CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761148Orig1s000

SUMMARY REVIEW

Summary Review for Regulatory Action

Date	August 2, 2021
From	Ellis Unger, MD Director, Office of Cardiology, Hematology, Endocrinology, and Nephrology
To	the file
Subject	Office Director Summary Review
Original BLA#	BLA 761148
Applicant	Spectrum Pharmaceuticals, Inc.
Date of Submission	October 24, 2019
PDUFA Goal Date	October 24, 2020
Proposed Trade Name	Rolontis
Established Name	eflapegrastim-xnst
Dosage Forms	Solution for Injection; 13.2 mg/0.6 mL
Recommendation	*Complete Response*
Recommended Indication	To decrease the incidence of infection, as manifested by febrile neutropenia, in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs

Summary Review for Regulatory Action:

I agree with the background and reviews of the principal studies per Drs. Dwyer, Lee, Ande, Hao, Robi Suh, Shanks, Wroblewski, and Deisseroth.

BLA Manufacturing Facility Assessment

It was necessary to miss the PDUFA action date pending the outcome of pre-approval facilities inspections, which were delayed secondary to the COVID 19 pandemic.

Inspections of manufacturing facilities were recently completed; however, deficiencies were noted and conveyed to the representatives of the facilities. Satisfactory resolution of these deficiencies will be required before this application may be approved.

Efficacy

I agree with the descriptions, results, conclusions, and interpretations of the principal studies as described by the review team. I will note, however, that I do not believe that the descriptions of the studies as presented in the draft proposed labeling would be readily interpretable to future prescribers or patients. Table 2 in the draft labeling summarizes the study results:

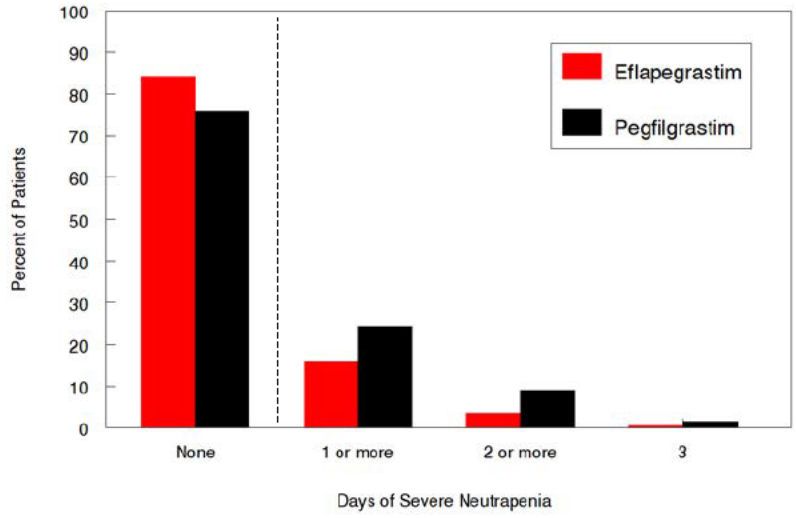
Table 2. Duration of Severe Neutropenia (DSN) in Cycle 1 (Study 1 and Study 2)

	Study 1		Study 2	
	(b) (4) (n=196)	Pegfilgrastim (n=210)	(b) (4) (n=118)	Pegfilgrastim (n=119)
Mean DSN (SD) (Days)	0.20 (0.503)	0.35 (0.683)	0.31 (0.688)	0.39 (0.949)
Median DSN (Range) (Days)	0 (0, 3)	0 (0, 3)	0 (0, 3)	0 (0, 7)
Difference in DSN (Days)	-0.148		-0.073	
*95% Confidence Interval[a]	-0.265, -0.033		-0.292, 0.129	

I recognize that the Division has typically expressed the results of such trials as reductions in mean days of severe neutropenia. I do not believe, however, that the numbers in the table above (-0.148 and -0.073 days, equivalent to -3.6 and -1.8 *hours*, respectively) would be readily interpretable or useful to practitioners.

In these studies, 76 to 80% of patients had no days of severe neutropenia, i.e., the data are not normally distributed. Thus, medians would be more appropriate to display; however, for these studies, the medians are zero in both treatment groups, and would convey no useful information. (To one significant figure, the means, medians, and modes are all zero for both treatment groups in both studies.)

That is not to say that there is no useful way to display the data. I suggest the use of either a table or a figure that summarizes the results as percentages of patients who have no days, at least one day, at least two days, and three days of severe neutropenia in both treatment groups. For example, a figure such as the one below could display the results of Study 301 (a table of these results would also be acceptable).



Safety

I agree with the reviews of Drs. Lee, Robi Suh, Wroblewski, and Deisseroth.

