CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761148Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

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 and Nephrology (OCHEN)
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 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.

1. Introduction

Rolvedon (eflapegrastim-xnst) injection, is a granulocyte colony stimulating factor (G-CSF) product produced by covalent coupling of a human G-CSF analog and Fc fragment of human immunoglobulin G4 (IgG4), both derived from recombinant E. coli, via a single 3.4 kDa polyethylene glycol linker. Eflapegrastim-xnst binds to G-CSF receptors on myeloid progenitor cells and neutrophils, triggering signaling pathways that control cell differentiation proliferation, migration, and survival. Eflapegrastim-xnst is a novel biologic and not a biosimilar to either filgrastim or pegfilgrastim by the virtue of the human IgG4 Fc fragment that is covalently coupled to the human G-CSF analog. Eflapegrastim-xnst has a molecular weight (72kDa) which is almost twice the size (39kDa) of the first clinically approved peg-filgrastim (Neulasta) which is in turn twice the size of the original filgrastim growth factor (19kDa), (Neupogen).

Eflapegrastim-xnst is presented as 13.2 mg/0.6 mL solution in a single-dose prefilled syringe for subcutaneous injection. The proposed dosing regimen of eflapegrastim-xnst in patients with cancer receiving myelosuppressive chemotherapy is 13.2 mg once per chemotherapy cycle approximately 24 hours after cytotoxic chemotherapy.

The Applicant submitted the original BLA on October 24, 2019. During the initial review cycle of the application, the PDFUA action date was missed pending the outcome of pre-approval facilities inspections which were delayed secondary to the COVID 19 pandemic. Subsequent inspections of manufacturing facilities were completed, and deficiencies were noted and conveyed to representatives of the facilities. A Complete Response letter was issued on August 3, 2021, that included facilities-related deficiencies; however, no clinical or deficiencies from other disciplines were identified (see review clinical review by Hyon-Zu Lee dated June 24, 2020, the cross-discipline team leader (CTDL) review by Kathie Robie-Suh dated October 13, 2020 and the Division Director Review dated October 16, 2020.

The Applicant submitted a response to the Complete Response Letter (CRL) on March 11, 2022. This CTDL review summarizes the Applicant's response to the CRL, as well as updated safety and outstanding labeling issues that were not fully resolved in the first review cycle.

2. Benefit-Risk Assessment

Table 1 Benefit-Risk Table

Dimension	Evidence and Uncertainties	Conclusions and Reasons

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Chemotherapy induce neutropenia (CIN) is a common and potentially life-threatening complication in patients receiving myelosuppressive chemotherapy damages more rapidly dividing cancer cells, platelets, red blood cells and a subset of white blood cells located in the bone marrow. Chemotherapy also adversely affects the developmental integrity of the gastrointestinal mucosa in patients with cancer are at risk for invasive infections due to colonizing bacteria and/or fungi that translocate across the intestinal mucosal surfaces damaged by the cytotoxic chemotherapy. • The risk of clinically important infections rises as the neutrophil count falls below 500 cells/uL (grade 4 neutropenia) and is higher in those with prolonged duration of severe neutropenia (> 7 days). • CIN usually occurs within 7- 12 days following Cycle 1 of chemotherapy but onset of neutropenia can occur as early as Day 4 and last up to day 15 or longer depending upon degree of myelosuppression of chemotherapy regimen, prior chemotherapy exposure, radiation treatment and performance status. • CIN Is associated with older age (>65 years), poor functional and nutritional status, presence of comorbidities and certain chemotherapeutic regimens.	CIN is a serious, potentially life-threatening complication of myelosuppressive chemotherapy. The risk of CIN to patients increases as it becomes more severe (grade 4 neutropenia) and prolonged (duration of severe neutropenia).
Current Treatment Options	• Primary prophylaxis for CIN with myeloid growth factors is recommended when the risk of febrile neutropenia is ≥ 20%. The estimate of risk is based on age, comorbid conditions, and type of chemotherapuetic agent. • Current treatment options for patients with CIN consist of FDA-approved pharmacological therapies including lekocyte growth factors (called granulocyte colon-stimuatling factors [G-CSFs]) which act to increase neutrophils thereby decreasing the incidence of infection, as manifested by febrile neutropenia, in patients with nonmyeloid malignancies receiving myelosuppresisve anticancer drugs	Available therapy exists (primarily G-CSF products) for the primary prophylaxis of chemotherapy induced neutropenia and is typically administered when the risk of febrile neutropenia is ≥ 20%.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	associated with a clinically significant incidence of febrile nuetropenia • Filgrastim is a short-acting leukoctye growth factor that was approved in 1991. • Pegfilgrastim is a long-acting leukocyte growth factor that was approved in 2002. • Tbo-filgrastim approved in 2012 is a short acting leuckocyte growth factor • In addition to these three approved products, there have been at least eight biosimilars to either filgrastim (3) or pegfilgrastim (5) approved since 2015. • Other treatment options include supportive care such as prophylactic antibiotics or dose-reduction of chemotherapueticc agents with subsequent cycles.	
Benefit	The efficacy of Rolvedon was evaluated in two randomized, controlled, non-inferiority trials enrolling a total of 643 patients with early-stage breast cancer receiving chemotherapy. The efficacy results of studies SPI-GCF-301 (Study 301) and SPI-GCF-302 (study 302) showed that eflapegrastim-xnst is non-inferior to pegfilgrastim for mean DSN in Cycle 1. For Study 301, the difference in mean DSN was -0.148 days (95% CI -0.256, -0.033) and for Study 302, the difference in mean DSN was -0.073 days (95% CI: -0.292, 0.129). In Study 301, the incidence of febrile neutropenia in Cycle 1 was 2% in the Rolvedon arm and 1% in the pegfilgrastim arm and in Study 302, the incidence of febrile neutropenia was 0.8% in the Rolvedon arm and 3.4% in the pegfilgrastim arm in Cycle 1.	**Studies 301 and 302 demonstrated that Rolvedon is non-inferior to pegfilgrastim in both studies for the endpoint of duration of severe neutropenia when compared to pegfilgrastim, an approved G-CSF.** **In studies, the similar incidence of febrile neutropenia between patients who received Rolvedon and pegfilgrastim, support the benefit of the study drug.**
Risk and Risk Management	Adverse events of special interest (AESI) attributed to the G-CSF drug class are rare. The most well known events include leukocytosis, musculoskeletal pain and allergic reaction. The remaining AESIs include: splenic rupture, acute respiratory distress syndrome, sickle cell crisis, glomerulonephritis, capillary leak syndrome, aortitis, Sweet syndrome, pulmonary alveolar hemorrhage, tumor growth or progression or disease, and injection site reaction. Overall, AESIs were	**The adverse reactions observed in the main trials were expected based on previous experience with approved G-CSFS in populations of patients receiving chemotherapy.**

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	not commonly seen with Rolvedon with leukocytosis, musculoskeletal pain occuring. The AESIs are listed under warnings and precautions in the labels of approved G-CSFs. The most common adverse reactions (≥ 20%) are fatigue,nausea,diarrhea, bone pain, headache, pyrexia, anemia, rash, myalgia, arhralgia and back pain. Serious adverse reactions were reported in 2% of patients which included arthralgia, back pain, bone pain, chest pain, pyrexia, supraventricular tachycardia, and leukocytosis occuring in 1 patient each.	**Adverse events of special interest are included in the warnings and precautions section of the USPI for Rolvedon** **No new safety signals were detected in patients treated with Rolvedon compared to pegfilgrastim in the pooled safety analysis of Studies 201 and 302. The risks are expected with this drug class.** **Not all G-CSF class adverse effects were seen in the clinical trials. Nonetheless, if approved Rolvedon must carry the appropriate class warnings to ensure safe use.**

CIN is a side effect of cancer treatment. Severe neutropenia (i.e., less than 500 cells/microL) can lead to fever, infections, hospitalizations, delays in chemotherapy treatment and all of these consequences can impact survival. Chemotherapy treatment guidelines strongly recommend granulocyte stimulating factors (G-CSFs) for patients receiving myelosuppressive chemotherapy to alleviate the chemotherapy effect on the bone marrow. G-CSFs with a short half-life are given daily following completion of each cycle of chemotherapy treatment. Examples of G-CSFs with a short half-life include the approved drugs, filgrastim and tbo-filgrastim. G-CSFs with a long half-life are given once following completion of each cycle of chemotherapy treatment. and include the approved drug, pegfilgrastim. G-CSFs allow for faster recovery of white blood cell counts for patients.

