Quality and Integrity

The quality of the original data submission was adequate. In general, the reviewers were able to perform independent review and confirm the Applicant's analysis results using the submitted datasets.

Dose/Dose Response

Refer to the Dose/Dose Response subsection under section 6.2.2.

Durability of Response

In Study 301 and 302, patients received study treatment for up to four 21-day cycles. Both studies, individually, met non-inferiority criteria for the primary endpoint of DSN in Cycle 1 in ITT population. Non-inferiority of eflapegrastim to pegfilgrastim was maintained in Cycle 2 to Cycle 4. Taken together, the consistent findings of non-inferiority in both studies show the durability of efficacy through 4 cycles of treatment across studies.

Persistence of Effect

In Study 301 and 302 patients received study treatment for up to 4 cycles of 21 days. In addition, patients were followed for 12 months after the last dose of the study treatment in the Phase 3 studies. Based on the primary efficacy variable, efficacy persisted for 4 cycles in both

studies. The reduction of DSN in all 4 cycles demonstrated the persistent non-inferiority of eflapegrastim to pegfilgrastim.

6.2. Study SPI-GCF-12-201

6.2.1. Study Design

Trial Design

Trial ID and Title:
SPI-GCF-12-201 (also referred to as study 201): Phase 2, open-label, dose-ranging study of HM10460A (SPI-2012, eflapegrastim) or pegfilgrastim use for the management of neutropenia in patients with breast cancer who are candidates for adjuvant and neoadjuvant chemotherapy with the docetaxel + cyclophosphamide (TC) regimen.

This was an open-label, multicenter, dose ranging (sequentially enrolled by study dose), non-inferiority study to compare the effectiveness of eflapegrastim relative to a fixed dose of pegfilgrastim as a concurrent control in patients with breast cancer who were candidates for adjuvant or neoadjuvant chemotherapy with TC. Study 201 was used to provide supportive evidence.

The study included a total of 4 arms (3 dose levels of eflapegrastim versus pegfilgrastim):

- Arm 1: Single-dose eflapegrastim (45 mcg/kg)
- Arm 2: Single-dose eflapegrastim (135 mcg/kg)
- Arm 3: Single-dose eflapegrastim (270 mcg/kg)
- Arm 4: Pegfilgrastim (6 mg, per prescribing information)

The TC chemotherapy was to be administered on Day 1 of each 21-day cycle according to the respective prescribing information as follows:

- Docetaxel at 75 mg/m^2 IV infusion over 1 hour, and
- Cyclophosphamide 600 mg/m^2 IV infusion over 30-60 minutes.

A maximum of 4 cycles of chemotherapy were to be administered. To begin full-dose chemotherapy on Day 1 of the next cycle (Day 22 of the previous cycle), patient must have recovered to ANC ≥ 2 x 10^9/L and platelet count ≥100 x 10^9/L. Patients were to receive oral corticosteroids as pre-medication for docetaxel. Eflapegrastim or pegfilgrastim was to be administered on Day 2 of each cycle, approximately 24 hours (±2 hours) after TC chemotherapy. The dose of eflapegrastim administered to each patient was to be based on the assigned arm. Pegfilgrastim was not to be administered between 14 days before or 24 hours after TC chemotherapy. Pegfilgrastim was to be administered according to prescribing information (6 mg SQ once per chemotherapy cycle). A total of 144 evaluable patients (36 patients in each of the 4 treatment arms) were planned to be enrolled in the study.

Chemotherapy dose modifications were not allowed in Cycle 1 but were allowed in Cycles 2-4 according to standard of care.

Patients were discontinued from study treatment when treated with a protocol-prohibited concomitant medication or required dose reduction of any chemotherapy component. Concomitant medications were all medications administered from 5 days prior to study treatment initiation through 20 days (± 2 days) after the last administration of study treatment. No other growth factors, steroids (other than oral corticosteroids as premedication for docetaxel), radiation therapy, other cytotoxic agents, biologic therapy, or immune response modifiers were allowed during the study treatment.

Trial Objectives:
The primary objective was to assess the test doses of eflapegrastim on the DSN during Cycle 1 in patients with breast cancer who are candidates for adjuvant or neoadjuvant chemotherapy.

The secondary objectives were to determine the effect of test doses of eflapegrastim on the following:

- DSN in Cycles 2-4
- ANC in Cycles 1-4
- Time to ANC recovery in Cycles 1-4
- Depth of ANC nadir in Cycles 1-4
- Febrile neutropenia rates by cycle and overall across Cycles 1-4
- Safety profile
- Number/duration of hospitalizations
- Immunogenicity

Eligibility Criteria:
Key Inclusion Criteria:

1. Patient with breast cancer who is a candidate for adjuvant or neoadjuvant chemotherapy
2. Candidate for docetaxel and cyclophosphamide chemotherapy
3. Female or male ≥ 18 years of age
4. ECOG performance status ≤ 2
5. ANC ≥ 1.5 x 10^9/L
6. Platelet count ≥ 100 x 10^9/L
7. Creatinine ≤ 1.5 x ULN
8. Total bilirubin ≤ 1.5 mg/dL
9. AST/ SGOT and/or ALT/SGPT ≤ 2.5 x ULN
10. Hemoglobin > 9 g/dL
11. Alkaline phosphatase ≤ 1.5 x ULN

Key Exclusion Criteria:

1. Known sensitivity to E. coli derived products (e.g., filgrastim, recombinant insulin [HUMULIN®], L-asparaginase, somatropin [HUMATROPE®] growth hormone, recombinant interferon alfa-2b [INTRON® A]) or known sensitivity to any of the products to be administered during dosing
2. Known human immunodeficiency virus (HIV) infection
3. Hepatitis B virus (HBV) or hepatitis C virus (HCV) diagnosis with detectable viral load or immunological evidence of chronic active disease
4. Active infection or any serious underlying medical condition, which would impair the ability of the patient to receive protocol treatment
5. Prior bone marrow or stem cell transplant
6. Major surgery (except for breast surgery related to the patient's breast cancer diagnosis) within 4 weeks prior to enrollment
7. Presence of any other malignancy or history of prior malignancy within 5 years of study entry. Within 5 years, patients treated with curative intent for Stage I or II cancers are eligible provided they have a life expectancy of > 5 years. The 5-year exclusion rule did not apply to non-melanoma skin tumors and in situ cervical cancer.
8. Currently enrolled in or 30 days have not passed since completing other investigational device or drug trial(s).
9. Prolonged exposure to glucocorticosteroids and immunosuppressive agents
10. Pregnant or breast-feeding (for patients of child-bearing potential)

Schedule of Events:

Figure 2 SPI-GCF-12-201: Schedule of Assessments

Procedure	Screening [1]	Cycle 1 through Cycle 4					End of Study[11]	Follow-Up AE Assessment[12]
		Day -1	Day 1	Day 2	Day 3	Days 4-20		
Informed consent	X							
Medical history	X							
Vital signs	X		X	X	X		X	
Body temperature	X		X	X	X		X	
Weight	X		X				X	
Height	X							
Physical exam w/ ECOG performance status	X		X				X	
CBC w/ 5-part differential	X		X	X	X[10]	X[10]	X	
Blood chemistry	X	X[2]					X	
Antibody sample collection		X[2]					X	
Serum (β-hCG) pregnancy testing [3]	X						X	
Urinalysis (micro & macro)	X						X	
Eligibility verification	X							
Enrollment approval/study arm assignment [4]	X							
Corticosteroids administration (oral)		X	X	X				
Docetaxel/cyclophosphamide (TC) chemotherapy [5]			X					
HM10460A [6]or pegfilgrastim Administration [7]				X				
Adverse events	X[8]	X	X	X	X	X	X	X
Concomitant medications [9]	X	X	X	X	X	X	X	

1. Within 21 days prior to start of study treatment (first dose of chemotherapy (TC) treatment)
2. The antibody sample and chemistry sample were to be drawn before administration of corticosteroids on Day -1, or can be drawn on Day -2 or Day -3
3. For patients who are not postmenopausal or surgically sterile; within 14 days of study drug administration
4. Sponsor (medical monitor) was to review eligibility documents to approve enrollment and assign the patient to one study dosing arm (45mcg/kg, 135mcg/kg, or 270mcg/kg eflapegrastim, or pegfilgrastim)
5. Four treatment cycles of docetaxel (75 mg/m2) and cyclophosphamide (600 mg/m^2) to be administered according to the manufacturer's prescribing information.
6. Study drug (eflapegrastim) was to be administered approximately 24 hours (±2 hours) post TC chemotherapy
7. Pegfilgrastim was to be administered according to the prescribing information
8. Only record AEs related to a study procedure. All other AEs/findings to be recorded as baseline findings where applicable.
9. Record all medications administered from 5 days prior to chemotherapy administration.
10. A CBC with 5-part differential were to be performed in each cycle on Day 3. If the ANC ≥ 1.5 x10^9/L, a CBC with 5-part differential will be collected twice weekly on a Monday, Thursday schedule or Tuesday, Friday schedule. If at any time the ANC is <1.5 x10^9/L a daily CBC with 5-part differential will be collected until the ANC is ≥ 1.5 x109/L.
11. The End of Study (EOS), Safety Follow-up visit was to be performed 20 (± 2) days after the last dose of study treatment but before any additional treatment after Cycle 4. If the patient withdrew consent or was discontinued prior to completing Cycle 4, the patient was to return for an EOS visit 30 (±2) days after the last dose of study treatment.
12. The AE Follow-up assessment was to be performed on Day 30 (+/- 2 days) and could be done by a telephone call.
[Source: SPI-GCF-12-201 protocol]

Statistical Analysis Plan

The primary efficacy endpoint was DSN in Cycle 1. The primary analysis population was based on the evaluable population which consisted of all randomized patients who received either eflapegrastim or pegfilgrastim and had completed Cycle 1.

Treatment differences in DSN in Cycle 1 were analyzed using confidence intervals (CIs) calculated based upon 10,000 bootstrap samples stratified by baseline weight (<65 kg, ≥65 and ≤75 kg, or >75 kg). For each sample, the difference between treatment arms was calculated. Percentile CI was obtained from the resampling. A 2-sided 95% upper CI was evaluated with respect to a non-inferiority margin of 1 day for pooled eflapegrastim treatment arms as compared to pegfilgrastim. Non-inferiority would be demonstrated if the upper confidence limit was <1 day.

6.2.2. Study Results

Compliance with Good Clinical Practices

Prior to study initiation, the clinical study protocol and the written informed consent form were reviewed and approved by the Independent Ethics Committees or Institutional Review Boards, as required by Part 56 of Title 21 of the US Code of Federal Regulations (21 CFR 56). This study was conducted in accordance with GCP and the Declaration of Helsinki. Written informed consent was obtained from each subject prior to performance of study-specific procedures.

Patient Disposition

In study SPI-GCF-12-201, a total of 148 patients (45 mcg/kg: 39 patients, 135 mcg/kg: 37 patients, 270 mcg/kg: 36 patients, pegfilgrastim: 36 patients) received at least one dose of the study treatment. One patient (364-131) in the eflapegrastim 135 mcg/kg treatment arm refused further treatment following TC dosing in Cycle 1 and was excluded from the Evaluable and PP Populations. The table below summarizes the Analysis Population.

Table 36 SPI-GCF-12-201: Analysis Populations

	Eflapegrastim			Pegfilgrastim 6 mg	Total
	45 mcg/kg	135 mcg/kg	270 mcg/kg		
Safety population	39 (100%)	37 (100%)	36 (100%)	36 (100%)	148 (100%)
Evaluable population	39 (100%)	36 (97%)	36 (100%)	36 (100%)	147 (99%)
PP population	39 (100%)	36 (97%)	36 (100%)	36 (100%)	147 (99%)

[Source: ADSL.xpt]

Throughout the 4 arms, most of the patients were enrolled from clinical sites in Hungary (60 patients, 41%) followed by US (46 patients, 31%), Australia (21 patients, 14%) and Poland (13 patients, 9%). Other countries were Georgia (4%) and Israel (1%).

The majority of the patients (93%) completed all 4 cycles of study treatment (45 mcg/kg: 97%, 135 mcg/kg: 86% 270 mcg/kg: 92%, pegfilgrastim: 97%). Ninety-nine percent of patients completed Cycle 1 (45 mcg/kg: 100%, 135 mcg/kg: 97% 270 mcg/kg: 100%, pegfilgrastim: 100%). Overall, a total of 10 patients (7%) discontinued study treatment; mostly in the eflapegrastim 135 mcg/kg arm (5 patients).

Table 37 SPI-GCF-12-201: Patient Disposition (Safety Population)

	Eflapegrastim			Pegfilgrastim 6 mg (n=36)	Total (n=148)
	45 mcg/kg (n=39)	135 mcg/kg (n=37)	270 mcg/kg (n=36)		
Completed Treatment Cycles					
Cycle 1	39 (100%)	36 (97%)	36 (100%)	36 (100%)	147 (99%)
Cycle 2	39 (100%)	34 (92%)	34 (94%)	36 (100%)	143 (97%)
Cycle 3	38 (97%)	32 (86%)	34 (94%)	36 (100%)	140 (95%)
Cycle 4	38 (97%)	32 (86%)	33 (92%)	35 (97%)	138 (93%)
Discontinued from treatment	1 (3%)	5 (14%)	3 (8%)	1 (3%)	10 (7%)
Primary reason for discontinuation					
Patient refused further treatment or withdrew consent	0	2 (5%)	1 (3%)	0	3 (2%)
AE/intercurrent illness	0	0	1 (3%)	1 (3%)	2 (1%)
Initiation of non-protocol therapy either for PD or due to intolerance of a TC regimen	0	2 (5%)	0	0	2 (1%)
Investigator's decision	0	1 (3%)	1 (3%)	0	2 (1%)
Need for chemo-therapy or chemo-therapy regimen change due to amended HER2 status	1 (3%)	0	0	0	1 (1%)

[Source: ADSL.xpt and CSR]

Review comment: The incidences of patients who discontinued study treatment were higher in studies 301 (15%) and 302 (13%) compared to study SPI-GCF-12-201 (7%). An information request was sent to the Applicant for possible reason. The Applicant responded as follows:

The main reason for patients discontinuing from the Phase 3 studies was "patient refused further treatment or withdrew consent". Although we could not ascertain completely the specific reasons for withdrawal of consent, the Sponsor attributed the observed difference to the significantly higher burden of blood draw intensity in SPI-GCF-301 and SPI-GCF-302 in Cycle 1 compared to SPI-GCF-12-201. In SPI-GCF-12-201, there were a total of 9 scheduled blood draws compared to 17 scheduled blood draws in Cycle 1 of the Phase 3 studies.