With respect to the Warnings and Precautions section of the label, I will note that there are a number of differences between the proposed eflapegrastim label and the pegfilgrastim label that may need to be reconciled.

For the Adverse Reactions section of the draft label, the table of adverse reactions in Section 6.1 contains some 35 entries, many of which would not be useful to practitioners. Ideally, the table would contain only adverse events that are thought to be causally related to eflapegrastim, i.e., adverse drug reactions. In order to be considered an adverse drug reaction, adverse events should be more frequent in the eflapegrastim groups than in the pegfilgrastim groups, perhaps with a risk differences of >2%. With the application of this principle, only the adverse events highlighted in yellow would be included in the table.

In addition, recognizing that bone pain and pain in extremity are adverse drug reactions for pegfilgrastim (with frequency greater than placebo), and the frequency of these adverse events was similar in eflapegrastim- and pegfilgrastim-treated patients in this development program, these adverse events should also be included in the table (highlighted in blue). Terms that are not highlighted should not be included in the adverse reaction table, which would leave some 13 terms.

Adverse Reaction	(b) (4) **= 314** **N (%)**	(b) (4) **N=329** **N (%)**
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%)
(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%)
[redacted] (b) (4)		
Local administration reactions*	34 (11%)	27 (8%)
[redacted] (b) (4)		
Flushing	32 (10%)	27 (8%)
[redacted] (b) (4)		

*Grouped Terms by FDA Medical Query (FMQ)

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/s/

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Summary Review for Regulatory Action

Date	October 16, 2020
From	Albert Deisseroth MD, PhD, Associate Director, Division of Nonmalignant Hematology
Subject	Division Director Summary Review
Original BLA #	BLA 761148
Applicant	Spectrum Pharmaceuticals, Inc.
Date of Submission	October 24, 2019
PDUFA Goal Date	October 24, 2020
Proper Name	Rolontis
Established Name	Eflapegrastim
Dosage Forms	Solution for Injection
Recommendation	Delayed Action Pending Outcome of Pre-approval Facilities Inspections Due to SARS CoV2 Pandemic.
Recommended Indication	To decrease the incidence of infection, as manifested by febrile neutropenia, in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs.

Material Reviewed/Consulted	
Medical/Statistics Review	Hyon-Zu Lee DPharm and Kathy Robie Suh, MD, PhD/ Kate Li Dwyer PhD and Yeh Fong Chen PhD

Summary Review for Regulatory Action:

(This review was derived in part from the reviews of Drs. HZ Lee, K Dwyer, YF Chen, and K Robi Suh.)

Background: On October 24, 2019, Spectrum Pharmaceuticals, Inc. submitted BLA 761148 to the FDA. In this BLA, the applicant asked for the approval of eflapegrastim (Rolontis) for the following indication: To decrease the incidence of infection, as manifested by febrile neutropenia, in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs.

Rolontis is a long acting myeloid growth factor which is comprised of a single analogue of human G-CSF (HM10411) which is attached to a 3.4 kDa polyethyleneglycol (PEG) linker which is connected in turn to a single IgG4Fc moiety (HNC001). Rolontis has a molecular weight (72 kDa) which is almost twice the size (39 kDa) of the first clinically approved peg-filgrastim (Neulasta) which is in turn twice the size (19 kDa) of the original filgrastim growth factor (Neupogen). The HM104411 and HNC001 are produced by recombinant DNA technology in E. coli. Rolontis is presented in single syringes pre-filled with 13.2 mg of Rolontis in 0.6 mL (b) (4) mg G-CSF and 6 mg Neulasta).

This request for approval relied upon the results of two randomized active controlled double-blind studies: SPI-GCSF-301 (Study 301), and SPI-GCSF-302 (Study 302). Patients with early-stage breast cancer were randomized to receive by subcutaneous injection 0.6 mL containing either 13.2 mg of Rolontis or 6 mg of Neulasta. In Study 301, 196 patients received Rolontis while 210 patients received Neulasta. In Study 302, 118 patients received Rolontis while 119 patients received Neulasta.

Either Rolontis or Neulasta was given 24 hours after completion of administration of TC chemotherapy (T=docetaxel 75 mg/M^2 IV infusion per institute's standard of care, and C=cyclophosphamide 600 mg/M^2 IV infusion per institutes standard of care). TC combination chemotherapy was given every 21 days for 4 cycles. The primary efficacy endpoint was the duration of severe neutropenia (DSN) in Cycle 1.