Substantial evidence of efficacy was demonstrated in two trials enrolling 643 patients with breast cancer receiving chemotherapy. The primary endpoint of both trials was duration of

severe neutropenia. Studies 301 and 302 both demonstrated that Rolvedon is non-inferior to pegfilgrastim for the endpoint of duration of severe neutropenia when compared to pegfilgrastim, an approved G-CSF. 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 201 and 302. The benefit-risk is favorable.

For a detailed and comprehensive discussion of BLA 761148, please see original CDTL review by Dr. Kathy Robie-Suh (10/13/2020) and the clinical and statistical review by Hyon-Zu Lee dated June 24, 2020 and updated clinical review dated September 8, 2022.

3. Center for Devices Research and Radiological Health (CDRH)

During the original review of application, a consult was requested from CDRH for the pre-filled syringes and the consult was completed by James Michael Simpson, Jr. and entered into DARRTs by Elizabeth Godwin (August 26, 2020). The review found that performance and performance stability data supported a shelf life of 24 months stored at 5+/- 3 C in 1mL syringe, (b) (4) (b) (4) (b) (4) to 24 months. The CDRH review recommended the device constituent parts of the combination product are approvable and had no deficiencies or recommendations for a PMC/PMR.

4. Product Quality

The Office of Pharmaceutical Quality (OPQ), CDER, has completed assessment of STN 761148 for Rolvedon manufactured by Spectrum Pharmaceuticals, Inc. The data submitted in this application are adequate to support the conclusion that the manufacture of Rolvedon is well-controlled and leads to a product that is pure and potent. OPQ recommends that this product be approved for human use under conditions specified in the package insert.

The resubmitted BLA is recommended for approval from a product quality, microbiology, facilities, immunogenicity assays, device constituent performance, and quality labeling perspectives. The deficiencies observed during the inspection of the (b) (4) Manufacturing facilities in the previous assessment cycle were resolved during the current assessment cycle.

A re-inspection was deemed necessary for the drug substance manufacturing site, (b) (4) and drug product manufacturing site, (b) (4) because significant CGMP deficiencies were identified for the drug substance and drug product operations during the pre-license inspections concluded in support of the BLA in the previous assessment cycle. In the current assessment cycle, (b) (4) was found

approvable based on resolution of CGMP deficiencies covered by the re-inspection of the facility by the Office of Regulatory Affairs (ORA) for other applications. A re-inspection was conducted at (b) (4), which resulted in a two-item FDA Form 483. The Office of Pharmaceutical Manufacturing Assessment (OPMA)compliance review of the firm's response to the issued FDA Form 483 was found adequate and OPMA concurred with filed recommendation of acceptable and approve for BLA 761148.

OPQ recommendations on post-marketing commitments: to qualify the bioburden test method with two additional drug product batches and submit the qualification report by April 2023.

5. Nonclinical Pharmacology/Toxicology

The original nonclinical pharmacology review was performed by Huiqing Hao and Federica Basso (DARRTS 6/25/2020). There are no new updates to this assessment; please refer to the review from 6/5/2020 for details. A pharmacology/toxicology memorandum by Anthony Parola stated that there no changes to the nonclinical information in the United States Prescribing Information (other than brand name change from Rolontis to Rolvedon) and there were no new nonclinical issues identified in the resubmission of BLA 761148. The nonclinical reviewers conclude that there are no deficiencies in the nonclinical data that would preclude approval of BLA 761148, and they recommend approval.

6. Clinical Pharmacology

The Office of Clinical Pharmacology reviewers were Anusha Ande, Eliford Kitabi, Justin Earp and Sudharshan Hariharan (DARRTS 7/2/2020). They recommend approval of Rolvedon 13.2 mg administered once per chemotherapy cycle administered approximately 24 hours after cytotoxic chemotherapy for the proposed indication. Recommendations were made for labeling including inclusion of pharmacokinetic characteristics of eflapegrastim-xsnt and absorption, elimination and metabolism of eflapegrastim-xsnt. Please refer to the initial review dated 7/2/2020 for pertinent details.

7. Efficacy Summary

Substantial evidence of effectiveness was demonstrated with two randomized (1:1), open-label, active-controlled non-inferiority clinical studies with similar design (Study SPI-GCF-301 [NCT02643420], and Study SPI-GCF-302 [NCT02953340]).

The two studies enrolled a total of 643 patients with early-stage breast cancer. Docetaxel 75 mg/m^2 and cyclophosphamide 600 mg/m^2 (TC regimen) 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 21-day cycle of TC chemotherapy. The primary efficacy endpoint in both studies was the duration of severe neutropenia (DSN) in Cycle 1.

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. There were no significant demographic differences between the studies with the sample size being the only main difference between studies.

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]

The non-inferiority (NI) of Rolvedon to Neulasta would be declared if the upper bound of the 95% confidence interval of the difference in mean DSN days between the test groups (i.e., Rolvedon minus Neulasta) was less than the NI margin of 0.62 days (refer to review by Dr. Kate Dwyer for a description of how the CI were obtained for efficacy analysis using 2.5 percentile and 97.5 percentile of the 1000,000 bootstrap samples with the treatment as stratification factor). Neupogen (filgrastim) was approved based on a placebo-controlled trial and Neulasta

(pegfilgrastim) was approved based on the NI comparison of Neulasta with Neupogen using the NI margin of 1 day for the difference of mean DSN in Cycle 1. The NI margin used for comparison of unapproved pegylated myeloid growth factors like Rolvedon with the pegfilgrastim was set at 0.62 days, in order to maintain the magnitude of the original effect size of Neulasta as compared to Neupogen.[1]

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; p < 0.0001) for the primary endpoint of mean DSN. The applicant claimed (b) (4)

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, p < 0.0001). In superiority testing, the nominal p value was 0.499.

Table 2. 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	-0.265, -0.033		-0.292, 0.129	

[1] The major efficacy outcome of the Neulasta vs Neupogen trial was that the mean days of severe neutropenia did not exceed that of filgrastim treated patients by more than 1 day in cycle 1. The mean days of severe neutropenia was 1.8 days in Neulasta arm compared to 1.6 days in filgrastim arm and in 2nd study mean DSN was 1.7 days in Neulasta arm compared to 1.6 days in filgrastim arm.