According to datasets, primary reasons for discontinuing study treatment in studies 301 and 302 were mostly due to consent withdrawal by patient (301: 6%, 302: 4%) and adverse event (301: 5%, 302: 5%).

Protocol Violations

Patients were to be enrolled in the study arms sequentially. However, according to the Applicant, during the first 9 months the first 4 patients were enrolled in Arm 1 (eflapegrastim 45mcg/kg: 3 patients) and the pegfilgrastim arm (1 patient). Subsequently, the enrollment scheme was revised so that only patients in Arm 2 and Arm 3 (135 mcg/kg and 270 mcg/kg eflapegrastim, respectively) were enrolled in addition the pegfilgrastim arm in order to catch up enrollment with the Arm 1 enrollment. From March 2014 to the end of the study, it has been reported that patients were enrolled sequentially.

A total of 22 patients (15%) had major protocol violations in study SPI-GCF-12-201. The most common protocol deviation was in the category of dosing of study medication (10 patients, 7%) and was mostly reported for patients in the 270 mcg/kg arm (7 patients). Of the 7 patients with study medication/dosing violations, a total of 4 subjects had dose reduction of eflapegrastim due to AEs.

Table 38 SPI-GCF-12-201: Major Protocol Violations (Safety Population)

	Eflapegrastim			Pegfilgrastim 6 mg (n=36)	Total (n=148)
	45 mcg/kg (n=39)	135 mcg/kg (n=37)	270 mcg/kg (n=36)		
All patients	5 (13%)	2 (5%)	9 (25%)	6 (17%)	22 (15%)
Study medication/ dosing	0	2 (5%)	7 (19%)	1 (3%)	10 (7%)
Laboratory/ procedures	1 (3%)	0	1 (3%)	0	2 (1%)
Randomization	0	0	0	1 (3%)[a]	1 (1%)
Prohibited/ Concomitant medication	0	0	0	1 (3%)	1 (1%)
Other	4 (10%)[b]	0	2 (6%)[c]	3 (8%)[d]	9 (6%)

a. Patient (b) (6) was randomized to the 135 mcg/kg eflapegrastim arm but received pegfilgrastim and remained on pegfilgrastim throughout study.

b. Includes the following for 4 patients: on C1D18, CBCs were not done after low ANC count; on C1D10, one CBC blood draw was missed following a low ANC count; on C1D9 and C1D10, CBCs were not done for 2 days after a low ANC count; C1D4 to C1D20, 3 blood draws were missed.
c. Includes the following for 2 patients: on C1D7, one CBC blood draw was missed following a low ANC count; on C1D11, hematology was not done.
d. Includes the following for 3 patients: on C1D8 and C1D9, CBCs were not done for 2 days after a low ANC count; on C1D1, C1D8 and C1D11, CBCs were not done 3 days; on C1D9, CBCs were not done.
[Source: DV.xpt]

Table of Demographic Characteristics

In study SPI-GCF-12-201, patient demographics were balanced between the 4 treatment arms and generally similar to studies 301 and 302. The median age was 59 years (range: 32-77), almost all patients were females (98%) and 95% of patients were White.

Table 39 SPI-GCF-12-201: Patient Demographics (Evaluable Population)

	Eflapegrastim			Pegfilgrastim 6 mg (n=36)	Total (n=147)
	45 mcg/kg (n=39)	135 mcg/kg (n=36)	270 mcg/kg (n=36)		
Age					
Median	62	59	56.5	60.5	59
Range	33-77	32-74	38-77	35-77	32-77
Gender					
Female	39 (100%)	35 (97%)	34 (94%)	36 (100%)	144 (98%)
Male	0	1 (3%)	2 (6%)	0	3 (2%)
Weight					
Mean	77.2	75.6	76.5	78.0	76.8
SD	13.18	23.06	17.56	17.20	17.85
Race					
White	36 (92%)	36 (100%)	35 (97%)	32 (89%)	139 (95%)
Black or African American	2 (5%)	0	0	0	2 (1%)
Asian	0	0	1 (3%)	0	1 (1%)
Others	1 (3%)	0	0	4 (11%)	5 (3%)
ECOG PS					
0	33 (85%)	32 (89%)	35 (97%)	33 (92%)	133 (90%)
1	5 (13%)	4 (11%)	1 (3%)	2 (6%)	12 (8%)
2	1 (3%)	0	0	0	1 (1%)

[Source: ADSL.xpt and CSR]

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

Baseline disease characteristics were also largely balanced between the 4 treatment arms. Most of the patients had Stage I, IIA or IIB breast cancer (78%) and the median ANC at baseline was 8 $x10^9$/L (range: 2 $x10^9$/L, 21 $x10^9$/L). Most of the patients had ductal invasive carcinoma

(84%) and 44% of patients were candidates to receive adjuvant chemotherapy.

Table 40 SPI-GCF-12-201: Baseline Disease Characteristics (Evaluable Population)

	Eflapegrastim			Pegfilgrastim 6 mg (n=36)	Total (n=147)
	45 mcg/kg (n=39)	135 mcg/kg (n=36)	270 mcg/kg (n=36)		
Baseline ANC (x10^9/L)					
Median	7.1	7.6	8.4	8.5	8.0
Range	2, 19	3, 17	3, 18	3, 21	2, 21
Stage					
I	8 (21%)	7 (19%)	6 (17%)	9 (25%)	30 (20%)
IIA	12 (31%)	12 (33%)	13 (36%)	10 (28%)	47 (32%)
IIB	8 (21%)	11 (31%)	11 (31%)	7 (19%)	37 (25%)
IIIA	6 (15%)	3 (8%)	2 (6%)	6 (17%)	17 (12%)
IIIB	3 (8%)	3 (8%)	2 (6%)	1 (3%)	9 (6%)
IIIC	2 (5%)	0	2 (6%)	1 (3%)	5 (3%)
IV	0	0	0	2 (6%)	2 (1%)
WHO Classification					
Carcinoma with metaplasia	1 (3%)	0	0	0	1 (1%)
Invasive ductal carcinoma	31 (79%)	27 (75%)	32 (89%)	33 (92%)	123 (84%)
Invasive lobular carcinoma	3 (8%)	3 (8%)	0	2 (6%)	8 (5%)
Medullary carcinoma	0	1 (3%)	0	0	1 (1%)
Other	4 (10%)	5 (14%)	4 (11%)	1 (3%)	14 (10%)
Medical history of cancer treatments					
Adjuvant HER-2 Targeted therapy	0	0	0	1 (3%)	1 (1%)
Adjuvant chemo-therapy	16 (41%)	14 (39%)	16 (44%)	18 (50%)	64 (44%)
Adjuvant hormonal therapy	1 (3%)	0	0	1 (3%)	2 (1%)
Neoadjuvant chemotherapy	3 (8%)	6 (17%)	2 (6%)	1 (3%)	12 (8%)
Other	17 (44%)	14 (39%)	17 (47%)	13 (36%)	61 (41%)
Hormone receptor status					
ER+/PR+	20 (51%)	18 (50%)	20 (56%)	23 (64%)	81 (55%)
ER+/PR-	7 (18%)	8 (22%)	5 (14%)	5 (14%)	25 (17%)
ER-/PR-	9 (23%)	9 (25%)	8 (22%)	8 (22%)	34 (23%)
Unknown	3 (8%)	1 (3%)	3 (8%)	0	7 (5%)

HER2 status					
HER2+	1 (3%)	7 (19%)	6 (17%)	3 (8%)	17 (12%)
HER2-	9 (23%)	9 (25%)	9 (25%)	10 (28%)	37 (25%)
Unknown	29 (74%)	20 (56%)	21 (58%)	23 (64%)	94 (64%)

[Source: CSR]

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

In study SPI-GCF-12-201, the median number of cycles with study treatment was 4 (range: 1, 4). The median dose compliance across all cycles with study treatment was 100% (range: 36, 108).

Table 41 SPI-GCF-12-201: Treatment Compliance with Study treatment (Evaluable Population)

	Eflapegrastim			Pegfilgrastim 6 mg (n=36)
	45 mcg/kg (n=39)	135 mcg/kg (n=36)	270 mcg/kg (n=36)	
Number of cycles administered				
Median	4	4	4	4
Range	2, 4	1, 4	1, 4	3, 4
Dosing compliance/ RDI across all cycles (%)				
Median	100	100	100	100
Range	96, 104	94, 108	36, 102	100, 100
Outside 80% to 120%	0	0	3 (8%)	0

RDI: Reference dose intensity.
[Source: CSR]

The median numbers of cycles with both docetaxel and cyclophosphamide were also 4 cycles (range: 1, 4).

Table 42 SPI-GCF-12-201: Treatment Compliance with Docetaxel (Evaluable Population)

	Eflapegrastim			Pegfilgrastim 6 mg (n=36)
	45 mcg/kg (n=39)	135 mcg/kg (n=36)	270 mcg/kg (n=36)	
Number of cycles administered				
Median	4	4	4	4
Range	2, 4	1, 4	2, 4	3, 4
Dosing compliance/ RDI across all cycles (%)				
Median	100	100	100	99
Range	86, 115	76, 102	78, 103	80, 105
Outside 80% to 120%	0	1 (3%)	1 (3%)	0

RDI: Reference dose intensity.
[Source: CSR]

Table 43 SPI-GCF-12-201: Treatment Compliance with Cyclophosphamide (Evaluable Population)

	Eflapegrastim			Pegfilgrastim 6 mg (n=36)
	45 mcg/kg (n=39)	135 mcg/kg (n=36)	270 mcg/kg (n=36)	
Number of cycles administered				
Median	4	4	4	4
Range	2, 4	1, 4	2, 4	3, 4
Dosing compliance/ RDI across all cycles (%)				
Median	100	100	100	99
Range	86, 115	80, 102	80, 101	80, 101
Outside 80% to 120%	0	0	0	0

RDI: Reference dose intensity.
[Source: CSR]

In study SPI-GCF-12-201, the most frequently reported concomitant medications were systemic glucocorticosteroids (i.e., dexamethasone, methylprednisolone), gastric acid suppressants (i.e., famotidine, ranitidine, pantoprazole), anti-nausea medications (i.e., ondansetron, palonosetron), and nonsteroidal anti-inflammatory drugs or pain medications (i.e., acetylsalicylic acid, ibuprofen, paracetamol) and the usage was comparable across the four arms.

Filgrastim was administered to one patient (b) (6) in the pegfilgrastim arm on Day 74. In addition, blood transfusions were given to 2 patients (b) (6) randomized to eflapegrastim 270 mcg/kg and 135 mcg/kg, respectively). Patient (b) (6) received blood transfusion on Day 44 and patient (b) (6) from Day 31 onwards, respectively. Therefore, it is not likely that these concomitant treatments affected the primary efficacy result of the study.

Efficacy Results – Primary Endpoint

The primary efficacy endpoint was DSN in Cycle 1. As presented in Table 44, the mean DSN for the 45 mcg/kg, 135 mcg/kg, and 270 mcg/kg eflapegrastim arms was 1.03 (±1.5) days, 0.44 (±1.3) days, and 0.03 (±0.2) days, respectively, compared with a mean DSN of 0.31 (±0.8) day in the pegfilgrastim Arm. A dose-effect trend was observed across the three doses of eflapegrastim, with the mean DSN (with ANC recovery to $>2.0\times10^9$/L) decreasing with increasing dose.

The difference in DSN between each eflapegrastim Arm and the pegfilgrastim Arm was -0.28 days (CI: -0.56, -0.06) in the 270 mcg/kg eflapegrastim arm, 0.14 days (CI: -0.28, 0.64) in the 135 mcg/kg arm, 0.72 days (CI: 0.19, 1.27) in the 45 mcg/kg arm. The upper limit of the 2-sided 95% CI for the difference was >1 day for the 45 mcg/kg arm, but <1 day for the 135 mcg/kg and 270 mcg/kg arms. Therefore, the 135 mcg/kg arm and 270 mcg/kg arm of eflapegrastim met the non-inferiority criteria to pegfilgrastim (lower bound of 95% CI less than 1 day), but not for the low dose of 45 mcg/kg arm (p=0.296). Only 270 mcg/kg eflapegrastim arm (0.03 days) compared to patients treated in the pegfilgrastim Arm (0.31 days) had nominal p-value less than 0.05 (p=0.023).

Table 44 SPI-GCF-12-201: Analysis of Duration of Severe Neutropenia in Cycle 1 (Evaluable Population)

	Eflapegrastim 45 mcg/kg (N=39)	Eflapegrastim 135 mcg/kg (N=39)	Eflapegrastim 270 mcg/kg (N=39)	Pegfilgrastim 6 mg (N=36)
DSN (Days) n(%)				
0	25 (64)	29 (81)	35 (97)	31 (86)
1	1 (3)	3 (8)	1 (3)	1 (3)
2	5 (13)	3 (8)	0	2 (6)
3	5 (13)	0	0	2 (6)
4+	3 (8)	1 (3)	0	0
Statistics				
Mean (SD)	1.03 (1.547)	0.44 (1.275)	0.03 (0.167)	0.31 (0.822)
95% Confidence Interval	0.56, 1.51	0.14, 0.86	0.00, 0.08	0.08, 0.58
Difference with Pegfilgrastim				
Difference with Pegfilgrastim	0.72	0.14	-0.28	NA
95% Confidence Interval [a]	(0.19, 1.27)	(0.28, 0.64)	(-0.56, -0.06)	NA
Non-inferiority p-value [b]	0.296	0.002	<0.001	NA
Superiority p-value [b, c]	0.006	0.528	0.023	NA

[a] Confidence intervals are obtained using 2.5 percentile and 97.5 percentile of the 10,000 bootstrap samples with treatment as stratification factor.

[b] Obtained using T-test with treatment as stratification factor.

[c] Nominal p-value.

Source: FDA Analysis

Dose/Dose Response

In the primary efficacy analysis of DSN in cycle 1 in the Evaluable Population, a dose-effect trend was observed across the three doses of eflapegrastim, with the mean DSN (with ANC recovery to $>2.0\times10^9$/L) decreasing with increasing dose. Please refer to the clinical pharmacology review for further discussion of dose-response.

7. Integrated Review of Effectiveness

7.1. Assessment of Efficacy Across Trials

SPI-GCF-301 and SPI-GCF-302 were randomized, open-label, active-controlled, multicenter studies to compare the efficacy and safety of eflapegrastim with pegfilgrastim in breast cancer patients who were treated with TC chemotherapy in the neoadjuvant or adjuvant setting. The design of the two studies was identical, however, the studies differ in the planned sample size (301: 406 patients; 302: 237 patients). The pooled analysis was conducted to combine data from Study 301 and Study 302.

