Office of Clinical Pharmacology Review

BLA Number/Supplement	125294/S-45
Link to EDR	\\CDSESUB1\evsprod\BLA125294\125294.enx
Submission Dates	01/31/18
Submission Type	Priority
Brand Name	Granix
Generic Name	Tbo-filgrastim
Dosage Forms and Strengths	300 µg/0.5 mL & 480 µg/0.8 mL solutions in single-dose prefilled syringes. 300 µg/1 mL & 480 µg/1.6 mL solutions in single-dose vials.
Route of Administration	Subcutaneous
Proposed Indications	Reduction in the duration of severe neutropenia in adult and pediatric patients 1 month and older with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a clinically significant incidence of febrile neutropenia.
Applicant	Sicor
Associated Applications	IND 103188
OCP Review Team	Sriram Subramaniam, PhD; Stacy Shord, PharmD (TL), Ruby Leong, Pharm.D. (TL)
OCP Final Signatory	NAM Atiqur Rahman, PhD Director, Division of Clinical Pharmacology V Office of Clinical Pharmacology

1 Executive Summary

The Applicant submitted a supplement to BLA 125294 in response to a Written Request (WR) for a pediatric study of tbo-filgrastim for pediatric exclusivity determination (WR issued on January 19, 2018; Reference ID:4209413). The requirement for investigating tbo-filgrastim in <1 month of age was waived. This supplement fulfills the clinical pharmacology components of the WR.

Tbo-filgrastim is a leukocyte growth factor approved for the reduction in the duration of severe neutropenia (DSN) in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a clinically significant incidence of febrile neutropenia. Based on safety in the pediatric population and the extrapolation of efficacy from adults supported by pharmacokinetics (PK) data in the pediatric population, the Applicant is requesting an indication for this population. The supplement includes proposed language to update Sections 1, 3, 6.2, 8.4 12.2, and 12.3 of the US prescribing information to describe the findings from the pediatric study.

PK and pharmacodynamics (PD) were characterized in an open-label study in pediatric patients (age range: 1.4 years to 16 years, N=50) with solid tumors without bone marrow involvement. A 5 µg/kg/day subcutaneous (SC) dose was administered 24 hours after the last chemotherapy (CTX) dose in Week 1 for a maximum of 14 consecutive days. The results showed that the area under the curve from 0 to 12 hours ($AUC_{0\text{-}12h}$) and maximal concentrations (C_{max}) in infants (1 month to <2 years, n=2), children (2 to <12 years, n=29) and adolescent (12 to <17 years, n=18) patients were comparable. A cross-study comparison of PK following tbo-filgrastim 5 µg/kg/day indicated that the $AUC_{0\text{-}12h}$ and C_{max} in the pediatric population overlapped with those in adult patients with high-risk breast cancer. The current pediatric trial was not designed to compare efficacy because of the small sample size of the trial and confounding factors, including baseline demographics, disease characteristics, and chemotherapy treatment. Also, cross-study comparison of DSN in pediatrics with solid tumors to that in adults with high-risk breast cancer receiving chemotherapy may not be relevant.

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2 Summary of Labeling Recommendations

- In Section 1, the patient population in the indication was amended to "adult and pediatric patients 1 month and older".
- In Section 3, single-dose vial information included.
- In Section 6.2, combined immunogenicity data for adult and pediatric patients, as the same assay, testing site, and appropriate cut-points were used for immunogenicity for both populations.
- In Section 8.4, modified description of the pediatric trial, and included a high level summary of PK results.
- In Section 12.2, "maximum recommended" was deleted as there is no recommended intravenous dose for this drug product.
- In Section 12.3, included PK results from the pediatric trial in the subsection titled "Pediatric patients" under "Specific Population". Also, Section 12.3 was reformatted per the current FDA clinical pharmacology labeling guidance (2016).

3 Overview of the Product and Regulatory Background

For brevity, only QBR questions related to the current submission are addressed below. For additional details, please refer to the original BLA 125294 (submission date of 2/29/2012) and the corresponding clinical pharmacology review in DAARTS (DARRTS date 8/2/2012).