The desired margin for the first NI trial for Neulasta vs Neupogen was 1 day and this estimated because of the RCT of Neupogen vs placebo. The NI trial design was decided to be used for the G-CSF biosimilar programs and if the 1 day margin used, there could have been gradual reduction in effect size in approving candidate biosimilar to avoid having a gradual decline in effect size, the NI margin was tightened to 0.67 days.

[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.

Each study, 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 the clinical and statistical review dated June 24, 2020, for additional details).

Safety Summary

For a detailed analysis of the safety results, please see the original review of Dr. Hyon-Zu Lee dated June 24, 2020, in DARRTs. The safety review of eflapegrastim-xnst was primarily based on the pooled population from Studies 301 and 302 for a total of 640 patients (eflapegrastim-xnst: 314 patients, pegfilgrastim: 326 patients) who participated in the two phase 3 trials (SPI-GCF-301 and SPI-GCF-302). A total of 272 patients received four 21-day treatment cycles. 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 in both studies was 4 cycles (range: 1, 4).

The most frequently reported SAEs (> 2 patients) in the eflapegrastim-xnst 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-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 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 in pediatric patients with solid tumors or lymphomas and treated with myelosuppressive chemotherapy. Datasets were not provided. 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.

6. Pediatric and Assessment of Effects on Growth

As noted above Study SPI-GCF-202, an open-label, phase 2 pediatric study (n=2) to evaluate the safety and PK of eflapegrastim in pediatric patients with solid tumors or lymphomas and treated with myelosuppressive chemotherapy is ongoing. At this time, the safety and efficacy eflapegrastim-xnst have not been established in pediatric patients.

7. Advisory Committee Meeting and Other External Consultations

There was no advisory committee meeting held for this application. The review team agreed that the efficacy and safety of the product were adequately characterized by the application and the application raised no novel or controversial issues needing advisory committee discussion.

8. Labeling

Indication:

During the first review cycle, the Sponsor's proposed indication was to "decrease the incidence of infection, as manifested by febrile neutropenia, in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs." The FDA revised the to add the phrase "associated with clinically significant incidence of febrile neutropenia" to the indication to make the indication consistent with other approved G-CSF products. Therefore, the proposed indication is "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**".

During this review cycle, the applicability of Rolvedon efficacy and safety data to patient populations not evaluated in the phase 3 trials: cancer types other than breast and other chemotherapeutic regimens other than those used in two trials, was reviewed. An information request was sent to the Sponsor asking them for justification for the proposed indication (which is considered 'broad'-see discussion below) and to justify the inclusion of a wide range of tumor types and chemotherapy regimens given that they had only studied patients with breast cancer. Rolvedon is a new molecular entity because of its unique structure and is a 351(a) application, therefore the application must contain all information and data necessary to demonstrate that the proposed product is safe, pure, and potent. Initially, the Sponsor relied on data from innovator product, Neulasta to provide justification for indication. However, extrapolation from previously approved products is not possible as this application is a 351(a). The Of note,

the trials did enroll black patients (18%) and 2 male patients. The Applicant provided further justification for the proposed broad 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 the underlying cancer that a patient may have developed.

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 appears adequate for eflapegrastim-xnst.

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

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

Warnings and Precautions Section 5:

The Warnings and Precautions were revised to include class effects for the rhG-CSG products (splenic rupture, acute respiratory distress syndrome, serious allergic reactions, use in patients with Sickle Cell Disorders, Glomerulonephritis, Leukocytosis, Thrombocytopenia, Capillary Leak Syndrome, Potential for Tumor Growth Stimulatory Effects on Malignant Cells, MDS and AML in Patients with Breast and Lung Cancer, Aortitis, Nuclear Imaging.

Adverse Reactions Section 6:

During this resubmission cycle, the Agency revised the adverse reactions table in the prescribing information. The review team evaluated the adverse events and identified adverse events thought to be casually related to eflapegrastim (adverse drug reactions). Because some adverse reactions that are observed in the investigational arm and the control arm are due to similar pharmacologic class or mechanism of action, omission of adverse reactions in the investigational arm that occur at a lower rate compared to the control arm may obscure the description of the adverse reactions observed in the investigational arm. Therefore, these were included in the adverse reaction table in the prescribing information. The adverse reaction table was revised to remove terms (highlighted in yellow) that are not mechanistically plausible and more likely to be an effect of the underlying disease or chemotherapy treatment.

Table 3. Common Adverse Reactions Through Week 14 in Patients with Early-Stage Breast Cancer with a Frequency of ≥10% in Study 1 and Study 2.

Adverse Reactions	**Rolvedon (N = 314) %**	**Pegfilgrastim (N=326) %**
Fatigue*	181 (58%)	192 (59%)
Nausea	162 (52%)	166 (51%)
(b) (4)		
Diarrhea	125 (40%)	126 (39%)
Bone pain	119 (38%)	121 (37%)
Headache*	92 (29%)	90 (28%)
(b) (4)		
Anemia*	(b) (4) (25%)	(b) (4)
Pyrexia*	87 (28%)	84 (26%)
Rash*	77 (25%)	99 (30%)
Myalgia	69 (22%)	49 (15%)
Arthralgia	66 (21%)	48 (15%)
Decreased appetite	61 (19%)	50 (15%)
Back pain*	63 (20%)	55 (17%)

Adverse Reactions	Rolvedon (N = 314) %	Pegfilgrastim (N=326) %
(b) (4)		
Edema peripheral*	57 (18%)	53 (16%)
(b) (4)		
Abdominal pain*	53 (17%)	67 (21%)
Dizziness*	50 (16%)	38 (12%)
(b) (4)		
Dyspnea*	49 (16%)	44 (13%)
Thrombocytopenia*	44 (14%)	17 (5%)
Cough*	48 (15%)	51 (16%)
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) from ADAE.xpt**

The adverse events highlighted, (b) (4) ere removed as these are more likely to be an effect of the underlying disease or chemotherapy. Thrombocytopenia was retained because it is listed in the Warnings and Precautions sections of other drugs in the class.

Serious adverse reactions identified during the review included chest pain, supraventricular tachycardia (SVT), arthralgia, back pain, bone pain, white blood cell increased and pyrexia, which each occurred in one subject. These serious adverse reactions were added to the labeling during the first cycle but upon further evaluation in this resubmission cycle, the determination was made to remove these from the label since arthralgia, back pain, bone pain, leukocytosis and pyrexia are described in table 6 of the label. Review of the narratives for chest pain and SVT provided by the Applicant was undertaken. Per the narrative, the chest pain was considered non-cardiac in origin and could be related to Rolvedon, docetaxel or cyclophosphamide. The clinical team assessed that the event is likely non-cardiac in nature and is not included as a separate serious adverse reaction. The narrative for the patient who experienced SVT was also reviewed. The patient had SVT 6 days after Rolvedon treatment (7

days after chemotherapy) during the first cycle of chemotherapy and reoccurrence again 6 days and 8 days after Rolvedon treatment (7 and 9 days after chemotherapy) in Cycle 2. In the pooled safety analysis, there was 5% tachycardia reported in each arm and overall cardiac events were 10% in the Rolvedon arm and 12% in the pegfilgrastim arm. The incidence of cardiac events was similar between both treatment arms and also occurred in setting of concurrent chemotherapy. The determination was made to not include SVT as separate listing in the label.

9. Post Marketing Requirements and Commitments

Two PREA PMRs and one OPMA PMC will be issued to the applicant. No safety-related (FDAAA) PMRs are required for this application.