The primary endpoint in both studies was DSN in Cycle 1. As presented in Table 45 for the pooled analysis, the difference in mean DSN between the eflapegrastim arm and the pegfilgrastim arm was -0.120 days (95% CI: -0.228, -0.015). The results from the pooled analysis were consistent with the results seen in the individual study.

Table 45 Pooled Analysis of 301 and 302: Analysis of Duration of Severe Neutropenia in Cycle 1 (ITT Population)

	SPI-GCF-301 and SPI-GCF-302	
	Eflapegrastim (N=314)	Pegfilgrastim (N=329)
DSN (Days), n (%)		
0	259 (82)	250 (76)
1	37 (12)	52 (16)
2	15 (5)	19 (6)
3 +	3 (1)	8 (<1)
Statistics		
Mean (SD)	0.24 (0.581)	0.36 (0.789)
95% Confidence Interval	0.18, 0.31	0.28, 0.45
Difference with Pegfilgrastim		
Difference with Pegfilgrastim	-0.120	
Percentile Method: Confidence Interval [a]	-0.228, -0.015	
95% Confidence Interval [b]	-0.227, -0.012	
Non-inferiority p-value [c]	<0.0001	

[a] Confidence intervals are obtained using 2.5 percentile and 97.5 percentile of the 100,000 bootstrap samples with treatment as stratification factor.

[b] Obtained using T-test with treatment as stratification factor.

[c] Nominal p-value.

Source: FDA Analysis

Incidence of Severe Neutropenia in Cycle 1 of the Pooled Analysis is presented in Table 46. During Cycle 1, 55 (17.5%) patients in the eflapegrastim Arm and 79 [24.0%] patients in the pegfilgrastim Arm experienced severe neutropenia. The absolute risk reduction was 6.5% (95% CI: -0.2, 12.7). and the relative risk reduction was 27.1 % (95% CI: 0.8, 46.4).

Table 46 Pooled Analysis of 301 and 302: Incidence of Severe Neutropenia in Cycle 1 of the Pooled Analysis (ITT Population)

	SPI-GCF-301 and SPI-GCF-302	
	Eflapegrastim (N=314)	Pegfilgrastim (N=329)
Incidence, n (%)	55 (17.5)	79 (24.0)
Absolute Risk Reduction [a]		
Risk Reduction (%)	6.5	
95% CI, %	0.2, 12.7	
Relative Risk Reduction [b]		
Risk Reduction (%)	27.1	
95% CI, %	0.8, 46.4	

a. 95% CIfor difference between eflapegrastim and pegfilgrastim is obtained based on Newcombe Score Confidence Limits.
b. 95% CI for difference between eflapegrastim and pegfilgrastim is obtained based on CMH.
Source: ISE Table 21

The subgroup analysis of the primary efficacy endpoint by age, race, disease status, weight and geographic region in the pooled dataset is presented in Table 47. The treatment effects were similar in the subgroup of age, race and geographic region, but favored Eflapegrastim Arm in adjuvant patients (difference -0.150 days; 95% CI -0.272 to -0.027) and patients weighing greater than 75 kg (difference -0.243 days; 95% CI -0.404 to -0.082).

Table 47 Pooled Analysis of 301 and 302: Subgroup Analysis of DSN in Cycle 1 of the Pooled Analysis (ITT Population)

	SPI-GCF-301 and SPI-GCF-302	
	Difference with Pegfilgrastim	95% CI [a]
Primary Analysis (n=643 [100%])	-0.120	-0.227, -0.012
Age (years)		
< 65 (n=400 [62.2%])	-0.112	-0.242, 0.019
≥ 65 (n=243 [37.8%])	-0.143	-0.328, 0.041
Race		
White (n=496 [77.4%])	-0.101	-0.221, 0.020

	SPI-GCF-301 and SPI-GCF-302	
	Difference with Pegfilgrastim	95% CI [a]
Non-White (n=147 [22.6%])	-0.186	-0.425, 0.053
Disease Status		
Adjuvant (n=527 [82.0%])	-0.150	-0.272, -0.027
Neoadjuvant (n=116 [18.0%])	0.007	-0.209, 0.224
Weight (kg)		
< 65 (n=149 [23.2%])	-0.006	-0.228, 0.216
65 to 75 (n=148 [23.0%])	0.053	-0.112, 0.217
> 75 (n=114 [48.1%])	-0.243	-0.404, -0.082
Geographic Region		
US (n=524 [81.5%])	-0.109	-0.233, 0.014
Non-US (n=119 [18.5%])	-0.154	-0.369, 0.060

[a] Obtained using T-test with treatment as stratification factor.
Source: FDA Analysis

7.2. Additional Efficacy Considerations

Not applicable.

7.3. Integrated Assessment of Effectiveness

The efficacy of eflapegrastim to decrease the incidence of infection, as manifested by febrile neutropenia, in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs was assessed in two open-label, multicenter, randomized, active-controlled, phase 3 studies: SPI-GCF-301 (Study 301) and SPI-GCF-302 (Study 302).

Overall, data from Study 301 and Study 302 individually demonstrated that eflapegrastim was non-inferior to pegfilgrastim for the mean DSN in Cycle 1 in patients with early stage breast cancer treated with TC in the adjuvant and/or neoadjuvant setting. The results of all key secondary endpoints in both studies showed no statistically significant differences between eflapegrastim and pegfilgrastim. Further, the results in the pivotal studies were consistent with the results seen in the supportive, phase 2 study SPI-GCF-12-201.

In conclusion, the statistical reviewer confirmed the applicant's efficacy results from all three efficacy studies and concluded that the non-inferiority of eflapegrastim to pegfilgrastim was demonstrated.

8. Review of Safety

8.1. Safety Review Approach

The BLA submission contained safety information from a total of 6 clinical studies as summarized in Table 5. The safety evaluation of eflapegrastim was primarily based on the pooled data of the two pivotal trials (301 and 302) and separately on study SPI-GCF-301-PK as the dose regimen of eflapegrastim and patient population in these 3 trials were consistent (see Table 5 regarding the trial design for study SPI-GCF-301-PK) and included the following:

- Electronic submissions of the clinical study reports and other relevant portions of the NDA were reviewed;
- Safety data were audited or reproduced;
- Safety information was also reviewed from the other studies when appropriate; and
- Applicant's responses to FDA information requests.

A treatment-emergent AE was defined as any AE that occurred from the first dose of study treatment through 12 months after the last dose of study treatment or 35 (±5) days after the date of patient early discontinuation. Safety was reported for two periods:

- Treatment Period: From the first dose of TC until 35 (±5) days after the last dose of study treatment.
- Long-Term Follow-up Period: From 35 (±5) days after the last dose of study treatment through 12 months.

Safety evaluation was conducted using the FDA Medical Queries (FMQs) (except when indicated otherwise in the review).

8.2. Review of the Safety Database

8.2.1. Overall Exposure

The BLA submission contained safety data from a total of 932 patients (eflapegrastim: 536, pegfilgrastim: 374, placebo: 22) as summarized in the table below.

Table 48 Safety Database

Study ID	Population	Eflapegrastim	Pegfilgrastim	placebo
SPI-GCF-301	Breast cancer receiving TC	197	208	0
SPI-GCF-302	Breast cancer receiving TC	117	118	0
SPI-GCF-301-PK	Breast cancer	26*	0	0

	receiving TC			
SPI-GCF-12-201	Breast cancer receiving TC	112	36	0
08-HM10460A-101	Healthy subjects	60	12	12
09-HM10460A-102	Healthy subjects	30	0	10
Total		536	374	22

* 6 patients in SPI-GCF-301-PK were also included SPI-GCF-301.
[Source: ISS]

Pooled analysis of studies 301 and 302:

In the pooled analysis of the two pivotal trials, the median number of cycles with study treatment was 4 cycles (range: 1, 4). The median dose compliance with study treatment across all cycles was 100% with none outside of the 80% to 120% range.

Table 49 Pooled analysis of 301 and 302: Exposure to Study Medication (Safety Population)

	Eflapegrastim (n=314)	Pegfilgrastim (n=326)	Total (n=640)
Number of patients analyzed	310*	324*	634
Duration of treatment (cycles)			
Median	4	4	4
Range	1, 4	1, 4	1, 4
Dosing compliance/RDI across all cycles (%)			
Median	100	100	100
Range	100, 100	100, 100	100, 100
Outside 80% to 120%	0	0	0

*In study 301: Patient (b) (6) was given eflapegrastim instead of pegfilgrastim on Cycle 2 Day 2. Patients (b) (6) were not treated with eflapegrastim or pegfilgrastim. These patients were therefore excluded from the analysis. In study 302: Patients (b) (6) were not treated with eflapegrastim or pegfilgrastim. These patients were therefore excluded from the analysis.
RDI: Reference dose intensity.
[Source: CSR]

The table below summarizes exposure to docetaxel and cyclophosphamide. The median numbers of cycles with both docetaxel and cyclophosphamide were also 4 cycles (range: 1, 4).

Table 50 Pooled analysis of 301 and 302: Exposure to Docetaxel and Cyclophosphamide (Safety Population)

	Docetaxel		Cyclophosphamide	
	Eflapegrastim (n=314)	Pegfilgrastim (n=326)	Eflapegrastim (n=314)	Pegfilgrastim (n=326)
Duration of treatment (cycles)				

Median	4	4	4	4
Range	1, 4	1, 4	1, 4	1, 4
Dosing compliance/RDI (%)				
Median	99.9	99.8	100.0	99.9
Range	57.2, 109.9	8.5, 114.8	69.2, 111.1	56.5, 110.4
Outside 80% to 120%	11 (4%)	7 (2%)	3 (1%)	5 (2%)

[Source: CSR]

SPI-GCF-301-PK:
In study SPI-GCF-301-PK, all 26 enrolled patients received at least one dose of eflapegrastim after the TC chemotherapy in each cycle. The median number of cycles was 4 (range: 1, 6 [one patient received a total of 6 cycles]) and the median dosing compliance/relative dose intensity across all cycles was 100% (range: 100, 100).

8.2.2. Relevant characteristics of the safety population:

Pooled analysis of studies 301 and 302:
The median age of the safety population was 60 years (range: 24, 88) (eflapegrastim: 60 years [range: 28, 83], pegfilgrastim: 60 years [range: 24, 88]). Almost all patients were females (99.7%) (both eflapegrastim and pegfilgrastim: 99.7%) and most were White (77%) (both eflapegrastim and pegfilgrastim: 77%).

Review comment: The demographics and baseline disease characteristics of the safety population were consistent with those of the ITT population for studies 301 and 302 (see Table 15 and Table 16).

SPI-GCF-301-PK:
In study SPI-GCF-301-PK, the median age was 56 years (range: 29, 77), 77% of patients were White (African American: 4%, Asian: 4%, other: 15%) and all patients were female.

8.2.3. Adequacy of the safety database:

The safety data supporting this BLA is primarily based on the clinical trials conducted in patients with breast cancer receiving TC therapy (SPI-GCF-301, SPI-GCF-302, SPI-GCF-301-PK, SPI-GCF-12-201) which enrolled a total of 808 patients (including 446 patients receiving eflapegrastim). Of the 808 patients, a total of 640 patients (eflapegrastim: 314, pegfilgrastim: 326) received treatment in the pivotal randomized studies (SPI-GCF-301 and SPI-GCF-302).

The safety data contained events throughout the study treatment period followed by safety follow-up for up to 1 year after last study treatment. Therefore, the safety database of eflapegrastim is adequate.

8.3. Adequacy of Applicant's Clinical Safety Assessments

8.3.1. Issues Regarding Data Integrity and Submission Quality

The overall quality of data appears to be adequate for safety evaluation. The submission contains appropriate analyses and reports. No major concerns regarding data integrity were identified during the safety review.

8.3.2. Categorization of Adverse Events

MedDRA terminology version 18.0 was used to categorize adverse events. AEs were graded according to the National Cancer Institute Common Technology Criteria for Adverse Events (NCI-CTCAE) version 4.03 coding system. Grade Mapping of the verbatim AE terms to MedDRA Preferred Term and System Organ Class (SOC) was acceptable.

8.3.3. Routine Clinical Tests

Routine clinical assessments in the 301 and 302 trials included physical examination, weight, ECOG performance status, vital signs, body temperature, immunogenicity and laboratory tests. See Table 6 and Table 7 of this review.

8.4. Safety Results

Pooled analysis of studies 301 and 302:

Table 51 summarizes the overall safety results of the pooled analysis of studies 301 and 302.

Table 51 Pooled Analysis of 301 and 302: Overall Summary of Safety (Treatment Period)

	Eflapegrastim (n=314)	Pegfilgrastim (n=326)
Deaths within 30 days of study treatment	0	2 (<1%)
TESAEs	48 (15%)	48 (15%)
Study treatment-related TESAEs	6 (2%)	9 (3%)
TEAEs	307 (98%)	320 (98%)
Study treatment-related TEAEs	238 (76%)	218 (67%)
Grade 3 or 4 TEAEs	233 (74%)	235 (72%)
AEs leading to any study drug withdrawal	13 (4%)	21 (6%)
TEAEs assessed as related to docetaxel and cyclophosphamide		
Docetaxel	297 (95%)	305 (94%)

Cyclophosphamide	289 (92%)	303 (93%)

Incidences are based on the number of patients, not the number of events. Although a patient may have had 2 or more clinical AEs, the patient is counted only once in a category. The same patient may appear in different categories.
[Source: ADAE.xpt]

SPI-GCF-301-PK:

Table 52 summarizes the safety results of the single-arm study, SPI-GCF-301-PK. The safety results of eflapegrastim were similar to those of the eflapegrastim arm in the pooled analysis of studies 301 and 302.

Table 52 SPI-GCF-301-PK: Overall Summary of Safety (Safety Population)

	Eflapegrastim (n=26)
Deaths within 30 days of study treatment	0
TESAEs	4 (15%)
Study treatment-related TESAEs	1 (4%)
TEAEs	26 (100%)
Study treatment-related TEAEs	21 (81%)
Grade 3 or 4 TEAEs	20 (77%)
AEs leading to any study drug withdrawal	1 (4%)
TEAEs assessed as related to docetaxel and cyclophosphamide	
Docetaxel	24 (92%)
Cyclophosphamide	23 (88%)

Incidences are based on the number of patients, not the number of events. Although a patient may have had 2 or more clinical AEs, the patient is counted only once in a category. The same patient may appear in different categories.
[Source: ADAE.xpt]

8.4.1. Deaths

Pooled analysis of studies 301 and 302:
A total of two patients, both who received treatment with pegfilgrastim (<1%) died within 30 days of the last dose of the study drug in studies 301 and 302. Neither of the deaths was assessed as related to the study drug.