Efficacy: The non-inferiority (NI) of Rolontis to Neulasta would be declared if the upper bound of the 95% confidence interval (CI) of the difference in the mean DSN in days between the test groups (i.e. Rolontis minus Neulasta) was less than the NI margin of 0.62 days. (For a description of how the confidence intervals were obtained for this efficacy analysis using 2.5 percentile and 97.5 percentile of the 100,000 bootstrap samples with treatment as stratification factor, please see the review of Dr. Kate Dwyer).

Neupogen was approved based on a placebo-controlled trial. Neulasta 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 the comparison of unapproved pegylated myeloid growth factors like Rolontis with the reference peg-filgrastim (Neulasta) was set at 0.62 days, in order to maintain the magnitude of the original effect size of the Neulasta as compared to Neupogen.

For Study 301, the difference in mean DSN between the Rolontis arm and the Neulasta arm was -0.148 days (95% CI: -0.265, -0.033). These results showed that Rolontis was non-inferior to Neulasta in Cycle 1 (upper bound of 95% CI <0.62 days; p<0.0001). In addition, the applicant claimed (b) (4)

For Study 302, the difference in mean DSN between the Rolontis arm and the Neulasta arm was -0.073 days (95% CI: -0.22, 0.129). This showed that Rolontis was non-inferior to Neulasta in Cycle 1 (upper bound of 95% CI <0.62 days; p<0.0001). In contrast to the results referred to above in Study 301, in Study 302, superiority of Rolontis to Neulasta was not shown (superiority nominal p=0.499).

Safety: (For a detailed analysis of the Safety Results, please see the review of Dr. Hyon-Zu Lee). The safety population consisted of patients pooled from Studies 301 and 302. A total of 314 patients received Rolontis and 329 patients received Neulasta. A total of 272 patients received four 21-day treatment cycles.

Study Deaths: Among the 314 patients who received Rolontis in the pooled safety population of Studies 301 and 302, there were no deaths within 30 days of the last therapy, whereas among the 329 patients who received Neulasta on Studies 301 and 302, there were 2 deaths within 30 days of the last exposure to Neulasta. The incidence of SAEs was similar (15%) in both the Rolontis and Neulasta arms. Serious adverse reactions assessed as occurring in greater than 2 patients in the Rolontis arm included arthralgias, back pain, bone pain, chest pain, pyrexia, supraventricular tachycardia and leukocytosis. Permanent discontinuation associated with an adverse reaction occurred in 4% of patients exposed to Rolontis and 6% in patients exposed to Neulasta.

In Table 1 (see below table developed by Dr. Hyon-Zu Lee working with Dr. Ellis Unger) are summarized adverse reactions that occurred in Studies 301 and 302 regardless of causality (including chemotherapy). The adverse reactions that were ≥5% higher in the Rolontis arm than in the Neulasta arm include: anemia, myalgia, arthralgia, insomnia, and thrombocytopenia. This result is consistent with the hypothesis outlined above in the second paragraph of the Background Section that Rolontis is a more potent myeloid growth factor than is Neulasta.

Table 1: Adverse Reactions in Patients with a Frequency of ≥10% in Study 301 and Study 302

Adverse Reaction	(b) (4) **N = 314**	(b) (4) **N=329**
	n (%)	**n (%)**
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%)
(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)

Benefit Risk Analysis: (For a detailed and comprehensive discussion of BLA 761148, please see the CDTL Review of Dr. Kathy Robi Suh). Based on the structural features (molecular weight) of Rolontis when compared to Neulasta and Neupogen (see paragraph #2 of the Background section above on page 2 of this review), (b) (4). This was observed nominally to be the case in terms of Study 301 but not Study 302 (possibly due to the smaller number of patients in Study 302). The NI analysis of Studies 301 and 302 showed that Rolontis is non-inferior to Neulasta in both studies. No new safety signals were detected in patients treated with Rolontis as compared to Neulasta, in the pooled safety analysis of Studies 301 and 302. The benefit risk is favorable.

PMRs/PMCs: The following PMRs were recommended by the clinical review team:

- Conduct a study to assess the safety, PK and PD of Rolontis 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 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 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.

The following PMRs were recommended from the OPQ review:

(b) (4)

Regulatory Recommendation of the Supervisory Associate Division Director DNH: There is no information so far which would prevent a recommendation for Approval of BLA 761148. However, the pre-approval manufacturing facilities inspection has not been completed as of this date. Therefore, the regulatory recommendation is for a Delayed Action. The timing of the final recommendation for regulatory action is contingent upon successful completion of the pre-approval facilities inspection of a manufacturing site in (b) (4) Travel to this manufacturing site is not feasible in the near term for the FDA inspection team due to the worldwide risk of infection by the SARS CoV-2 virus. An addendum possibly with a revised and final regulatory recommendation will be provided once this issue is resolved.

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/s/

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