PMR 3891-1
Conduct a study to assess the safety, pharmacokinetics and pharmacodynamics of eflapegrastim-xnst in pediatric patients 1 month to <17 years of age with solid tumors treated with myelosuppressive chemotherapy. Submit the final clinical study report including datasets as a supplemental BLA.

Study/Trial Completion:	12/2024
Final Report Submission:	12/2025

PMR 3891-2
Submit pediatric assessments for Rolvedon (eflapegrastim-xnst) 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 Rolvedon (eflapegrastim-xnst) to pediatric patients (1 month to <17 years of age). Conduct any necessary human factors studies to evaluate the ability of healthcare providers and caregivers to measure the appropriate doses.

Interim (Submission of plan for pediatric presentation):	12/2023
Final Report Submission:	12/2024

PMC 3891-3
To qualify the bioburden test method with two additional drug product batches and submit the qualification report.

Final Report Submission	4/30/2023

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

TANYA M WROBLEWSKI
09/08/2022 02:44:15 PM

LISA B YANOFF
09/08/2022 03:24:26 PM

Cross-Discipline Team Leader Review

Date	October 13, 2020
From	Kathy M. Robie Suh, M.D., Ph.D.
Subject	Cross-Discipline Team Leader Review
BLA	761148
Applicant	Spectrum Pharmaceuticals, Inc.
Date of Submission	October 24, 2019
BSUFA Goal Date	October 24, 2020
Proprietary Name / proper name	Rolontis (eflapegrastim)
Dosage forms / Strength	(b) (4)
Proposed Indication	To decrease the incidence of infection, as manifested by febrile neutropenia, in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs
Recommended Action:	[Delay action]

1. Introduction

Eflapegrastim (Rolontis®, SPI-2012, HM10460A) is a long-acting granulocyte-colony stimulating factor (G-CSF) that has been developed to decrease the incidence of neutropenic complications associated with the use of myelosuppressive anti-cancer drugs. Eflapegrastim is produced by covalent coupling of a human G-CSF analog and human immunoglobulin G4 (IgG4) Fc fragment, both derived from recombinant *Escherichia coli,* via a single 3.4 kDa polyethylene glycol (PEG) linker.

Eflapegrastim is a novel biologic and not a biosimilar to either filgrastim or pegfilgrastim by virtue of the human IgG4 Fc fragment that is covalently coupled to the human G-CSF analog. Eflapegrastim, by elimination of renal clearance due to an increase in molecular weight compared to G-CSF, is intended to increase the circulating half-life and duration of biological response to G-CSF as compared to filgrastim, which has a half-life of only a few hours (approximately 3.5 hours), potentially allowing for a more convenient dosing schedule and enhanced patient treatment compliance. The Fc fragment may also increase half-life by neonatal Fc receptor (FcRn)-mediated recycling, a known mechanism for the prolonged half-life of IgG. Human IgG4 Fc fragment was chosen because IgG4 does not bind to complement 1q (C1q) and has much less affinity to Fc gamma receptors, decreasing Fc-mediated effector functions such as antibody dependent cell mediate cytotoxicity (ADCC) and complement dependent cytotoxicity (CDC).

This application proposes approval of eflapegrastim for the following indication:

> *Eflapegrastim is indicated to decrease the incidence of infection, as manifested by febrile neutropenia, in patients with non-myeloid malignancies receiving myelosuppressive anticancer drugs.*

The proposed dosing for eflapegrastim is a fixed-dose of 13.2 mg/0.6 mL (b) (4) mg G-CSF) administered by subcutaneous (SC) injection once per chemotherapy cycle approximately 24 hours after chemotherapy administration.

To support the application the applicant has conducted two pivotal, randomized, open-label, active-controlled, Phase 3 studies (SPI-GCF-301 and SPI-GCF-302) to evaluate the efficacy and safety of fixed-dose eflapegrastim. These studies were previously submitted to the Agency for the currently proposed indication under BLA (b) (4) in December 2018; however, that application was withdrawn by the applicant in March 2019 due to CMC filing deficiencies.

2. CMC/Device

The quality assessment review of the chemistry, manufacturing and controls (CMC) aspects of this application was conducted by the Office of Pharmaceutical Quality Review Team as listed:

Quality Review Team

Discipline	Reviewer	Branch/Division
Drug Substance	Zhong Zhao	DBRR III/OBP/OPQ
Drug Product	Zhong Zhao	DBRR III/OBP/OPQ
Immunogenicity	Zhong Zhao	DBRR III/OBP/OPQ
Labeling	Scott Dallas and James Barlow	OBP/OPQ
Facility	Michael Shanks	DBM/OPMA/OPQ
Microbiology (DS)	Reyes Candau-Chacon	DBM/OPMA/OPQ
Microbiology (DP)	Madushini Dharmasena	DBM/OPMA/OPQ
Business Process Manager	Melinda Bauerlien	RBPMB I/OPRO/OPQ
Team Lead for OBP	Ramesh Potla	DBRR III/OBP/OPQ
Tertiary Reviewer for OBP	Susan Kirshner	DBRR III/OBP/OPQ
Microbiology Team Lead (DS)	Patricia Hughes	DBM/OPMA/OPQ
Microbiology Team Lead (DP)	Reyes Candau-Chacon	DBM/OPMA/OPQ
Microbiology Tertiary Reviewer	Patricia Hughes	DBM/OPMA/OPQ
Facilities Team Lead	Peter Qiu	DBM/OPMA/OPQ
Application Team Lead	Ramesh Potla	DBRR III/OBP/OPQ

The Executive Summary of the Review completed by Ramesh Potla and Susan Kirshner (final signature 7/2/2020) states:

I. Recommendations:

A. Recommendation and Conclusion on Approvability:

Recommendation: Pending.

Currently, there are no product quality deficiencies precluding approval of this BLA. However, a final recommendation regarding product quality is currently pending and will be made in an addendum to this report after satisfactory resolution of the following outstanding items:

1. A pre-license inspection of [redacted] (b) (4) drug substance manufacturing facility [redacted] (b) (4) is required to verify that the firm's manufacturing operations are in compliance with cGMPs and that the product quality data submitted to the eflapegrastim BLA is accurate, reliable, and complete. This facility has never been inspected by the FDA before.

2. Sponsor responses to all outstanding information requests.

3. Updates to the BLA reflecting all changes made in response to FDA product quality information requests.

B. Approval Action Letter Language:

Manufacturing location:

- Drug Substance: (b) (4)
- Drug Product:
  - (b) (4)

- Fill size and dosage form – 13.2 mg/0.6 mL solution in a single-dose pre-filled syringe

- Dating period:
  - Drug Product: (b) (4) months; 2-8 °C
  - Drug Substance: (b) (4) months; (b) (4)

- Exempt from lot release
  - Rolontis® is exempted from lot release per FR 95-29960.

C. Benefit/Risk Considerations:

Rolontis (eflapegrastim) is indicated 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.

A review of benefit-risk assessment will be documented in the addendum to this report once all outstanding information has been reviewed.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Requirements, Agreements, and/or Risk Management Steps, if approvable:

(b) (4)

Other potential post marketing commitments/requirements will be documented in the addendum to this report once all outstanding information has been reviewed.

Special product quality recommendations for labeling included: Store in a refrigerator at 2˚C to 8˚C (36˚F to 46˚F); protect from light until use; do not shake; do not freeze.