In study 301, patient (b) (6) in the pegfilgrastim arm died during Cycle 2 due to cardiac arrest that was assessed as not related to study treatment.

In study 302, patient (b) (6) in the pegfilgrastim arm died during Cycle 4 due to COPD that was considered unrelated to study treatment.

Table 53 Pooled Analysis of 301 and 302: TEAEs Resulting in Death (Safety Population)

Preferred Terms	Eflapegrastim (n=314)	Pegfilgrastim (n=326)
All	0	2 (<1%)
Cardiac arrest	0	1 (<1%)
Chronic obstructive pulmonary disease	0	1 (<1%)

[Source: ADAE.xpt]

In addition, in study 301, one patient (b) (6) in the pegfilgrastim arm died during the 12-month follow-up due to disease progression.

SPI-GCF-301-PK:
No deaths were reported in study SPI-GCF-301-PK.

8.4.2. Serious Adverse Events

Pooled analysis of studies 301 and 302:
The overall incidence of SAEs was similar between the two arms (eflapegrastim: 15%, pegfilgrastim: 15%). The table below summarizes the SAEs that were reported in more than 1 patient in the eflapegrastim arm that occurred during the treatment period. Serious AEs that occurred in more than 2 patients in the eflapegrastim arm were pyrexia, sepsis, febrile neutropenia, diarrhea and chest pain.

Table 54 Pooled Analysis of 301 and 302: TESAEs Reported in >1 Patient in the Eflapegrastim Arm (Safety Population)

FMQ (Narrow)	Eflapegrastim (n=314)	Pegfilgrastim (n=326)
All	48 (15%)	48 (15%)
Pyrexia[a]	5 (2%)	7 (2%)
Sepsis[b]	3 (1%)	5 (2%)
Febrile neutropenia	3 (1%)	4 (1%)
Diarrhea	3 (1%)	1 (<1%)
Chest pain	3 (1%)	1 (<1%)
Pneumonia	2 (<1%)	5 (2%)
Bronchitis	2 (<1%)	3 (1%)

Syncope	2 (<1%)	3 (1%)
Dyspnea	2 (<1%)	2 (<1%)
Colitis	2 (<1%)	0
Colonic abscess	2 (<1%)	0
Diverticulitis	2 (<1%)	0
Fall	2 (<1%)	0

a. Includes body temperature increased.
b. Includes septic shock
[Source: ADAE.xpt]

Serious AEs considered related to study treatment occurred in 2% of patients in the eflapegrastim arm and 3% in pegfilgrastim arm. No study treatment-related SAEs were reported in more than one patient.

Table 55 Pooled Analysis of 301 and 302: Treatment-Related SAEs Reported in **≥1** Patient in the Eflapegrastim Arm (Safety Population)

Preferred Term	Eflapegrastim (n=314)	Pegfilgrastim (n=326)
All	6 (2%)	9 (3%)
Arthralgia	1 (<1%)	0
Back pain	1 (<1%)	1 (<1%)
Bone pain	1 (<1%)	0
Chest pain	1 (<1%)	0
Pyrexia	1 (<1%)	1 (<1%)
Supraventricular tachycardia	1 (<1%)	0
WBC count increased	1 (<1%)	0

Incidences are based on the number of patients, not the number of events. Although a patient may have had 2 or more clinical AEs, the patient is counted only once in a category. The same patient may appear in different categories.
[Source: ADAE.xpt]

SPI-GCF-301-PK:
A total of 5 SAEs were reported in 4 patients (15%) which were headache, neuropathy peripheral, sepsis, rectal hemorrhage and vomiting. Of these, only headache was considered possibly related to eflapegrastim. No SAEs occurred in more than 1 patient. All events resolved.

8.4.3. Dropouts and/or Discontinuations Due to Adverse Effects

Pooled analysis of studies 301 and 302:
The incidence of patients discontinued from the study due to AEs during the treatment period was also similar between the arms (eflapegrastim: 4%, pegfilgrastim: 6%). Oher than rash, there

were no specific AEs that occurred in more than 1 patient in the eflapegrastim arm that resulted in discontinuation of the study treatment.

Table 56 Pooled Analysis of 301 and 302: TEAEs Leading to Study Drug Withdrawal in **≥1** Patient in the Eflapegrastim Arm (Safety Population)

FMQ	Eflapegrastim (n=314)	Pegfilgrastim (n=326)
All	13 (4%)	21 (6%)
Rash*	3 (1%)	2 (<1%)
Bone pain	1 (<1%)	1 (<1%)
Hypersensitivity	1 (<1%)	1 (<1%)
Arthralgia	1 (<1%)	0
Breast cellulitis	1 (<1%)	0
Clostridium difficile sepsis	1 (<1%)	0
Drug eruption	1 (<1%)	0
Hypoesthesia oral	1 (<1%)	0
Migraine	1 (<1%)	0
Pulmonary toxicity	1 (<1%)	0
Supraventricular tachycardia	1 (<1%)	0
White blood cell count increased	1 (<1%)	0

Incidences are based on the number of patients, not the number of events. Although a patient may have had 2 or more clinical AEs, the patient is counted only once in a category. The same patient may appear in different categories.
* Includes rash generalized, rash macular and rash pustular
[Source: ADAE.xpt]

SPI-GCF-301-PK:
In study SPI-GCF-301-PK, one patient (b) (6) discontinued study treatment due to AEs. This patient experienced discomfort, dysphagia, lip swelling, esophageal pain, pruritus generalized and urticaria within a two-day period during Cycle 3, which led to study drug discontinuation. All 6 events were assessed as unrelated to eflapegrastim treatment but related to docetaxel. All events resolved.

8.4.4. Significant Adverse Events

Pooled analysis of studies 301 and 302:
The overall incidence of grade 3 or higher TEAEs that occurred during the treatment period was also similar between the two arms (eflapegrastim: 74%, pegfilgrastim: 72%) in the pooled analysis of the two pivotal trials. The most frequently occurring ≥ grade 3 TEAEs (>10%) were

cytopenias; the incidences were similar between the two arms (lymphopenia [eflapegrastim: 46%, pegfilgrastim: 47%], neutropenia [eflapegrastim: 46%, pegfilgrastim: 46%], leukopenia [eflapegrastim: 22%, pegfilgrastim: 25%]).

A total of 6 patients (eflapegrastim: 5 patients, pegfilgrastim: 1 patient) were reported to have experienced grade 3 white blood cell increased count that was considered study treatment related. Based on the CTCAE version 4.03, the criterion for Grade 3 WBC increased is WBC >100×10^9/L. However, the actual WBC values for these 6 patients were all <100×10^9/L and, therefore, did not actually meet the criterion for Grade 3 WBC increased.

Table 57 Pooled Analysis of 301 and 302: Grade 3 or Higher TEAEs in >1% of Patient in the Eflapegrastim Arm (Safety Population)

FMQ (Narrow)	Eflapegrastim (n=314)	Pegfilgrastim (n=326)
All	233 (74%)	235 (72%)
Lymphopenia[a]	146 (46%)	153 (47%)
Neutropenia[b]	145 (46%)	150 (46%)
Leukopenia[c]	69 (22%)	83 (25%)
Anemia[d]	22 (7%)	10 (3%)
Thrombocytopenia[e]	14 (4%)	4 (1%)
Bone pain	13 (4%)	4 (1%)
Febrile neutropenia	10 (3%)	9 (3%)
Hypokalemia	9 (3%)	3 (1%)
White blood cell count increased	6 (2%)	1 (<1%)
Back pain	6 (2%)	3 (1%)
Arthralgia	5 (2%)	3 (1%)
Dyspnea	5 (2%)	4 (1%)
Hypertension	5 (2%)	4 (1%)
Hypocalcemia	5 (2%)	2 (<1%)
Hyponatremia	5 (2%)	3 (1%)
Rash[f]	5 (2%)	4 (1%)
Pyrexia	5 (2%)	2 (<1%)
Diarrhea	4 (1%)	2 (<1%)
Fatigue	4 (1%)	4 (1%)
Syncope	4 (1%)	5 (2%)

a. Includes lymphocyte count decreased.
b. Includes neutrophil count decreased.
c. Includes white blood cell count decreased.
d. Includes hemoglobin decreased.
e. Includes platelet count decreased.

f. Includes rash generalized, rash maculo-papular, rash pustular.
Incidences are based on the number of patients, not the number of events. Although a patient may have had 2 or more clinical AEs, the patient is counted only once in a category. The same patient may appear in different categories.
[Source: ADAE.xpt]

SPI-GCF-301-PK:
Grade 3 or 4 AEs occurred in 77% of patients. The most common grade 3/4 AEs were lymphocyte count decreased/lymphopenia (50%) and neutrophil count decreased/neutropenia (19%). No other grade 3 or 4 AEs occurred in more than 1 patient.

8.4.5. Treatment Emergent Adverse Events and Adverse Reactions

Pooled analysis of studies 301 and 302:
Overall, the proportions of patients who experienced TEAEs were similar between the two arms (eflapegrastim: 98%, pegfilgrastim: 98%). It was reported, however, that more than 90% of patients in each arm experienced TEAEs that were assessed as related to docetaxel or cyclophosphamide.

The most frequently reported TEAEs (>10%) that occurred in the eflapegrastim arm and at least 5% greater incidence compared to the pegfilgrastim arm by SOC were blood and lymphatic system disorders (54% vs. 46%), metabolism and nutrition disorders (35% vs. 30%) and psychiatric disorders (26% vs. 21%).

Table 58 Pooled Analysis of 301 and 302: TEAEs in ≥ 10% of Patients in the Eflapegrastim Arm by SOC (Safety Population)

System Organ Class	Eflapegrastim (n=314)	Pegfilgrastim (n=326)
All	307 (98%)	320 (98%)
General disorders and administration site conditions	241 (77%)	249 (76%)
Gastrointestinal disorders	240 (76%)	246 (76%)
Musculoskeletal and connective tissue disorders	232 (74%)	229 (70%)
Skin and subcutaneous tissue disorders	196 (62%)	216 (66%)
Investigations	188 (60%)	182 (56%)
Blood and lymphatic system disorders	168 (54%)	151 (46%)
Nervous system disorders	164 (52%)	179 (55%)
Respiratory, thoracic and mediastinal disorders	119 (38%)	128 (39%)

Infections and infestations	113 (36%)	134 (41%)
Metabolism and nutrition disorders	111 (35%)	97 (30%)
Vascular disorders	93 (30%)	93 (29%)
Psychiatric disorders	80 (26%)	69 (21%)
Injury, poisoning and procedural complications	50 (16%)	47 (14%)
Eye disorders	41 (13%)	43 (13%)
Cardiac disorders	32 (10%)	40 (12%)

Incidences are based on the number of patients, not the number of events. Although a patient may have had 2 or more clinical AEs, the patient is counted only once in a category. The same patient may appear in different categories.
[Source: ADAE.xpt]

Grade 3 or 4 TEAEs occurred in 74% and 72% of patients in the eflapegrastim and pegfilgrastim arms, respectively (also see section 8.4.4). TEAEs that occurred in at least 10% of patients in the eflapegrastim arm and ≥ 5% greater incidence compared to the pegfilgrastim arm were constipation (28% vs. 22%), anemia (25% vs. 17%), myalgia (22% vs. 15%), arthralgia (21% vs. 15%), insomnia (18% vs. 13%), thrombocytopenia (14% vs. 5%) and leukocytosis (13% vs. 8%).

Table 59 SPI-GCF-301 and SPI-GCF-302: TEAEs that Occurred ≥ 10% of Patients in the Eflapegrastim Arm (Safety Population)

FMQ (Narrow)	Eflapegrastim (n=314)		Pegfilgrastim (n=326)	
	Any grade	Grade 3/4	Any grade	Grade 3/4
All	307 (98%)	233 (74%)	320 (98%)	235 (72%)
Fatigue[a]	181 (58%)	5 (2%)	192 (59%)	5 (2%)
Nausea	162 (52%)	1 (<1%)	166 (51%)	3 (1%)
Lymphopenia[b]	152 (48%)	146 (46%)	159 (49%)	153 (47%)
Neutropenia[c]	149 (47%)	145 (46%)	156 (48%)	150 (46%)
Alopecia	135 (43%)	2 (<1%)	136 (42%)	7 (2%)
Diarrhea	125 (40%)	4 (1%)	126 (39%)	2 (<1%)
Bone pain	119 (38%)	13 (4%)	121 (37%)	4 (1%)
Headache[d]	92 (29%)	1 (<1%)	90 (28%)	2 (<1%)
Constipation	88 (28%)	1 (<1%)	72 (22%)	3 (1%)
Leukopenia[e]	82 (26%)	69 (22%)	90 (28%)	83 (25%)
Anemia[f]	79 (25%)	22 (7%)	54 (17%)	10 (3%)
Pyrexia[g]	78 (25%)	5 (2%)	76 (23%)	2 (<1%)
Rash[h]	77 (25%)	6 (2%)	99 (30%)	6 (2%)
Myalgia	69 (22%)	2 (<1%)	49 (15%)	1 (<1%)
Arthralgia	66 (21%)	5 (2%)	48 (15%)	3 (1%)
Decreased appetite	61 (19%)	0	50 (15%)	0

Back pain	60 (19%)	6 (2%)	55 (17%)	3 (1%)
Insomnia	57 (18%)	1 (<1%)	43 (13%)	0
Edema peripheral[i]	57 (18%)	0	53 (16%)	0
Vomiting	54 (17%)	1 (<1%)	55 (17%)	4 (1%)
Abdominal pain[j]	53 (17%)	2 (<1%)	67 (21%)	4 (1%)
Dizziness[k]	50 (16%)	0	38 (12%)	0
Dysgeusia[l]	49 (16%)	1 (<1%)	49 (15%)	0
Dyspnea[m]	49 (16%)	5 (2%)	44 (13%)	4 (1%)
Thrombocytopenia[n]	44 (14%)	14 (4%)	17 (5%)	4 (1%)
				(b) (4)
Cough	(b) (4)	0	(b) (4)	0
Pain	37 (12%)	2 (<1%)	42 (13%)	3 (1%)
Pain in extremity	36 (11%)	1 (<1%)	42 (13%)	0
Stomatitis	36 (11%)	1 (<1%)	35 (11%)	0
Dyspepsia	34 (11%)	0	34 (10%)	0
Flushing	32 (10%)	2 (<1%)	27 (8%)	0
Pruritus[p]				(b) (4)

a. Includes asthenia, lethargy, malaise.
b. Includes lymphocyte count decreased.
c. Includes neutrophil count decreased.
d. Includes migraine, tension headache.
e. Includes white blood cell count decreased.
f. Includes hemoglobin decreased.
g. Includes body temperature increased.
h. Includes rash erythematous, rash generalized, rash macular, rash maculo-papular, rash papular, rash pruritic, rash pustular, rash vesicular, blister, catheter site rash, dermatitis, erythema multiforme, genital rash, skin exfoliation, skin reaction, urticaria, vulvovaginal rash.
i. Includes peripheral swelling
j. Includes abdominal pain lower, abdominal pain upper, abdominal discomfort, abdominal distension, abdominal rigidity.
k. Includes balance disorder, dizziness postural, presyncope, vertigo.
l. Includes ageusia, hypogeusia.
m. Includes dyspnea exertional
n. Includes pancytopenia, platelet count decreased.
o. Includes white blood cell count increased.
p. Includes anal pruritus, pruritus generalized, rash pruritic.
Incidences are based on the number of patients, not the number of events. Although a patient may have had 2 or more clinical AEs, the patient is counted only once in a category. The same patient may appear in different categories.
[Source: ADAE.xpt]

Treatment-emergent AEs considered related to the study treatment occurred more often in the eflapegrastim arm (76%) compared to the pegfilgrastim arm (67%). The most common study treatment related AEs (>10%) in both arms were generally consistent with the safety profile of myeloid growth factors which include musculoskeletal and connective tissue disorders and

increased white blood cell counts.