PERTINENT REGULATORY HISTORY

- On August 11, 2010, a partial waiver of < 1 month of age was granted, due to the rare incidence of non-myeloid cancers requiring myelosuppressive chemotherapy in the neonatal population, which makes it unfeasible or highly impracticable to study tbo-filgrastim in the neonatal population.
- On August 29, 2012 the Applicant received initial BLA approval, and agreed to PMR 2333-1:
  Phase 2 trial in 50 pediatric patients 1 month to 16 years of age to evaluate PK, PD, and safety data in patients with solid tumors without bone marrow involvement.
- April 1, 2014, FDA found pediatric Protocol XM02-ONC-201 in patients with solid tumors without bone marrow involvement was acceptable to fulfill PMR for tbo-filgrastim under IND103188.
- May 11, 2016, FDA agreed to revise milestone dates for trial completion (from 6/2016 to 7/2017) and final report submission (from 12/2016 to 12/2017)
- May 31, 2017, the Applicant formally submitted a PPSR to obtain WR with Protocol XM02-ONC-201 as the basis for the WR.
- On January 19, 2018, an amendment to the September 21, 2017 WR was issued to BLA with a due date of March 31, 2018 replacing January 31, 2018.

4 Clinical Pharmacology Questions

4.1 What are the design features of the clinical pharmacology and clinical study used to support dosing or claims?

The clinical study XM02-ONC-201 was included in the application. The design features of the study are listed in the Table 1:

Table 1: Study design

Purpose	Parameters
Study Design	Multicenter, Open-Label
Primary Objective	Safety and tolerability
Secondary Objectives	• Febrile neutropenia • PK • PD (incidence & duration of DSN, absolute neutrophil count (ANC) AUC, ANC Max, ANC nadir, time to ANC nadir from start of tbo-filgrastim administration and start of CTX to occurrence of ANC nadir, time to ANC recovery ≥1x 10^9/L and ≥2 x 10^9/L from ANC nadir, and time to ANC recovery ≥1x 10^9/L and ≥2 x 10^9/L from start of tbo-filgrastim treatment and start of CTX-Day1) • Immunogenicity
Study Population	50 patients with solid tumors without bone marrow involvement: n=2 infants (1 month to <2 years) n=30 children (2 to < 12 years) n=18 adolescents (12 to < 16 years)
Proposed Dose	5 µg/kg/day starting 24 hours after the last CTX dose in week 1 for a maximum of 14 consecutive days.
PK	Predose, and at 2, 4, 6, 8, and 12 hours after the tbo-filgrastim dose on Day 1
PD (ANC)	Pre-dose on Day 1, and on Days 5, 6, 7, 10, 12, 15 (if CTX is shorter than a week) and 21
Immunogenicity	Baseline, 21 days after 1st dose, and 30 and 90 days after last dose

The study design and PK and PD endpoints are consistent with the revised WR.

4.2 What is the PK characteristics of the drug?

Tbo-filgrastim PK is similar in children (2 to < 12 years), and adolescents (12 to <16 years). PK parameters for infants appeared higher; however, the sample size was limited to only 2 patients. PK parameters obtained from non-compartmental analyses of data from Study XM02-ONC-201 are summarized in Table 2.

Table 2: Mean tbo-filgrastim PK parameters across pediatric age groups at the 5 µg/kg/day dose in Study XM02-ONC-201

Age Group	C_{max} (ng/mL)				$AUC_{0\text{-}12h}$ (ng*hr/mL)			
	n	Mean*	%CV*	Min, Max	n	Mean*	%CV*	Min, Max
Total	49	18	56	5, 46	45	130	52	39, 317
1 month < 2years	2	--	--	20, 32	2	--	--	131, 245
2 years to <12 years	29	18	54	5, 45	28	130	53	39, 301
12 years to < 16 years	18	16	60	6, 46	15	125	54	57, 317

*Geometric mean and CV

Source: Reviewer's Analysis

A cross-study comparison suggests that the mean AUC and Cmax in pediatric patients overlap with the PK in adults due to the high inter-patient variability (24-65% CV: see Table 3).