Immunogenicity: The 351(a) BLA Immunogenicity Assay Validation Assessment was completed by Zhong Zhao (final signature in Panorama 6/24/2020). The Assessment described that, " In total, immunogenicity to eflapegrastim was evaluated in 5 clinical studies: two Phase

1 studies in healthy volunteers (08-HM10460A-101 and 09-HM10460A-102), one Phase 2 study in early stage breast cancer patients (SPI-GCF-12-201) and two Phase 3 studies in early-stage breast cancer patients (SPI-GCF-301 and SPI-GCF-302). In the Phase 1 and Phase 2 studies, the immunogenicity assessment was limited to anti-eflapegrastim antibodies (ADAs) and anti-G-CSF antibodies. For the Phase 3 studies, the assay was modified by introducing an acid dissociation step in sample preparation and introducing domain specificity assay to determine antibodies against the Fc domain. In addition, a separate assay was used to detect anti-PEG antibodies. Immunogenicity sample analysis for antibodies to eflapegrastim and its protein domains was performed following a standard tiered testing strategy. Samples were initially subjected to a screening assay and putative positive samples from the screening assay were subjected to a confirmatory assay. Samples that were positive in the confirmatory assay were tested in a titer assay." Validation data for anti-drug antibody assay, neutralizing antibody assay and anti-polyethylene glycol (PEG) antibody assay were examined. The review states the fundamental parameters for validation include: cut-point, sensitivity and drug tolerance, specificity and selectivity, precision, robustness, and stability of critical reagents. The Assessment concluded:

- *For anti-drug antibody assay: In conclusion, the data presented in this validation study demonstrate that the acceptance criteria specified in* (b) (4) *study 8336-070 have been successfully met and testing method ELISA-0692 is validated for the detection, confirmation, and titration of anti-eflapegrastim antibodies in human to support clinical studies.*
- *For neutralizing antibody assay: The data generated in this validation study demonstrate that the acceptance criteria specified in TQF-18-012-VP have been successfully met and test method TM-TQF-0001 was validated for the detection of anti-eflapegrastim neutralizing antibodies in human to support clinical studies.*
- *For Anti-PEG antibody assay: The data generated in this validation study demonstrate that the acceptance criteria specified in TQF-18-020-VP have been successfully met and test method TM-TQF-0002 is validated for the detection of anti-PEG antibodies in human to support clinical studies sponsored.*

Regarding immunogenicity risk the Assessment stated: "The primary effects of G-CSF on normal hematopoietic cells are limited to cells of the neutrophil lineage. Apart from increasing the levels of neutrophils, G-CSF is not known to have immunomodulatory activities. It has been reported that chronic administration of filgrastim to patients with severe chronic neutropenia (SCN) did not lead to generation of anti-G-CSF antibodies. The Fc fragment of eflapegrastim did not show reactivity to Fcγ receptors or show the potential for inducing effector functions such as antibody-dependent cellular cytotoxicity (ADCC) or complement-dependent cytotoxicity (CDC). Thus, the risk of immunogenicity due to intrinsic immunomodulatory properties of eflapegrastim is low." No deficiencies were identified and there were no immunogenicity related PMC.

The Assessment summarized the immunogenicity findings from the clinical studies as follows:

The integrated analysis for anti-eflapegrastim antibodies for studies SPI-GCF-301 and SPI-GCF-302 comprised a total of 639 patients. Of these, 603 (94.4%) patients met the criteria for evaluable (patients with a baseline sample and at least one post-dose sample) for anti-eflapegrastim antibodies.

The Sponsor determined that the prevalence of preexisting anti-eflapegrastim antibodies in the pooled data was similar in the two treatment arms, with 2.0% in the Eflapegrastim Arm and 2.5% in the Pegfilgrastim Arm. The cumulative incidence of treatment-emergent anti-eflapegrastim antibodies at 12-month follow-up visit was 9.4% (28/297) in the eflapegrastim arm and 3.3% (10/306) in the pegfilgrastim arm. The difference between the two arms was statistically significant. The cause for this difference might be that the Tier 1 screening assay employed a bridging assay design using labeled forms of eflapegrastim for both ADA capture and detection. The Sponsor also provided the information that the magnitude of the median titer values tended to be lower in the Eflapegrastim Arm compared to the pegfilgrastim Arm.

Of the 28 patients positive for treatment-emergent (treatment-induced and treatment-boosted) anti-eflapegrastim antibodies in the Eflapegrastim Arm, 18 (64.3%) patients demonstrated reactivity to the G-CSF domain, while 3 of 10 patients (30%) in the Pegfilgrastim Arm were reactive to the G-CSF domain. For both treatment arms, nearly all patients who were reactive to the G-CSF domain were also reactive to lenograstim, suggesting that the antibodies are directed against epitopes common to the G-CSF domain and lenograstim. 5 out of 28 patients (17.9%) in the eflapegrastim arm and 5 out of 10 patients (50%) in the pegfilgrastim arm tested positive for IgG4 Fc reactivity.

Only one patient was positive for treatment-induced NAb at only one out of seven post-treatment time points. None of the pegfilgrastim treated patients were positive for NAb. These results suggest that administration of either therapeutic did not elicit a meaningful NAb response in patients. The one eflapegrastim-treated patient who was positive for treatment-induced NAb showed no temporal correlation between occurrence of NAb and Grade 4 neutropenia. Another eflapegrastim treated patient had samples that were positive for NAb at baseline and at cycle 2 and at the 12 month follow-up visit had no grade 4 neutropenia.

Anti-PEG antibody was assessed using a separate assay. Due to the high prevalence of preexisting anti-PEG antibodies (60-70%), an approach involving evaluation of treatment emergent anti-PEG antibodies was employed. The incidence of treatment-emergent anti-PEG antibodies in the titer assay was 46.3% (124/268) in the eflapegrastim arm and 63.5% (167/263) in the pegfilgrastim arm. The difference between the two arms was statistically significant. Only 2 patients demonstrated specific reactivity to eflapegrastim, indicating that anti-PEG antibodies are essentially non-reactive to eflapegrastim.

Anti-eflapegrastim and anti-PEG antibodies were not found to impact the clearance of eflapegrastim following the forward addition and backward elimination procedure used for population PK model development. The occurrence of Grade 4 neutropenia (absolute neutrophil count $<0.5\times10^9$/L) was found to be independent of the presence of anti-eflapegrastim antibodies. Analysis of data for individual patients also did not show any temporal correlation between occurrence of anti-eflapegrastim antibodies and grade 4 neutropenia. A statistically significant negative correlation was observed between the probability of occurrence of grade 4 neutropenia and anti-PEG titer in cycle 1 but not in cycle 3.

The applicant proposed the following text for the label:

(b) (4)

Antibodies to eflapegrastim were detected using bridging enzyme-linked immunosorbent assay (ELISA) with a sensitivity of 65 ng/mL. (b) (4)

(b) (4)

> Neutralizing antibodies were detected by a cell-based assay with a sensitivity of (b) (4) ug/mL. (b) (4) one patient out of 297 (0.3%) in the eflapegrastim arm (b) (4) tested positive (b) (4) (b) (4) (b) (4)

The Assessment found that the information in the immunogenicity section in the label is accurate. However, in the Assessment the reviewer commented that in the clinical studies: "the Sponsor used the same assay for evaluating anti-eflapegrastim antibodies and anti-pegfilgrastim antibodies and did not validate that the assay performs well for detecting anti-pegfilgrastim, so we are not able to assess whether the anti-pegfilgrastim antibody rates are accurate. The results also suggested no meaningful NAb response in the eflapegrastim treatment. Finally, there is no demonstrable impact on pharmacokinetics, clinical safety or efficacy for the emergent anti-eflapegrastim antibodies and anti-PEG antibodies." (b) (4)

Facilities: As of the date of this review the facilities inspection for this application has not been completed due to travel issues related to COVID 19. In a Discipline Review Letter to the applicant issued 8/14/2020, the Office of Pharmaceutical Quality stated:

> An inspection of the (b) (4) facility and the (b) (4) (b) (4) facility is required before the application can be approved. FDA must assess the ability of that facility to conduct the listed manufacturing operations in compliance with CGMP. Due to restrictions on travel we may be unable to conduct an inspection of the (b) (4) facility and the (b) (4) facility prior to the User Fee Date. We will continue to monitor the public health situation as well as travel restrictions. We are actively working to define an approach for scheduling outstanding inspections, once safe travel may resume and based on public health need and other factors.