The most common treatment-related AEs in the eflapegrastim arm (≥ 5%) with at least 5% higher incidence compared to the pegfilgrastim arm were arthralgia (15% vs. 10%), myalgia (15% vs. 9%), back pain (14% vs. 9%), leukocytosis (11% vs. 6%) and diarrhea (9% vs. 3%).

Review comment: While most of "thrombocytopenia" and "platelet count decreased" events were assessed as not related to study treatment, when pooling these two preferred terms the incidence in the SPI-2012 arm was higher (14%) compared to the pegfilgrastim arm (5%) in the pooled analysis of studies 301 and 302 (Table 59). An information request was sent to the Applicant for an explanation. The Applicant responded as follows:

> *Although the pooled data shows that all grade thrombocytopenia/platelet count decreased was 14% in the Eflapegrastim Arm and 5% in the Pegfilgrastim Arm, Studies SPI-GCF-301 and SPI-GCF-302 show some variability in the severity across grades. Most of these events were Grade 1-2 (Eflapegrastim Arm-9%; Pegfilgrastim Arm-4%). In SPI-GCF-302, Grade 3 events were 6% in the Eflapegrastim Arm and 0% in the Pegfilgrastim Arm, whereas in SPI-GCF-301, the difference was less pronounced (3% vs 1%, respectively). Grade 4 events were reported in 1 patient in the Eflapegrastim Arm and 2 patients in the Pegfilgrastim Arm. All of these adverse events were transient and all patients recovered to Grade ≤1 by the beginning of the next cycle allowing administration of chemotherapy without dose reductions due to thrombocytopenia or platelet count decreased. Although the platelet counts in the pooled analysis trended lower in the Eflapegrastim Arm, bleeding events were actually higher in the Pegfilgrastim Arm (14%) compared to the Eflapegrastim Arm (10%). Of note, no serious adverse events of thrombocytopenia or platelet count decreased were reported across the Phase 3 studies or across treatment arms, and no patients received platelet transfusions. In conclusion, analysis of the pooled data for thrombocytopenia/platelet count decreased did not translate into a meaningful clinical impact.*

Table 60 Pooled Analysis of 301 and 302: Treatment-Related AEs in ≥ 5% of Patients in the Eflapegrastim Arm (Safety Population)

FMQ (Narrow)	Eflapegrastim (n=314)		Pegfilgrastim (n=326)	
	Any grade	Grade 3/4	Any grade	Grade 3/4
All	238 (76%)	52 (17%)	218 (67%)	30 (9%)
Bone pain	103 (33%)	11 (4%)	112 (34%)	2 (<1%)
Arthralgia	47 (15%)	5 (2%)	33 (10%)	2 (<1%)
Myalgia	47 (15%)	2 (1%)	30 (9%)	0
Back pain	43 (14%)	6 (2%)	29 (9%)	1 (<1%)
Leukocytosis[a]	35 (11%)	5 (2%)	20 (6%)	1 (<1%)
Headache[b]	33 (11%)	1 (<1%)	25 (8%)	2 (<1%)

Pain	24 (8%)	1 (<1%)	28 (9%)	3 (1%)
Fatigue[c]	29 (9%)	2 (1%)	37 (11%)	1 (<1%)
Diarrhea	27 (9%)	2 (1%)	11 (3%)	1 (<1%)
Nausea	25 (8%)	0	14 (4%)	0
Pyrexia[d]	25 (8%)	1 (<1%)	26 (8%)	1 (<1%)
Rash[e]	20 (6%)	3 (1%)	22 (7%)	2 (<1%)
Pain in extremity	18 (6%)	1 (<1%)	17 (5%)	0
Neutrophilia[f]	18 (6%)	1 (<1%)	10 (3%)	0

a. Includes white blood cell count increased.
b. Includes migraine and tension headache.
c. Includes asthenia, lethargy, malaise.
d. Includes body temperature increased.
e. Includes rash erythematous, rash generalized, rash maculo-papular, rash pruritic, rash pustular, dermatitis, skin exfoliation, urticaria.
f. Includes neutrophil count increased.
Incidences are based on the number of patients, not the number of events. Although a patient may have had 2 or more clinical AEs, the patient is counted only once in a category. The same patient may appear in different categories.
[Source: ADAE.xpt]

SPI-GCF-301-PK:

In study SPI-GCF-301-PK, all 26 patients experienced AEs. The most frequently reported AEs (≥20%) are shown in the table below. With a small sample size of study SPI-GCF-301-PK, the individual incidences of AEs were generally higher compared to pivotal studies 301 and 302.

Table 61 SPI-GCF-301-PK: TEAEs that Occurred ≥ 20% of Patients (Safety Population)

FMQ (Narrow)	Eflapegrastim (n=26)	
	Any grade	Grade 3 or 4
All	26 (100%)	20 (77%)
Fatigue	21 (81%)	1 (4%)
Nausea	17 (65%)	0
Diarrhea	16 (62%)	0
Headache	16 (62%)	1 (4%)
Constipation	15 (58%)	0
Alopecia	13 (50%)	0
Lymphopenia[a]	13 (50%)	13 (50%)
Dizziness	12 (46%)	0
Bone pain	11 (42%)	0
Abdominal pain[b]	10 (38%)	0
Back Pain	9 (35%)	0
Decreased appetite	8 (31%)	0
Dysgeusia	8 (31%)	0

Dyspnea	8 (31%)	0
Rash[c]	8 (31%)	1 (4%)
Vomiting	8 (31%)	1 (4%)
Hypoesthesia	7 (27%)	0
Insomnia	7 (27%)	0
Oropharyngeal pain	7 (27%)	0
Asthenia	6 (23%)	0
Chest Pain	6 (23%)	0
Musculoskeletal pain	6 (23%)	0
Nail discoloration	6 (23%)	0
Tachycardia	6 (23%)	0

a. Includes lymphocyte count decreased.
b. Includes abdominal pain upper
c. Includes rash generalized and rash pruritic.
Incidences are based on the number of patients, not the number of events. Although a patient may have had 2 or more clinical AEs, the patient is counted only once in a category. The same patient may appear in different categories.
[Source: ADAE.xpt]

8.4.6. Laboratory Findings

Pooled analysis of studies 301 and 302:
Post-baseline laboratory abnormalities that occurred during the treatment period are summarized in Table 62 and Table 63. The incidences of post-baseline laboratory abnormalities were generally similar between the arms except the incidences of patients who were "not graded" at baseline to grade 1/2 lymphocytes decreased (eflapegrastim: 44%, pegfilgrastim: 38%), grade 1/2 platelet count decreased (eflapegrastim: 71%, pegfilgrastim: 54%), grade 1/2 ALT (eflapegrastim: 24%, pegfilgrastim: 17%) and grade 1/2 ALP (eflapegrastim: 33%, pegfilgrastim: 7%) were higher in the eflapegrastim arm. In addition, the incidences of laboratory tests that were "not graded" were high. The Applicant states that this was due to results that did not qualify for the CTCAE term which were included in the "not graded" category.

Table 62 Pooled Analysis of 301 and 302: Shifts in Hematology Values by CTCAE From Baseline to Worst Grade During Treatment Period (Safety Population)

	Eflapegrastim (n=314)				Pegfilgrastim (n=326)			
		Worst On-study Toxicity Grade				Worst On-study Toxicity Grade		
	Baseline	Not graded (n)	Grade 1/2	Grade 3/4	Baseline	Not graded (n)	Grade 1/2	Grade 3/4
Hemoglobin decreased	Not graded*	13 (4%)	245 (78%)	8 (3%)	Not graded*	37 (11%)	238 (73%)	6 (2%)
	Grade 1	2 (<1%)	32 (10%)	9 (3%)	Grade 1	2 (<1%)	38 (12%)	2 (<1%)

	Grade 2	0	2 (<1%)	3 (1%)	Grade 2	0	2 (<1%)	1 (<1%)
	Grade 3	0	0	0	Grade 3	0	0	0
Lymphocytes decreased	Not graded	14 (4%)	138 (44%)	117 (37%)	Not graded	23 (7%)	123 (38%)	131 (40%)
	Grade 1	0	1 (<1%)	5 (2%)	Grade 1	0	5 (2%)	5 (2%)
	Grade 2	0	11 (4%)	26 (8%)	Grade 2	3	8 (2%)	21 (6%)
	Grade 3	0	0	2 (<1%)	Grade 3	0	1 (<1%)	6 (2%)
Neutrophils decreased	Not graded	98 (31%)	64 (20%)	146 (46%)	Not graded	104 (32%)	70 (21%)	150 (46%)
	Grade 1	0	3 (1%)	2 (<1%)	Grade 1	0	0	0
	Grade 2	0	1 (<1%)	0	Grade 2	0	0	1 (<1%)
	Grade 3	0	0	0	Grade 3	0	0	1 (<1%)
Platelets decreased	Not graded	77 (25%)	224 (71%)	9 (3%)	Not graded	143 (44%)	176 (54%)	3 (1%)
	Grade 1	0	2 (<1%)	1 (<1%)	Grade 1	0	2 (<1%)	1 (<1%)
	Grade 2	0	0	1 (<1%)	Grade 2	0	1 (<1%)	0
	Grade 3	0	0	0	Grade 3	0	0	0
White blood cells decreased	Not graded	91 (29%)	116 (37%)	100 (32%)	Not graded	101 (31%)	106 (33%)	116 (36%)
	Grade 1	1 (<1%)	3 (1%)	3 (1%)	Grade 1	0	0	0
	Grade 2	0	0	0	Grade 2	0	1 (<1%)	2 (<1%)
	Grade 3	0	0	0	Grade 3	0	0	0

*Not graded counts include evaluations that do not qualify for the CTCAE term.
[Source: Adapted from Sponsor's submission]

Table 63 Pooled Analysis of 301 and 302: Shifts in Chemistry Values by CTCAE From Baseline to Worst Grade During Treatment Period (Safety Population)

	Eflapegrastim (n=314)				Pegfilgrastim (n=326)			
		Worst On-study Toxicity Grade				Worst On-study Toxicity Grade		
	Baseline	Not graded (n)	Grade ½	Grade ¾	Baseline	Not graded (n)	Grade ½	Grade ¾
ALT	Not graded*	210 (67%)	74 (24%)	0	Not graded*	239 (73%)	55 (17%)	2 (<1%)
	Grade 1	15 (5%)	14 (4%)	1 (<1%)	Grade 1	8 (2%)	22 (7%)	0
	Grade 2	0	0	0	Grade 2	0	0	0
	Grade 3	0	0	0	Grade 3	0	0	0
ALP	Not graded	189 (60%)	103 (33%)	0	Not graded	286 (88%)	22 (7%)	0
	Grade 1	0	22 (7%)	0	Grade 1	2 (<1%)	16 (5%)	0
	Grade 2	0	0	0	Grade 2	0	0	0
	Grade 3	0	0	0	Grade 3	0	0	0
AST	Not graded	273 (87%)	29 (9%)	0	Not graded	279 (86%)	27 (8%)	1 (<1%)
	Grade 1	5 (2%)	7 (2%)	0	Grade 1	8 (2%)	11 (3%)	0
	Grade 2	0	0	0	Grade 2	0	0	0

	Grade 3	0	0	0	Grade 3	0	0	0
Bilirubin	Not graded	311 (99%)	1 (<1%)	0	Not graded	320 (98%)	4 (1%)	0
	Grade 1	1 (<1%)	1 (<1%)	0	Grade 1	1 (<1%)	0	0
	Grade 2	0	0	0	Grade 2	1 (<1%)	0	0
	Grade 3	0	0	0	Grade 3	0	0	0
Creatinine	Not graded	300 (96%)	6 (2%)	0	Not graded	306 (94%)	13 (4%)	0
	Grade 1	1 (<1%)	6 (2%)	0	Grade 1	3 (1%)	4 (1%)	0
	Grade 2	0	1 (<1%)	0	Grade 2	0	0	0
	Grade 3	0	0	0	Grade 3	0	0	0
Cholesterol increased	Not graded	299 (95%)	6 (2%)	0	Not graded	303 (93%)	10 (3%)	0
	Grade 1	3 (1%)	2 (<1%)	0	Grade 1	0	3 (1%)	0
	Grade 2	3 (1%)	1 (<1%)	0	Grade 2	4 (1%)	5 (2%)	1 (<1%)
	Grade 3	0	0	0	Grade 3	0	0	0
Calcium decreased	Not graded	279 (89%)	23 (7%)	5 (2%)	Not graded	297 (91%)	22 (7%)	2 (<1%)
	Grade 1	2 (<1%)	0	0	Grade 1	2 (<1%)	3 (1%)	0
	Grade 2	1 (<1%)	2 (<1%)	0	Grade 2	0	0	0
	Grade 3	1 (<1%)	0	1 (<1%)	Grade 3	0	0	0
Potassium decreased	Not graded	271 (86%)	24 (8%)	3 (1%)	Not graded	279 (86%)	23 (7%)	2 (<1%)
	Grade 1	5 (2%)	9 (3%)	1 (<1%)	Grade 1	11 (3%)	7 (2%)	2 (<1%)
	Grade 2	0	0	0	Grade 2	0	0	1 (<1%)
	Grade 3	0	1 (<1%)	0	Grade 3	0	1 (<1%)	0
Sodium decreased	Not graded	267 (85%)	23 (7%)	2 (<1%)	Not graded	273 (84%)	24 (7%)	1 (<1%)
	Grade 1	8 (3%)	13 (4%)	1 (<1%)	Grade 1	8 (2%)	17 (5%)	1 (<1%)
	Grade 2	0	0	0	Grade 2	0	0	0
	Grade 3	0	0	0	Grade 3	0	1 (<1%)	1 (<1%)

*Not graded counts include evaluations that do not qualify for the CTCAE term.
[Source: Adapted from Sponsor's submission]

The Applicant provided plots of mean ANC over time in Cycles 1, 2, 3, and 4. The Figure below shows the mean ANC over time using log transformed ANC values for study 301. Study 302 showed similar results. For both arms, the changes in median ANC over time showed similar biphasic trend (initial peak on Day 4, followed by a nadir around Day 6 to Day 8 before reaching the second mean ANC peak between Day 10 and Day 12) in all 4 cycles. The median and mean ANC returned to normal ranges by end-of-treatment after 4 cycles in both arms. The ANC peaks were generally higher in the eflapegrastim arm (with a higher second peak between Days 9 to 13) returning to near-normal values by Day 15. No cases of splenic rupture were reported in either treatment arm during the treatment period.