Table 3: Cross-study comparison of mean tbo-filgrastim PK parameters in pediatric and adult patients at the 5 µg/kg/day dose

		Geometric Means (CV%) Range		Median	
Study	**n**	**C_{max}** [ng/mL]	**$AUC_{0\text{-}12h}$** [ng*h/mL]	**t_{max}** [hours]	**$t_{1/2}$** [hours]
Pediatric Patients					
XM02-ONC-201	49	18 (56%)	130 (52%)	4.1	2.4 (1.5, 3.5)
Adult Patients					
XM02-04-INT (NHL)*	11	20 (24%)	151 (24%)	6.0	3.2 (2.7, 4.6)
XM02-03-INT (Lung)*	13	25 (60%)	194 (60%)	6.0	3.8 (2.6, 7.4)
XM02-02-INT (Breast)*	12	31 (65%)	227 (58%)	4.0	3.6 (2.4, 9.1)

Source: SCP, Module 2.7.2, SDN 446

4.3 What are the characteristics of the exposure-response relationship for efficacy?

No exposure-response (E-R) analysis was conducted, consistent with the WR. The trial is required to evaluate the safety in the pediatric population and confirm the validity of efficacy extrapolation from adults by evaluating PK and PD in the pediatric population and assumption of similar disease progression, response to intervention, and E-R in pediatrics and adults.

A summary of the efficacy and selected PD results are provided in Table 4. The results suggest that the mean DSN and the incidence of febrile and severe neutropenia were lower in adolescents compared to those in children at 5 µg/kg/day. Also, the mean DSN in adolescents appeared to be comparable to that in adult patients with high-risk breast cancer undergoing chemotherapy (Granix labeling: 1.1 days in treatment arm versus 3.8 days in placebo arm) at the same dose of 5 ug/kg/day. However, per DHP Clinical Team, the current pediatric trial was not designed to compare efficacy due to the small sample size and confounding variables including, baseline demographics, disease characteristics, and chemotherapy treatment. Additionally, the cross-study comparison of DSN in pediatrics with solid tumors with that in adults with high-risk breast cancer receiving chemotherapy may not be relevant.

Table 4: Comparison of Efficacy and PD parameters in pediatric patients at the 5 µg/kg/day dose in Study XM02-ONC-201

Variable	1 mo to <2 yrs (n=2)	2 to <12 yrs (n=30)	12 to <16 yrs (n=18)
Duration Severe Neutropenia (DSN), days [95% CI]	NA	2.5 [1.5, 3.4]	0.7 [0.1, 1.2]
Febrile Neutropenia, % (95% CI)	50%	30% [15, 49]	17% [4, 41]
Severe Neutropenia, % (95% CI)	50%	63% [44, 80]	33% [13, 59]

ANC AUC (x10^9*days/ L) (95% CI)	NA	39 [28, 53]	74 [57, 97]
ANC Max (x 10^9/L) (%CV)	NA	9.6 (80)	16.9 (98)

5 Bioanalytical Measurement of Tbo-filgrastim

An enzyme-linked immunosorbent assay (ELISA) was used to measure tbo-filgrastim in the study. The assay range was 0.5 to 16 ng/mL, and quality controls at 1.5, 5, and 12 ng/mL were used in duplicates in the analytical runs, along with dilution QCs at 50 ng/mL. Ninety five percent of the analytical runs were acceptable, and the in-study assay precision (%CV < 7%) and accuracy (<5% of nominal) were well within acceptable limits. Incurred sample reanalysis demonstrated that ~97% of reanalyzed samples had differences < 30% compared to their original values. Long-term stability was validated for 203 days at -80°C. There was no anti-drug antibody (ADA) interference at ADA 500 ng/mL.

6 Immunogenicity

Immunogenicity sampling was collected at screening, 21 days after the first tbo-filgrastim dose, 30 and 90 days after the last dose, and at follow-up in 50 patients from Study XM02-ONC-201. Samples were analyzed for ADA using a homogeneous ELISA method which was used for detection of ADA in adult patients. No pediatric patients developed ADA after administration of tbo-filgrastim in Study XM02-ONC-201 (refer to the OPQ's Office of Biologic Products review).

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/

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07/06/2018

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I concur with the recommendation.