Device/ CDRH Consult: A consult was requested from Center for Devices Research and Radiological Health (CDRH) for the pre-filled syringes. The consult primary Review Memorandum was completed by James Michael Simpson, Jr., Division of Drug Delivery, General Hospital and Human Factors/Office of Product Evaluation and Quality (DHT3C/OPEQ) (signed in Panorama 8/4/2020; entered into DARRTS by Elizabeth Godwin 8/26/2020). The Review examined device performance, device performance on stability, and essential performance requirements (EPR) control strategy. The Review described the primary container closure system for eflapegrastim Drug Product as consisting of a 1-mL glass syringe with a staked needle, elastomeric needle cap, elastomeric plunger, and plunger rod. This primary container system is inserted into the passive needle guard accessory. The components of the proposed container/closure system comply with USP <660> and USP <381> requirements for glass containers and elastomeric closures for injections, respectively. Several information requests were sent during the review. The Review found that performance and performance stability EPR data supported shelf life of 24 months stored at 5+3°C in 1 mL syringe and the applicant (b) (4) (b) (4) months to 24

months. The Review recommended the device constituent parts of the combination product are approvable. There were no deficiencies or recommendations for PMC/PMR.

3. Nonclinical Pharmacology/Toxicology

The primary Pharmacology/Toxicology BLA Review and Evaluation of this application was conducted by Huiqing Hao (final signature in DARRTS 6/25/2020).

The Review summarized the major findings of the non-clinical studies as follows:

Pharmacology, pharmacokinetics, general toxicology, reproductive toxicology, and genotoxicity studies were conducted with eflapegrastim administered by subcutaneous injection, the clinical route of administration. Safety margins relative to the maximum recommended human dose (MRHD) of 13.2 mg were calculated based Day 1 AUCs.

General toxicology studies were conducted in rats and monkeys with treatment durations of a single dose and 4 weeks in both species, and 26 weeks in monkeys. Treatment-related findings in both rats and monkeys were consistent with the known pharmacological effects of G-CSF, mainly increases in blood neutrophil counts, granulopoiesis in the bone marrow, and increased extramedullary granulopoiesis in the spleen, liver, kidney, and lymph nodes. In the 4-week studies, high doses were associated with mortality and severe toxicities including joint inflammation, reduced bone area, marrow necrosis in rats (≥11-fold MRHD) and hemorrhage in the lung and brain in monkeys (212-fold MRHD) in the early sacrificed animals. A 26-week study in monkeys did not reveal additional toxicities other than neutrophil count reduction (-78% by Week 26, -85% by end of the recovery) after a transient increase during the first 4 weeks at all doses tested. The neutrophil counts reduction was likely attributable to the presence of neutralizing anti-drug antibodies. Safety margins to the NOAEL were 0.2-, 39- and 82-fold the MRHD in the 4-week rat study, 4-week monkey study and 26-week monkey study, respectively.

Eflapegrastim did not affect the CNS and respiratory system in rats, or the cardiovascular system in monkeys.

Eflapegrastim did not bind to C1q, FcγRI, FcγRIIB, and FcγRIIIA suggesting low potential to induce Fc-mediated effector functions such as complement dependent cytotoxicity (CDC) and antibody dependent cell mediate cytotoxicity (ADCC).

Eflapegrastim was not mutagenic or clastogenic in a standard battery of genotoxicity studies.

Eflapegrastim did not affect fertility, embryofetal development, and pre- and post-natal development in rats at doses up to 7-fold the MRHD. Pregnant rabbits given eflapegrastim during organogenesis (GD7-GD19) exhibited increased post-implantation loss (mostly early resorption) and related reduction in litter size, increased incidence of dams with no viable fetuses, as well as decreased fetal weights at ≥6-fold MRHD). NOAEL for fetal development was 2-fold MRHD.

The Review concluded the nonclinical data support market approval of eflapegrastim. The Review provided recommendations for the non-clinical sections of the labeling.

4. Clinical Pharmacology/Biopharmaceutics

The Office of Clinical Pharmacology Integrated Review of this application was conducted by Anusha Ande, Eliford Kitabi, Justin Earp and Sudharshan Hariharan (signed in DARRTS 7/2/2020).

The primary focus of the Clinical Pharmacology Review was to evaluate the acceptability of general dosing recommendations and to explore the need for dose optimization based on extrinsic and intrinsic factors. The main review findings for pharmacology and clinical pharmacokinetics of eflapegrastim are summarized in the following table from the Clinical Pharmacology Review:

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

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

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

The Review indicated the proposed dose of 13.2 mg administered once per chemotherapy cycle was acceptable. Rolontis is to be administered approximately 24 hours after cytotoxic chemotherapy and is not to be administered between 14 days before and 24 hours after administration of cytotoxic chemotherapy. No dose adjustments were recommended based on extrinsic or extrinsic factors (age, race sex, body weight, renal impairment or hepatic impairment). The Review stated no drug-drug interactions were expected based on the mechanism of action and molecular properties of eflapegrastim.

The immunogenicity results from the two Phase 3 studies showed higher cumulative incidence of ADAs in patients treated with eflapegrastim compared to pegfilgrastim (9.4% vs. 3.3%). Incidence of treatment-emergent anti-PEG antibodies was significantly higher in the pegfilgrastim arm (63.5%) than in the eflapegrastim arm (47%). One patient in the eflapegrastim arm (0.3%) and no patients in the pegfilgrastim arm had treatment-induced neutralizing anti-drug antibodies. No effect of anti-eflapegrastim antibodies was found on clearance of eflapegrastim or efficacy. The incidence of allergic reactions was found to be independent of the presence of anti-eflapegrastim antibodies.

The Review recommended approval of the Rolontis 13.2 mg administered once per chemotherapy cycle administered approximately 24 hours after cytotoxic chemotherapy for the proposed indication. Recommendations were made for labeling including inclusion of pharmacokinetic (PK) characteristics of eflapegrastim and absorption, elimination and metabolism of eflapegrastim. There were no recommendations for post-marketing requirements or commitments (PMR/PMC).

5. Clinical Microbiology

N/A. [There was no Clinical Microbiology review for this application. CMC microbiology aspects of the application were reviewed by the Office of Product Quality. (See section 2. CMC/Device above)].

6. Clinical/Statistical- Efficacy

The primary Clinical and Statistical Review of this application was completed by Hyon-Zu Lee and Kate Dwyer (final signature in DARRTS 6/24/2020).

As summarized in the review:

> 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.