Figure 3 Study 301: Mean (SE) ANC Over Time Using Log Transformed ANC Values

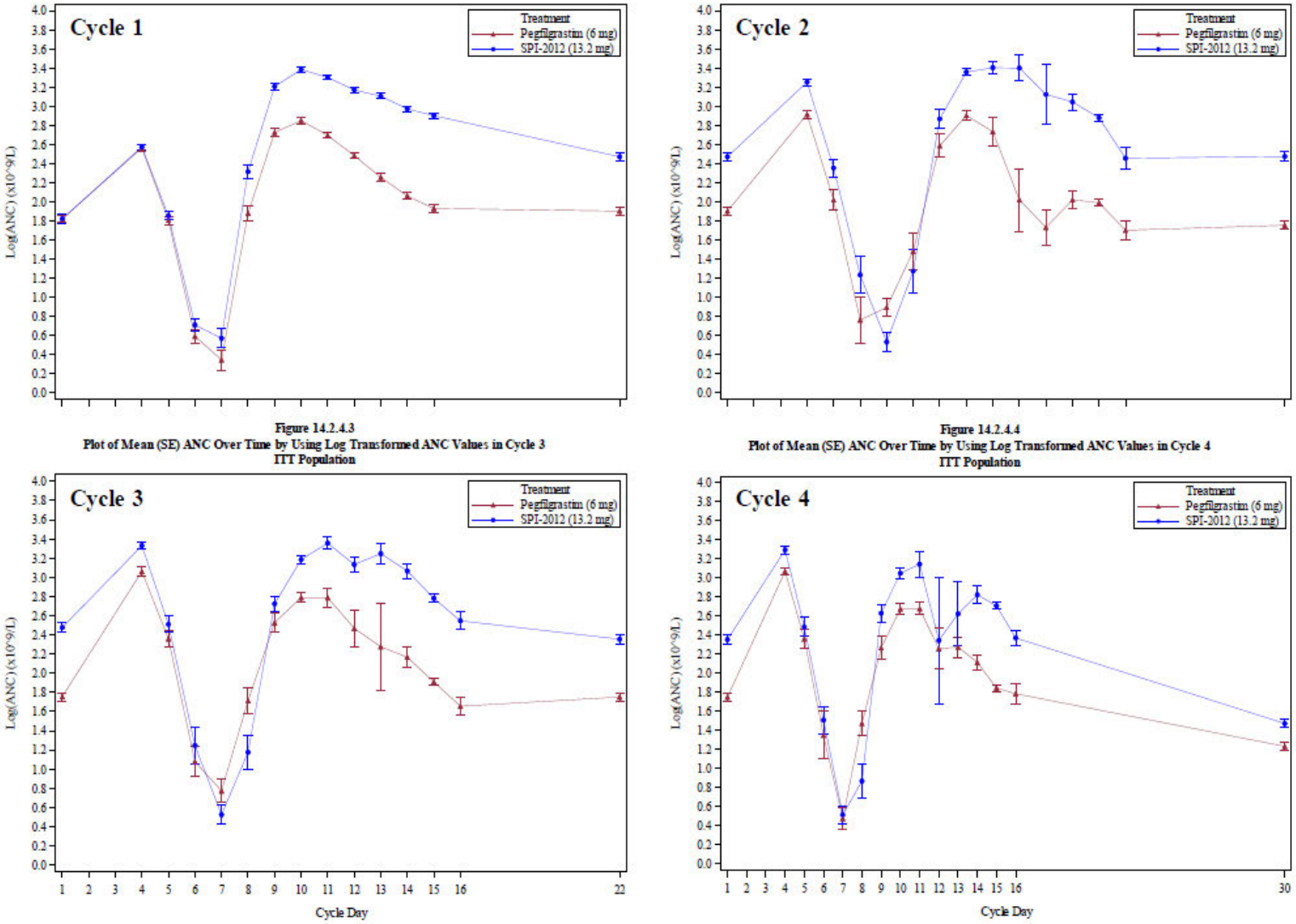


Figure 14.2.4.3
Plot of Mean (SE) ANC Over Time by Using Log Transformed ANC Values in Cycle 3
ITT Population

Figure 14.2.4.4
Plot of Mean (SE) ANC Over Time by Using Log Transformed ANC Values in Cycle 4
ITT Population

[Source: CSR]

8.4.7. Vital Signs

In studies 301 and 302, vital signs included systolic and diastolic blood pressure, heart rate, and body temperature. Vital signs were to be recorded prior to treatment and 30 and 60 minutes after drug administration on Day 2 of each cycle. Temperature was to be checked twice daily throughout the study. In studies 301 and 302, the mean and median changes in vital signs from baseline were similar between the two arms.

Hypotension occurred in 21 patients (7%) and 14 patients (4%) in the eflapegrastim and pegfilgrastim arms, respectively. Hypertension was reported in 11 patients (4%) and 13 patients (4%) in the eflapegrastim and pegfilgrastim arms, respectively. No cases of serious hypotension

or hypertension were reported in the eflapegrastim arm.

8.4.8. Electrocardiograms (ECGs)

In studies 301 and 302, ECG analyses were not conducted. However, in the pooled analysis of studies 301 and 302, similar proportion of patients experienced AEs in the cardiac disorders SOC (eflapegrastim: 10%, pegfilgrastim: 12%).

Table 64 Pooled Analysis of 301 and 302: Cardiac AEs (Safety Population)

Preferred Terms	Eflapegrastim (n=314)	Pegfilgrastim (n=326)
All	32 (10%)	40 (12%)
Tachycardia	16 (5%)	16 (5%)
Palpitations	12 (4%)	11 (3%)
Sinus tachycardia	6 (2%)	6 (2%)
Bradycardia	2 (<1%)	5 (2%)
Cardiac arrest	1 (<1%)	1 (<1%)
Cardiac failure chronic	1 (<1%)	0
Cardiac failure congestive	1 (<1%)	1 (<1%)
Left ventricular dysfunction	1 (<1%)	0
Myocardial infarction	1 (<1%)	1 (<1%)
Supraventricular tachycardia	1 (<1%)	0
Ventricular arrhythmia	1 (<1%)	0
Angina pectoris	1 (<1%)	1 (<1%)
Atrial fibrillation	0	5 (2%)
Acute myocardial infarction	0	1 (<1%)
Pericarditis	0	1 (<1%)
Sinus bradycardia	0	2 (<1%)

Incidences are based on the number of patients, not the number of events. Although a patient may have had 2 or more clinical AEs, the patient is counted only once in a category. The same patient may appear in different categories.
[Source: ADAE.xpt]

8.4.9. QT

In study SPI-GCF-301-PK, ECG data was recorded from the 26 enrolled patients. The mean changes from baseline in heart rate, PR and QRS intervals showed minimal clinical relevance. The mean change from baseline in QTcF interval was 8 ms and 4 ms at 10 hours and 24 hours, respectively, with upper 90% confidence intervals of 10 to 12 ms.

Review comment: According to Guidance for Industry, E14 Clinical Evaluation of QT/QTc Interval

Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs, the threshold level of regulatory concern for QT/QTc prolongation is around 5 ms as evidenced by an upper bound of the 95% confidence interval around the mean effect on QTc of 10 ms in healthy volunteers. Drugs that prolong the mean QT/QTc interval by around 5 ms or less do not appear to cause TdP. The data on drugs that prolong the mean QT/QTc interval by more than around 5 and less than 20 ms are inconclusive, but some of these compounds have been associated with proarrhythmic risk. Drugs that prolong the mean QT/QTc interval by >20 ms have a substantially increased likelihood of being proarrhythmic.

There is no evidence that G-CSF products prolong QTc interval to date.

The table below summarizes the mean changes in cardiac parameters.

Table 65 SPI-GCF-301-PK: Mean Changes in Cardiac Parameters from Baseline to Cycle 1, Day 2 Post-dose Time Points (Safety Population)

Parameter	10 hours post-dose (n=26)	24 hours post-dose (n=26)
Heart rate (bpm)	1.6	7.2
PR (ms)	-3.6	-3.4
QRS (ms)	1.1	-0.3
QT (ms)	5.7	-8.0
QTcF (ms)	8.3 (uCI=11.5)	4.0 (uCI=9.7)

bpm = beats per minute; ECG = electrocardiogram; ms = milliseconds; QTcF = Fridericia's correction; uCI= upper 90% confidence interval.
Results are based on the replicate mean of the ECGs at Baseline (Cycle 1, Day 2, pre-dose) and on the replicate means obtained at 10 hours post-dose and 24 hours post-dose.
[Source: SCS]

No patients were reported with an abnormal U wave or a new QTcF >500 ms or a >60 ms change from baseline for QTcF. A total of 2 patients (8%) had a 30 to 60 ms change in QTcF from baseline.

A total of 2 patients (patients (b) (6) had nonspecific ST- and T-wave changes from baseline. It has been reported that patient (b) (6) had no cardiac AEs. Patient (b) (6) experienced dizziness/lightheadedness (on Cycle 1, Day 1 before receiving eflapegrastim) and chest discomfort (on Cycle 1, Day 12). Neither AE was assessed as related to eflapegrastim. No other patients developed new ECG morphologic events. The narrative for patient (b) (6) is provided below:

> Patient (b) (6) was a 55-year old White female with a history of depression and obesity taking lorazepam, sertraline, and propranolol for depression and taking Ritalin and topiramate for obesity. The patient experienced Grade 1 dizziness on Cycle 1, Day 1 (before receiving eflapegrastim) that lasted 10 days and had a second episode of Grade 1 dizziness

on Cycle 2, Day 4 that was ongoing at the End-of-Treatment Visit. No treatment was given for these adverse events. Another AE of Grade 1 chest discomfort was reported on Cycle 1, Day 12 that lasted 2 days and resolved without treatment. The patient also experienced an episode of Grade 2 syncope of one day duration during the follow-up period, 34 days after the last dose of eflapegrastim, which resolved without treatment. These events were not assessed as serious or related to eflapegrastim. This patient had ST-T wave changes from baseline and had self-limiting events of dizziness x 2, chest discomfort and a syncopal episode with stable vital signs at each event. The association between the non-specific ST-T wave ECG changes and these events could not be established. In addition, lorazepam, sertraline, propranolol, Ritalin, and topiramate all can cause dizziness. Sertraline can cause syncope.

Eflapegrastim had no significant effect on cardiac repolarization as measured by the slope of eflapegrastim concentration in the PK-pharmacodynamic model (p=0.6167). The model predicted a 6 ms change from baseline in QTcF at a mean Cmax of 193 ng/mL (upper CI: 9 ms).

A QT consult review was requested to the Interdisciplinary Review Team (IRT) for cardiac safety studies. Overall comments were as follows:

1) The available ECG and cardiac safety data do not suggest an unexpected effect on the QTc interval. The findings in Study SPI-GCF-301-PK are consistent with prior experience for large targeted proteins which have low likelihood of direct interaction with cardiac ion channels.
2) The Applicant did not propose any QT-related language on the proposed product label. This is consistent with the IRT's practice for other monoclonal antibodies and large proteins for which a dedicated QT study is usually not conducted.

Also see Clinical Pharmacology and QT-IRT reviews.

8.4.10. Immunogenicity

In studies 301 and 302, three different assays were used for immunogenicity assessment: a bridging enzyme-linked immunosorbent assay (ELISA) for anti-eflapegrastim antibodies, a cell-based assay to detect eflapegrastim-neutralizing antibodies (NAb), and a direct-binding ELISA to test all samples for antibodies to polyethylene glycol (PEG). The Applicant provided the immunogenicity results for studies 301 and 302. To be considered evaluable for ADA, samples from both baseline and at least one post-dose were required.

At baseline, a total of 306 and 315 patients in the eflapegrastim and pegfilgrastim arms, respectively, had immunogenicity results (a total of 6 [2%] and 8 patients [2.5%] in the eflapegrastim and pegfilgrastim arms, respectively, were ADA positive at baseline). Among these patients, a total of 297 and 306 patients in the eflapegrastim and pegfilgrastim arms, respectively, had at least one post-dose result and were considered evaluable for treatment-

emergent antibodies. Of these evaluable patients, a total of 28 patients (9.4%) and 10 patients (3.3%) in the eflapegrastim and pegfilgrastim arms, respectively, developed antibodies following treatment.

In study 301, the incidences of either treatment-induced or treatment-boosted ADAs to eflapegrastim were 8.7% in the eflapegrastim arm and 2.6% in the pegfilgrastim arm. In study 302, the incidences were 10.5% and 4.4% in the eflapegrastim and pegfilgrastim arms, respectively. According to the Applicant, the differences could have been due to the assay being optimized for detecting anti-eflapegrastim antibodies.

The incidence of treatment-emergent anti-PEG antibodies was higher in the pegfilgrastim arm in both studies (301 [eflapegrastim: 52%, pegfilgrastim: 63%], 302 [eflapegrastim: 40%, pegfilgrastim: 65%]). There was one patient in the eflapegrastim arm in study 301 who developed treatment-induced neutralizing antibodies. It has been reported that the formation of Nab in this patient had no effect on the duration of severe neutropenia (DSN) in any cycle. No other cases of Nab were reported in studies 301 and 302.

Table 66 Study 301: Summary of Immunogenicity Incidence

Assay	SPI-2012		Pegfilgrastim		Difference p-Value
	n/N	%	n/N	%	
Treatment-Induced or Treatment-Boosted Antibodies to SPI-2012	16/183	8.7%	5/193	2.6%	<0.05
Treatment-Emergent Anti-PEG Antibodies Titer	82/157	52.2%	95/152	62.5%	0.061
Treatment-Induced Neutralizing Antibodies	1/183 [a]	0.5%	0/193	0.0%	NA

Abbreviations: n = number of patients with positive results; N = number of evaluable patients; NA = not available; PEG = polyethylene glycol

a) Positive only at one out of seven timepoints

[Source: Study 301 CSR]

Table 67 Study 302: Summary of Immunogenicity Incidence

Assay	SPI-2012		Pegfilgrastim		Difference p-Value
	n/N	%	n/N	%	
Treatment-Induced or Treatment-Boosted Antibodies to SPI-2012	12/114	10.5	5/113	4.4	0.081
Treatment-Emergent Anti-PEG Antibodies Titer	44/111	39.6	72/111	64.9	<0.001
Treatment-Induced Neutralizing Antibodies	0/114	0.0	0/113	0.0	NA

Abbreviations: n = number of patients with positive results; N = number of evaluable patients; NA = not available; PEG = polyethylene glycol

[Source: Study 302 CSR]

In studies 301 and 302, patients who were positive to ADAs to eflapegrastim were evaluated for development of hypersensitivity reactions and correlation to DSN. The Preferred Terms searched for potential hypersensitivity reactions were: rash, rash generalized, rash maculopapular, rash macular, dermatitis, rash pruritic, urticaria, anaphylaxis, injection site reactions and arthralgia. There was no apparent temporal correlation between the formation of ADAs and the development of hypersensitivity reactions or DSN in any cycle in the eflapegrastim arm.

8.4.11. Long-Term Safety Follow-up

The long-term follow-up period was defined as from the End-of-Treatment Visit (35 [±5] days after the last dose of study treatment) through 12 months after the last dose of study treatment. In study 301, a similar proportion of patients completed the 12-Month follow-up period in the two arms (eflapegrastim: 72%, pegfilgrastim: 69%), while in study 302, a higher proportion of patients in the eflapegrastim completed the study (eflapegrastim: 81%, pegfilgrastim: 71%). See Table 12.

When pooling studies 301 and 302, the incidence of TEAEs was similar between the two arms (eflapegrastim: 41%, pegfilgrastim: 40%). The incidence of TESAEs (eflapegrastim: 3%, pegfilgrastim: 2%) and grade 3/4 TEAEs (eflapegrastim: 6%, pegfilgrastim: 5%) were also similar between the arms. One patient (b) (6) in the pegfilgrastim arm died due to disease progression. There were no AEs that had a fatal outcome.

Table 68 Pooled Analysis of 301 and 302: Overall Summary of Safety During the 12-Month Follow-up Period (Safety Population)

	Eflapegrastim (n=314)	Pegfilgrastim (n=326)
Deaths	0	1 (<1%)
TESAEs	10 (3%)	6 (2%)
Study treatment-related TESAEs	0	0
TEAEs	128 (41%)	131 (40%)
Study treatment-related TEAEs	9 (3%)	7 (2%)
Grade 3 or 4 TEAEs	18 (6%)	16 (5%)
AEs leading to any study drug withdrawal	0	0
AEs assessed as related to docetaxel and cyclophosphamide		
Docetaxel	41 (13%)	31 (10%)
Cyclophosphamide	33 (11%)	22 (7%)

[Source: ADAE.xpt]

During the 12-month follow-up period, the most common TEAEs (≥ 5%) that occurred in the eflapegrastim arm were arthralgia, hot flush and fatigue. The table below summarizes the TEAEs that occurred during the follow-up period reported in at least 5 patients in the eflapegrastim arm.

Table 69 Pooled Analysis of 301 and 302: TEAEs that Occurred During the 12-Month Follow-up Period in ≥ 5 Patients in the Eflapegrastim Arm (Safety Population)

Preferred Terms	Eflapegrastim (n=314)	Pegfilgrastim (n=326)
All	128 (41%)	131 (40%)
Arthralgia	24 (8%)	18 (6%)
Hot flush	16 (5%)	19 (6%)
Fatigue	14 (5%)	11 (3%)
Radiation skin injury	12 (4%)	13 (4%)
Nausea	12 (4%)	8 (3%)
Breast pain	10 (3%)	6 (2%)
Neuropathy peripheral	9 (3%)	5 (2%)
Pain in extremity	9 (3%)	7 (2%)
Myalgia[a]	8 (3%)	16 (5%)
Rash[b]	8 (3%)	4 (1%)
Cough	8 (3%)	8 (3%)

Dizziness	8 (3%)	3 (1%)
Bone pain	7 (2%)	6 (2%)
Back pain	6 (2%)	11 (3%)
Insomnia	6 (2%)	6 (2%)
Abdominal pain	6 (2%)	4 (1%)
Dyspnea	6 (2%)	2 (<1%)
Depression	5 (2%)	6 (2%)
Headache	5 (2%)	6 (2%)
Lymphoedema	5 (2%)	6 (2%)
Edema peripheral	5 (2%)	5 (2%)
Upper respiratory tract infection	5 (2%)	2 (<1%)
Vomiting	5 (2%)	2 (<1%)

a. Includes muscle spasm, muscular weakness and musculoskeletal pain.
b. Includes rash erythematous, rash generalized, rash maculo-papular, rash pustular.
Incidences are based on the number of patients, not the number of events. Although a patient may have had 2 or more clinical AEs, the patient is counted only once in a category. The same patient may appear in different categories.
[Source: ADAE.xpt]

During the 12-month follow-up period, a total of 11 SAEs occurred in 10 patients in the eflapegrastim arm in studies 301 and 302. The SAEs were cellulitis, incision site cellulitis, pyrexia, neutropenia, febrile neutropenia, embolism, non-cardiac chest pain, abdominal pain, dyspnea, myocardial infarction and cardiac arrest. None of these SAEs were considered related to the study treatment.

8.5. Analysis of Submission-Specific Safety Issues

Based on the safety profile of myeloid growth factors and prior clinical experience with eflapegrastim, adverse events of specific interest were the following: musculoskeletal pain, injection site reactions, hypersensitivity reactions, splenic rupture, acute respiratory distress syndrome (ARDS), serious allergic reactions, sickle cell crises in patients with sickle cell disorders, glomerulonephritis, leukocytosis, capillary leak syndrome, potential for tumor growth stimulatory effects on malignant cells and aortitis.

8.5.1. Musculoskeletal Pain

Pooled analysis of studies 301 and 302:
Overall, the incidences of any grade and grade 3/4 musculoskeletal pain TEAEs were similar between the two arms (any grade [eflapegrastim: 79%, pegfilgrastim: 77%], grade 3/4 (eflapegrastim: 8%, pegfilgrastim: 4%]). Musculoskeletal pain TEAEs that occurred at a greater incidence in the eflapegrastim arm included arthralgia (27% vs. 19%) and myalgia (23% vs. 17%). No ≥ grade 4 TEAEs were reported in either arm.

The most frequently reported TEAE related to musculoskeletal pain in both arms was bone pain (eflapegrastim: 39%, pegfilgrastim: 38%). One patient in the eflapegrastim arm had serious bone pain that occurred in Cycle 3 and resolved in 5 days with acetaminophen treatment. All TEAEs of grade 3 bone pain resolved with the use of non-steroidal anti-inflammatory agents and other analgesics. Several patients received antihistamines prophylactically.

Other serious musculoskeletal pain TEAEs that occurred in studies 301 and 302 were back pain (eflapegrastim: 1 patient, pegfilgrastim: 1 patient), arthralgia (1 patient in eflapegrastim arm) and muscular weakness (1 patient in pegfilgrastim arm).

Table 70 SPI-GCF-301 and SPI-GCF-302: Musculoskeletal Pain TEAEs that Occurred in ≥ 4% of Patients in the Eflapegrastim Arm (Safety Population)

	Eflapegrastim (n=314)		Pegfilgrastim (n=326)	
	Any grade	Grade 3/4	Any grade	Grade 3/4
All	249 (79%)	25 (8%)	251 (77%)	12 (4%)
General Disorders and Administration Site Conditions	38 (12%)	2 (<1%)	43 (13%)	3 (1%)
Pain	38 (12%)	2 (<1%)	43 (13%)	3 (1%)
Musculoskeletal and Connective Tissue Disorders	238 (76%)	24 (8%)	239 (73%)	9 (3%)
Bone pain	122 (39%)	13 (4%)	123 (38%)	4 (1%)
Arthralgia	84 (27%)	5 (2%)	61 (19%)	3 (1%)
Myalgia	71 (23%)	2 (<1%)	54 (17%)	1 (<1%)
Back pain	65 (21%)	7 (2%)	64 (20%)	3 (1%)
Pain in extremity	44 (14%)	1 (<1%)	47 (14%)	1 (<1%)
Muscle spasms	15 (5%)	0	12 (4%)	0
Muscular weakness	13 (4%)	2 (<1%)	14 (4%)	1 (<1%)

Incidences are based on the number of patients, not the number of events. Although a patient may have had 2 or more clinical AEs, the patient is counted only once in a category. The same patient may appear in different categories.
[Source: ADAE.xpt]

8.5.2. Injection Site Reactions

Pooled analysis of studies 301 and 302:

In studies 301 and 302, a total of 8 patients (3%) and 1 patient (<1%) in the SPI- eflapegrastim and pegfilgrastim arms, respectively, reported injection site reactions. All cases resolved and none of these reactions were serious or grade 3/4 in severity.

Table 71 SPI-GCF-301 and SPI-GCF-302: Injection Site Reactions that (Safety Population)

	Eflapegrastim (n=314)		Pegfilgrastim (n=326)	
	Any grade	Grade 3/4	Any grade	Grade 3/4
All	8 (3%)	0	1 (<1%)	0
General disorders and administration site conditions	8 (3%)	0	1 (<1%)	0
Injection site pain	6 (2%)	0	1 (<1%)	0
Injection site reaction	2 (<1%)	0	0	0

Incidences are based on the number of patients, not the number of events. Although a patient may have had 2 or more clinical AEs, the patient is counted only once in a category. The same patient may appear in different categories.
[Source: ADAE.xpt]

8.5.3. Hypersensitivity Reactions

Pooled analysis of studies 301 and 302:
The overall incidence of hypersensitivity reactions was slightly higher in the pegfilgrastim arm (eflapegrastim: 30%, pegfilgrastim: 35%) while grade 3 or 4 events were similar between the two arms (eflapegrastim: 2%, pegfilgrastim: 2%). The most commonly reported hypersensitivity reactions (≥5%) were rash (eflapegrastim: 15%, pegfilgrastim: 17%) and urticaria (eflapegrastim: 4%, pegfilgrastim: 5%). A total of 4 patients (eflapegrastim: 1 patient [drug eruption], pegfilgrastim: 3 patients [hypersensitivity vasculitis, hypersensitivity and rash generalized, 1 patient each]) had serious hypersensitivity reactions. No grade 4 events were reported.

Most of the hypersensitivity reactions, however, were assessed as not related to study treatment; a total of 22 patients (7%) and 23 patients (7%) in the eflapegrastim and pegfilgrastim arms, respectively, had hypersensitivity reactions that were considered study treatment-related.

Table 72 SPI-GCF-301 and SPI-GCF-302: Potential Hypersensitivity Reactions that Occurred in **≥1%** of Patients in the Eflapegrastim Arm (Safety Population)

	Eflapegrastim (n=314)		Pegfilgrastim (n=326)	
	Any grade	Grade 3/4	Any grade	Grade 3/4
All	95 (30%)	7 (2%)	113 (35%)	7 (2%)

Skin and Subcutaneous Tissue Disorders	82 (26%)	7 (2%)	96 (29%)	5 (2%)
Rash	46 (15%)	2 (<1%)	56 (17%)	1 (<1%)
Urticaria	14 (4%)	1 (<1%)	17 (5%)	2 (<1%)
Rash maculopapular	10 (3%)	2 (<1%)	11 (3%)	0
Dermatitis	7 (2%)	0	4 (1%)	0
Rash generalized	4 (1%)	1 (<1%)	4 (1%)	2 (<1%)
Rash erythematous	4 (1%)	0	0	0
Immune System Disorders	10 (3%)	0	8 (2%)	1 (<1%)
Hypersensitivity	9 (3%)	0	8 (2%)	1 (<1%)
Eye Disorders	5 (2%)	0	5 (2%)	0
General Disorders and Administration Site Conditions	4 (1%)	0	4 (1%)	0

Incidences are based on the number of patients, not the number of events. Although a patient may have had 2 or more clinical AEs, the patient is counted only once in a category. The same patient may appear in different categories.
[Source: ADAE.xpt]

8.5.4. Other Adverse Events of Special Interest

Pooled analysis of studies 301 and 302:
Other AEs of specific interest were splenic rupture, acute respiratory distress syndrome (ARDS), sickle cell crises in patients with sickle cell disorders, glomerulonephritis, leukocytosis, capillary leak syndrome, potential for tumor growth stimulatory effects on malignant cells and aortitis.

In studies 301 and 302, a total of 2 patients in the pegfilgrastim arm developed signs of ARDS (1 patient) or capillary leak syndrome (1 patient). No patient in the eflapegrastim arm had ARDS or capillary leak syndrome.

One patient in the pegfilgrastim arm had thoracic aortic aneurysm considered not related to study treatment. No other TEAEs related to aortitis were identified in studies 301 and 302.

A total of 8 patients (3%) in the eflapegrastim arm and 3 patients (1%) in the pegfilgrastim arm developed TEAEs in the Neoplasms benign, malignant and unspecified SOC (eflapegrastim [benign breast neoplasm, metastases to lymph nodes, 2 patients each; and cancer pain, renal cell carcinoma, meningioma, uterine leiomyoma, 1 patient each], pegfilgrastim [benign ovarian tumor, meningioma and skin papilloma, 1 patient each]). None of the TEAEs were considered related to the study treatment.

No TEAEs of splenic rupture or glomerulonephritis were reported. Patients with sickle cell disease were not enrolled in studies 301 and 302. For leukocytosis see sections 8.4.4, 8.4.5 and 8.4.6.

8.6. Safety Analyses by Demographic Subgroups

Safety analyses by age:

Table 73 summarizes AEs that occurred by age (<65 years vs. ≥65 years) in studies 301 and 302. The incidences of all AEs, SAEs, AEs leading to withdrawal and AEs leading to death were similar between the two treatment arms in both <65 years and ≥65 years categories; and also similar between patients <65 years and ≥65 years among patients who received eflapegrastim.