Study SPI-GCF-301 (Study 301) and Study SPI-GCF-302 (Study 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 (docetaxel and cyclophosphamide) chemotherapy. The two studies had identical endpoints, statistical hypotheses and methods but differed in the planned numbers of patient enrollment (Study 301: 400 patients, Study 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 (b) (4) mg G-CSF) 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. Pegfilgrastim was to be supplied by Spectrum to all sites (US and ex-US) in 6 mg/0.6 mL prefilled single-use syringes. Patients could receive pre-medications per standard of care

prior to the TC chemotherapy administration. 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 both studies, 4 cycles were to be evaluated. The primary efficacy endpoint for these studies was the comparison of the duration of severe neutropenia (DSN) in Cycle 1 between the eflapegrastim arm and the pegfilgrastim arm. 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 noninferiority hypothesis in the intent-to-treat (ITT) population. The review found the study design and primary endpoint adequate. The statistical analysis plan stated 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. The Review commented, "*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.*"

Study 301 enrolled a total of 406 patients and Study 302 enrolled 237 patients. All but 2 patients were female. Median age was approximately 60 years and patients were predominantly white (approximately 77%). In Study SPI-GCF-301 97% of patients were enrolled in the U.S. and in Study 302 55% of patients were enrolled in the U.S. Most patients in both studies had Stage I or IIA cancer (74% in Study 301 and 66% in Study 302). Predominant histology in both studies was ductal invasive cancer (88% in Study 301 and 80% in Study 302). Approximately 58% of patients in both studies were ER+/PR+/HER2-. In both studies demographics and baseline disease characteristics were largely balanced between the treatment arms.

Treatment compliance was nearly 100% in both studies and only approximately 5% of patients had major protocol violations, which did not affect the overall efficacy analysis of the primary endpoint. Of the randomized patients, 71% in Study 301 and 76% in Study 302 completed the study. The main reasons for withdrawal were due to withdrawal by patient (301: 11%, 302: 8%) and initiation of non-protocol therapy for breast cancer (301: 4%, 302: 8%).

Results of the primary efficacy analyses for the two studies are shown in Tables 21 and 22 from the Clinical and Statistical Review shown below.

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		
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

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

The frequency of missing samples was comparable between the two treatment arms in both studies. Simulations and sensitivity analyses conducted to evaluate the impact of sampling and handling of dropouts or missing data did not reveal concerns. The sensitivity analyses support the primary analysis as the upper bound of all of the 95% CIs were less than the non-inferiority margin of 0.62 days. Thus, the noninferiority results seem robust in both studies. Subgroup analyses for age, race, disease status, and weight were generally found to support the findings from the primary efficacy analysis. In Study 302 analyses were similar for U.S. and non-U.S. patients. The results of a pooled analysis of Studies 301 and 302 were consistent with those of the individual studies.

Effect of dose was evaluated in a supportive study (Study SPI-GCF-12-201 [Study 201]), which was an open-label, multicenter, dose-ranging (sequentially enrolled by study dose), noninferiority 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. The study included 4 treatment arms:

- Single-dose eflapegrastim (45 mcg/kg)
- Single-dose eflapegrastim (135 mcg/kg)
- Single-dose eflapegrastim (270 mcg/kg)
- 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 (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.

Study 201 enrolled 148 patients. Patient demographics and baseline disease characteristics generally were balanced across the 4 treatment arms and were generally similar to those in studies 301 and 302. The median age was 59 years, 98% of patients were females, and 95% of patients were White. Most patients had Stage I, IIA or IIB breast cancer (78%) and the median ANC at baseline was 8 x10^9/L. Most of the patients (84%) had ductal invasive carcinoma and 44% were candidates for adjuvant chemotherapy. The primary efficacy results for Study 201 are shown in Table 44 from the Clinical and Statistical Review shown below.

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

The primary efficacy analysis showed a dose-effect trend across the three doses of eflapegrastim, with the mean DSN (with ANC recovery to 2.0 x 10^9/L) decreasing with increasing dose. As stated in the review, the analysis showed 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 the 270 mcg/kg eflapegrastim arm (0.03 days) compared to patients treated in the pegfilgrastim arm (0.31 days) had a nominal p-value < 0.05 (p=0.023).

Conclusions of the assessment of effectiveness were stated as follows in the Review:

> 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.

7. Safety

The primary clinical review of safety for this application was conducted by Hyon-Zu Lee (Clinical and Statistical Review, final signature in DARRTS 6/24/2020).

The review summarized the safety results:

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.

The review concluded that the toxicity of eflapegrastim is manageable with adequate recommendations for monitoring and treatment modifications to be described in the prescribing information. There was no recommendation for Risk Evaluation and Mitigation Strategies (REMS) for the product. The review stated that, "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)."

The Division of Risk Management/Office of Medication Error Prevention and Risk Management/Office of Surveillance and Epidemiology (DRM/OMEPRM/OSE) reviewed the application with regard to whether a REMS is necessary to ensure the benefits of Rolontis outweigh its risks. The DRM Review (Mei-Yean Chen, final signature 9/11/2020) stated, "The Division of Risk Management (DRM) and the Division of Hematology Products (DHP) agree that a REMS is not needed for eflapegrastim-xnst to ensure the benefits of outweigh its risks. The risks of eflapegrastim-xnst include serious allergic reactions, splenic rupture, leukocytosis, and fatal sickle cell crises and these will be communicated in Section 5 Warnings and Precautions. These risks have been reported with other drugs in this class and oncologists, the likely prescribers, are already familiar with these risks as other G-CSFs have been on the market since 2002."

The Interdisciplinary Review Team for Cardiac Safety Studies reviewed the applicant's QT cardiac safety report (primary review Nan Zheng, final signature 3/17/2020). The review 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 our prior experience for large targeted proteins which have low likelihood of direct interaction with cardiac ion channels.
2) The sponsor 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.

8. Advisory Committee Meeting

There was no advisory committee meeting held for this application. The review team agreed that the efficacy and safety of the product were adequately characterized by the applicant, and the application raised no novel or controversial issues.

9. Pediatrics

No pediatric patients were studied for the current BLA. 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) because of the rarity of solid tumors in the age group, such that studies are highly impracticable; deferral for pediatric patients 1 month to <18 years of age for a phase 2 PK/PD study. The Clinical and Statistical Review (signed 6/24/2020) comments that the applicant has submitted the protocol for the pediatric PK/PD 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" on April 2, 2019. This deferred study will be listed as a required postmarketing study.

The Review also notes and comments regarding the eflapegrastim presentation planned for marketing:

A Consult Review Memo by the Division of Pediatrics and Maternal Health (DPMH) (Anissa Davis, 9/1/2020) indicated that advice had been issued to the Applicant regarding the PMRs in PMR/PMC/General Correspondence on August 14, 2020 and also in the Late Cycle Meeting minutes to the Applicant on August 27, 2020 and reflected the Agency's current thinking and DPMH's input accordingly. DPMH had no further comment.

The recommended wording of the PMRs as stated in the Late Cycle Meeting Minutes (meeting held 8/5/2020; minutes issued 8/27/2020) is:

- 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.

- 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 (1 month to <18 years of age) and conduct any necessary human factors studies to evaluate the ability of healthcare providers and/or caregivers to measure the appropriate doses.