Table 73 Pooled Analysis of 301 and 302: AEs by Age (<65 Years vs. **≥65** years) (Safety Population)

	Eflapegrastim (n=314)		Pegfilgrastim (n=326)	
	<65 years (n=192)	≥65 years (n=122)	<65 years (n=205)	≥65 years (n=121)
All AEs	186 (97%)	121 (99%)	201 (98%)	119 (98%)
Serious AEs	32 (17%)	24 (20%)	28 (14%)	23 (19%)
AEs leading to withdrawal	8 (4%)	5 (4%)	13 (6%)	8 (7%)
AEs leading to death	0	0	1 (<1%)	1 (<1%)

[Source: ADAE.xpt]

The table below summarizes AEs by age (<75 years vs. ≥75 years). The incidences of AEs, SAEs, AEs leading to death were similar between the two arms in both <75 years and ≥75 years categories. However, the incidence of AEs leading to withdrawal was higher in the pegfilgrastim arm (14%) compared to the eflapegrastim arm (6%) in the ≥75 years category (with small sample sizes [eflapegrastim: 18 patients, pegfilgrastim: 29 patients]).

Among patients who received eflapegrastim, the incidences of all AEs, AEs leading to withdrawal and AEs leading to death were also similar between patients <75 years and ≥75 years of age, except SAEs occurred more often in patients ≥75 years of age (33%) compared to patients <75 years of age (17%) with small number of patients in the ≥75 years category (n=18).

Table 74 Pooled Analysis of 301 and 302: AEs by Age (<75 Years vs. **≥75** years) (Safety Population)

	Eflapegrastim (n=314)		Pegfilgrastim (n=326)	
	<75 years (n=296)	≥75 years (n=18)	<75 years (n=297)	≥75 years (n=29)
All AEs	289 (98%)	18 (100%)	292 (98%)	28 (97%)
Serious AEs	51 (17%)	6 (33%)	43 (14%)	8 (28%)
AEs leading to withdrawal	12 (4%)	1 (6%)	17 (6%)	4 (14%)

AEs leading to death	0	0	1 (<1%)	1 (<1%)

[Source: ADAE.xpt]

Safety analyses by gender:
The number of males who received study treatment in studies 301 and 302 was too small (n=2) to conduct safety analysis by gender.

8.7. Specific Safety Studies/Clinical Trials

No specific safety studies were included in the BLA submission.

8.8. Additional Safety Explorations

8.8.1. Human Carcinogenicity or Tumor Development

In studies 301 and 302, 3% of patients in the eflapegrastim arm and 1% of patients in the pegfilgrastim arm developed TEAEs in the Neoplasms benign, malignant and unspecified SOC See section 8.5.4.

8.8.2. Human Reproduction and Pregnancy

No cases of pregnancies were reported.

8.8.3. Pediatrics and Assessment of Effects on Growth

Pediatric patients (age <18 years) were not included in the eflapegrastim studies. The safety and efficacy of eflapegrastim have not been evaluated in pediatric patients.

There is an Amended Agreed initial Pediatric Study Plan (iPSP) for eflapegrastim (waiver for neonates [0 to <1 month] and deferral for pediatric patients 1 month to <18 years of age). See the table below.

Table 75 Table of Clinical Studies for Eflapegrastim in Pediatric Patients

Age Group	Type of Study	Comments	Deferral Request Planned for the Study
Neonates (0-<1 month)	Waiver Requested	Solid tumors are extremely rare in this age group and studies are highly impracticable	-
1 month-<18 years	Phase 2 PK/PD Study	The objective of the study will be to evaluate the safety of **SPI-2012** in pediatric patients with solid tumors	Yes

[Source: Amended Agreed iPSP letter dated September 28, 2018]

The Applicant's estimated submission date for the Phase 2 pediatric protocol is March 2019, the estimated study initiation date is September 2020 and the estimated final report submission date for the Phase 2 protocol is December 2025.

Review comment: The protocol for the phase 2 safety and PK pediatric study, SPI-GCF-202, entitled "Multicenter, Open-Label, Phase 2 Study to Evaluate the Safety and Pharmacokinetics of Eflapegrastim in Pediatric Patients with Solid Tumors and Treated with Myelosuppressive Chemotherapy" was submitted on April 2, 2019. This deferred study will be a required postmarketing study.

Eflapegrastim is presented as 13.2 mg/0.6 mL (equivalent to (b) (4) solution in a single-dose prefilled syringe. According the agreed iPSP letter, (b) (4)

Review comment: The concentration of eflapegrastim is 13.2 mg/0.6 mL (22 mg/mL). In study SPI-GCF-202, eflapegrastim will be supplied (b) (4)

Refer to the Amended Agreed iPSP letter dated September 28, 2018 (under IND 103461).

8.8.4. Overdose, Drug Abuse Potential, Withdrawal, and Rebound

No cases of overdose, withdrawal or rebound effects with eflapegrastim have been reported. Overdose of eflapegrastim may result in leukocytosis and bone pain. There is no known potential abuse with eflageprastim. Withdrawal effects is not expected considering the pharmacologic effects of eflapegrastim.

8.9. Safety in the Postmarket Setting

8.9.1. Safety Concerns Identified Through Postmarket Experience

Eflapegrastim is a new molecular entity and is not approved for marketing in any country at this time. There is no post-marketing experience with eflapegrastim.

8.9.2. Expectations on Safety in the Postmarket Setting

Safety in the postmarket setting is expected to be similar to that observed in the clinical trials.

8.10. Integrated Assessment of Safety

The safety assessment of eflapegrastim was primarily based on a total of 640 patients (eflapegrastim: 314 patients, pegfilgrastim: 326 patients) who participated in the two phase 3 pivotal trials (SPI-GCF-301 and SPI-GCF-302) for the management of chemotherapy-induced neutropenia in patients with early-stage breast cancer treated with docetaxel and cyclophosphamide (TC). Patients in the eflapegrastim arm received 13.2 mg/0.6 mL SQ injections on Day 2 of each cycle (24 hours after the last dose of TC chemotherapy) for a total of 4 cycles. The median exposure of eflapegrastim in both studies was 4 cycles (range: 1, 4). The median exposures of both docetaxel and cyclophosphamide were also 4 cycles (range: 1, 4). The safety review was primarily based on the pooled data of the two phase 3 randomized trials. The safety findings were as follows:

- There were no deaths among patients who received eflapegrastim in studies SPI-GCF-301 and SPI-GCF-302.
- With regard to SAEs, the overall incidences were similar between the two arms (eflapegrastim: 15%, pegfilgrastim: 15%). Serious AEs that occurred in more than 2 patients in the eflapegrastim arm were pyrexia, sepsis, febrile neutropenia, diarrhea and chest pain.
- The incidence of patients that discontinued from the study due to AEs was also similar between the arms (eflapegrastim:4%, pegfilgrastim: 6%). Rash was the only AE that led to treatment discontinuation in more than 1 patient in the eflapegrastim arm.
- The incidence of grade 3 or higher AEs that occurred during the treatment period was 74% and 72% in the eflapegrastim and pegfilgrastim arms, respectively. The most frequently occurring ≥ grade 3 AEs (>10%) were cytopenias and the incidences were similar between the two arms (lymphopenia [eflapegrastim: 46%, pegfilgrastim: 47%], neutropenia [eflapegrastim: 46%, pegfilgrastim: 46%], leukopenia [eflapegrastim: 22%, pegfilgrastim: 25%]).
- The incidences of TEAEs were similar between the two arms (eflapegrastim: 98%, pegfilgrastim: 98%). Most of the TEAEs (>90%) in each arm, however, were considered related to docetaxel or cyclophosphamide therapy. The most common TEAEs (≥10%) that occurred in the eflapegrastim arm and ≥ 5% greater incidence compared to the pegfilgrastim arm were constipation (28% vs. 22%), anemia (25% vs. 17%), myalgia (22% vs. 15%), arthralgia (21% vs. 15%), insomnia (18% vs. 13%), thrombocytopenia (14% vs. 5%) and leukocytosis (13% vs. 8%).
- The incidence of TEAEs considered related to the study treatment was higher in the eflapegrastim arm (76%) compared to the pegfilgrastim arm (67%). The most common study treatment related AEs (>10%) in both arms were consistent with the safety profile

of myeloid growth factors which include musculoskeletal and connective tissue disorders and increased white blood cell counts. The most common study treatment-related AEs in the eflapegrastim arm (≥ 5%) with at least 5% higher incidence compared to the pegfilgrastim arm were arthralgia (15% vs. 10%), myalgia (15% vs. 9%), back pain (14% vs. 9%), leukocytosis (11% vs. 6%) and diarrhea (9% vs. 3%).

- Based on the safety profile of myeloid growth factors and prior clinical experience with eflapegrastim, adverse events of specific interest were the following: musculoskeletal pain, injection site reactions, hypersensitivity reactions, splenic rupture, acute respiratory distress syndrome (ARDS), serious allergic reactions, sickle cell crises in patients with sickle cell disorders, glomerulonephritis, leukocytosis, capillary leak syndrome, potential for tumor growth stimulatory effects on malignant cells and aortitis. The overall incidences of musculoskeletal pain, injection site reactions, and TEAEs in the neoplasms benign, malignant and unspecified SOC were similar between the two arms while the incidence of hypersensitivity reactions was slightly higher in the pegfilgrastim arm (eflapegrastim: 30%, pegfilgrastim: 35%). No cases of splenic rupture, ARDS, glomerulonephritis, capillary leak syndrome or aortitis were reported in the eflapegrastim arm. Patients with sickle cell disease were not enrolled in the two trials.
- The available ECG and cardiac safety data do not suggest an unexpected effect of eflapegrastim on the QTc interval.
- There was no apparent temporal correlation between the formation of ADAs and the development of hypersensitivity reactions or DSN in any cycle in the eflapegrastim arm.

9. Advisory Committee Meeting and Other External Consultations

This application was not presented to an Advisory Committee or any other external consultants.

10.Labeling Recommendations

10.1. Prescription Drug Labeling

The following are recommended major changes to the eflapegrastim prescribing information based on this review:

- 1 INDICATIONS and USAGE: Revise the indication 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.” consistent with indication of other G-CSF drug products.

- 5 WARNINGS AND PRECAUTIONS: Add "Use in Patients with Sickle Cell Disorders ", "Potential for Tumor Growth Stimulatory Effects on Malignant Cells" and "Nuclear Imaging" subsections consistent with other G-CSF drug products labeling.

- 6 ADVERSE REACTIONS: Revise the Adverse Reactions table to summarize the pooled analysis of studies 301 and 302 and to include AEs that were reported in ≥ 10% of patients in the eflapegrastim arm.

- 14 CLINICAL STUDIES: Revise the patient demographics information to the pooled analysis of studies 301 and 302 and only include pre-specified efficacy endpoint results.

- 17 PATIENT COUNSELING INFORMATION: Revise the section to be consistent with the updated WARNINGS AND PRECAUTIONS section.

10.2. Nonprescription Drug Labeling

This section is not applicable.

11.Risk Evaluation and Mitigation Strategies (REMS)

There are no additional risk management strategies proposed beyond recommended labeling. Based on review of the safety data in the submission, a REMS is not necessary to ensure that the benefits of eflapegrastim outweigh its risks. Consistent with other C-GSF products, the Applicant should submit adverse experience reports under the adverse experience reporting requirements for licensed biological products (21 CFR 600.80).

12.Postmarketing Requirements and Commitments

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

As agreed in the iPSP letter dated September 28, 2018, the pediatric submission will be deferred until December 2025. The following PMRs will be issued for this application:

1. Conduct a study to assess the safety, PK and PD of eflapegrastim in pediatric patients 1 month to <18 years of age with solid tumors treated with myelosuppressive

chemotherapy. Submit the final clinical study report including datasets as a supplemental BLA.

2. Submit pediatric assessments for Rolontis (eflapegrastim) as described in section 505B(a)(2)(A) of the FD&C Act, including development of an "appropriate formulation" (presentation) that can be used to directly and accurately administer Rolontis (eflapegrastim) to pediatric patients and conduct any necessary human factors studies to evaluate the ability of healthcare providers and/or caregivers to measure the appropriate doses.

13.Appendices

13.1. References

1. National Comprehensive Cancer Network. Breast Cancer (Version 2.2020, February 2, 2020).
2. American Cancer Society - Cancer Facts and Figures 2020.
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13.2. Financial Disclosure

Covered Clinical Study (Name and/or Number): SPI-GCF-301

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)

Total number of investigators identified: Approximately 650		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 1		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 0 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in Sponsor of covered study: 1 Sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) N/A		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

Covered Clinical Study (Name and/or Number): SPI-GCF-302

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: Approximately 450		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 1		
If there are investigators with disclosable financial interests/arrangements, identify the		

number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 0 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in Sponsor of covered study: 1 Sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) N/A		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

13.3. Additional Efficacy Tables

Table 76 SPI-GCF-302: Simulation Results of DSN in Cycle 1 (ITT Population)

Starting Seed	Trt. Difference	Confidence Interval [a]	Repetitions
201502	-0.074	-0.292, -0.129 [b]	10,000
	-0.073	-0.292, -0.129	100,000
202002	-0.073	-0.292, -0.129	10,000
	-0.073	-0.292, -0.130	100,000
2262020	-0.075	-0.292, -0.122	10,000
	-0.073	-0.292, -0.129	100,000
1111964	-0.072	-0.284, -0.129	10,000
	-0.073	-0.292, -0.129	100,000
2292020	-0.073	-0.292, -0.129	10,000
	-0.073	-0.292, -0.129	100,000
12345	-0.075	-0.292, -0.121	10,000
	-0.073	-0.292, -0.129	100,000

[a] Confidence intervals are obtained using 2.5 percentile and 97.5 percentile of bootstrap samples with treatment as stratification factor.

[b] Same as what reported in Table 16, CSR.

Source: FDA Analysis

Table 77 SPI-GCF-301: Additional Sensitivity Analysis of DSN in Cycle 1 (ITT Population)

	Difference with Pegfilgrastim	95% CI	Non-inferiority P - Value
Poisson Distribution	-0.149	-0.250, -0.047	<0.0001
Negative binomial distribution	-0.149	-0.269, -0.028	<0.0001
Adjusting Study Site	-0.148	-0.236, -0.061	<0.0001
Disease Status Analysis	-0.149	-0.262, -0.035	<0.0001
Worst-Case Scenario	0.091	-0.044, 0.232	<0.0001

Source: FDA Analysis

Table 78 SPI-GCF-302: Additional Sensitivity Analysis of DSN in Cycle 1 (ITT Population)

	Difference with Pegfilgrastim	95% CI	Non-inferiority P - Value
Poisson Distribution	-0.073	-0.224, 0.078	<0.0001
Negative binomial distribution	-0.073	-0.282, 0.136	<0.0001
Adjusting Study Site	-0.073	-0.351, 0.168	<0.0001
Disease Status Analysis	-0.073	-0.291, 0.136	<0.0001
Worst-Case Scenario	0.300	0.111, 0.488	<0.0001

Source: FDA Analysis

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/s/

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