10. Other Relevant Regulatory Issues

Review of the list of four-letter suffixes proposed by the applicant for inclusion in the nonproprietary name of the product was conducted by the Division of Medication Error Prevention and Analysis (DMEPA)/Office of Medication Error Prevention and Risk Management (OMEPRM) (Carlos Mena-Grillasca, final signature in DARRTS 6/29/2020). The review concluded that the applicant's first choice suffix '-xnst' was conditionally acceptable (i.e., provided the application is approved. If the application receives a Complete Response (CR), the suffix will be re-evaluated when the applicant responds to the deficiencies.

Proprietary Name Review was completed by Devin Kane (final signature in DARRTS, 1/14/2020). The applicant previously submitted the proposed proprietary name, Rolontis on June 3, 2016 under IND 103461 and DMEPA found the name acceptable on October 23, 2016. For the BLA 761148 the applicant submitted the name, Rolontis, for review on October 24, 2019 under BLA 761148. The proposed name was evaluated for safety with respect to: USAN stem, components of the proposed proprietary name, comments from other review disciplines, FDA name simulations studies, phonetic and orthographic characteristics, name pair similarity, and spelling similarities. The review concluded the proposed proprietary name, Rolontis, is acceptable.

11. Labeling

The applicant included proposed labeling in the submission. Final wording for the labeling was developed by the DNH review team with discussion and consideration of the recommendations from each of the review disciplines and consulting review divisions and with negotiation with the applicant.

Major recommendations for changes to the applicant-proposed labeling from the Clinical and Statistical Review included the following:

- **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.

Labeling recommendations for the prescribing information (PI), patient package insert (PPI), and carton and container labeling were provided by Office of Prescription Drug Promotion (OPDP) (Rebecca Falter, 6/16/2020). Labeling recommendations were provided for the package insert. OPDP recommendations for the PPI were included in the recommendation in

the DMPP review (6/12/2020). There were no recommendations for the carton and container labeling.

Patient Labeling Review of the applicant's proposed Patient Package Insert (PPI) was conducted by Sharon Mills, Division of Medical Policy Programs (DMPP) and Rebecca Falter (OPDP) (signed 6/12/2020). The review recommended changes to the PPI to simplify wording and clarify concepts, ensure consistency of the PPI with the PI, remove unnecessary or redundant information to ensure that the PPI is free of promotional language, and to ensure that the PPI meets current FDA guidance criteria. The recommendations from the Patient Labeling Review were communicated to the applicant and final wording was negotiated with the applicant.

A primary risk assessment review of the labeling was performed by the Division of Medication Error Prevention and Analysis (DMEPA)/Office of Medication Error Prevention and Risk Management (OMEPRM) (Stephanie DeGraw, final signature 5/13/2020) to identify areas of vulnerability that could lead to medication errors. Recommendations were made to improve the prescribing information and the carton and container labeling. The recommendations were communicated to the applicant and the applicant submitted revised container and carton labeling. Additional recommendations were provided to the applicant (DMEPA Review, Stephanie DeGraw, 6/11/2020) and the applicant made the requested additional revisions and resubmitted the container and carton labeling which was found acceptable (DMEPA Review, Stephanie DeGraw, 7/28/2020). Labeling recommendations for the prescribing information were considered in the labeling discussions with the entire review team and negotiated with the applicant.

The labeling was reviewed by the Division of Nonmalignant Hematology (DNH) Associate Director of Labeling (Virginia Kwitkowski, final signature 9/28/2020). Recommendations were provided for the content and format of the Warnings and Precautions section of the prescribing information (PI) to help ensure that the PI is compliant with Physician Labeling Rule (PLR) and Pregnancy and Lactation Labeling Rule (PLLR) requirements, is consistent with labeling guidance recommendations and with CDER/OND best labeling practices and policies, conveys the essential scientific information needed for safe and effective use of the product, is clinically meaningful and scientifically accurate, is a useful communication tool for health care providers, and is consistent with other PIs with the same active moiety, drug class, or similar indication. The recommendations were considered in labeling discussions with the entire review team. The review recommended the BLA for approval upon completion of the labeling negotiations.

12. Recommendations/Risk Benefit Assessment

This application provides substantial support for the approval of Rolontis (eflapegrastim) injection, a granulocyte colony stimulating factor (G-CSF), for the indication: 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 (equivalent to (b) (4) mg G-CSF) solution in a single-dose prefilled syringe. The 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.

Review of the data submitted for the application by CMC (Office of Biopharmaceutical Products), Nonclinical Pharmacology and Toxicology, Office of Clinical Pharmacology, clinical and statistical review and consulting divisions found the data adequate to support approval of the application.

Efficacy of Rolontis was demonstrated in two similarly designed, randomized (1:1), open-label, noninferiority, 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 injection, in patients with early-stage breast cancer receiving docetaxel and cyclophosphamide (TC) chemotherapy. Study 301 randomized a total of 406 patients (196 eflapegrastim, 210 pegfilgrastim) and Study 302 randomized 237 patients (118 eflapegrastim, 119 pegfilgrastim). The primary efficacy endpoint in the two trials was the duration of severe neutropenia (DSN) in Cycle 1. The non-inferiority margin for the between treatment comparison was 0.62 days. In both studies, the treatment of eflapegrastim was non-inferior to pegfilgrastim therapy for the mean DSN in Cycle 1 with a mean DSN in Cycle 1 of eflapegrastim compared to pegfilgrastim of -0.148 days (95% CI: -0.265, -0.033) in Study 301 and a mean DSN in Cycle 1 of eflapegrastim compared to pegfilgrastim of -0.073 days (95% CI: -0.292, 0.129).

The major safety concerns for Rolontis are consistent with those for other products in this class. These include serious allergic reactions (contraindication for use in patients with a history of serious allergic reactions to eflapegrastim, pegfilgrastim or filgrastim products), splenic rupture, leukocytosis, and potential for tumor growth stimulatory effects on malignant cells. Also, use in patients with sickle cell disease can cause severe and sometimes fatal sickle cell crisis. In the clinical trials the most frequently reported serious adverse events (SAEs) in the eflapegrastim arm were pyrexia, sepsis, febrile neutropenia, diarrhea, and chest pain; the incidences of these SAEs were similar to those observed in the pegfilgrastim arm.

There were recommendations for the following PMRs from the clinical review:

- 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.

- 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 (1 month to <18 years of age) and conduct any necessary human factors studies to evaluate the ability of healthcare providers and/or caregivers to measure the appropriate doses.

Also, OPQ has the following PMRs:

(b) (4)

All review disciplines, including consulting divisions provided input in the labeling negotiations.

OPQ special product quality recommendations for labeling included: Store in a refrigerator at 2˚C to 8˚C (36˚F to 46˚F); protect from light until use; do not shake; do not freeze. The CDRH review of the pre-filled syringes recommended a shelf life of 24 months.

As summarized above, the material included in this BLA provides substantial evidence of efficacy in support of this application. However, as discussed under section 2, CMC/Device, above, a facility inspection is required and is still pending at this time because of delay due to current restrictions on travel due to the current public health situation. Consequently, although the data reviewed in this BLA support approval with final wording in the labeling as negotiated with the applicant and with the additional recommendations described above as post-marketing requirements, the application cannot be approved until the facility inspection has been conducted and found satisfactory.

Because of the current public health situation, the Agency has established an approach to regulatory actions during this time when inspections cannot be conducted. (See attached e-mail communication in Appendix). Based on this current policy, it is recommended that no regulatory action for approval or Complete Response of the BLA be taken at this time. Rather, action on the application should be delayed until the inspection is completed.

APPENDIX

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

KATHY M ROBIE SUH
10/13/2020 02:48:54 PM