Clinical Review of PMR Report and
Response to Written Request
Division of Hematology Products

BLA #:	125,294.446.0179
Sponsor:	Teva
Related Files:	IND 103188
Application:	Commercial
Date Received:	1/31/2018
Drug(s):	Granix (tbo-filgrastim)
Dosage Formulation:	300 mcg/0.5 mL PFS and 480 mcg/0.8 Ml
Drug Status:	PFS Approved

Date Review Completed:	6/29/2018
Primary Clinical:	Lea Cunningham, MD
Primary Statistical:	Yaping Wang, PhD
Clinical Team Leader:	Donna Przepiorka, MD, PhD
Statistical Team Leader	Yuan Li Shen, PhD
Supervisory Statistical	Thomas Gwise, PhD

Regulatory Background: Granix was approved 8/29/2012 as an NME "for the reduction in the duration of severe neutropenia in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a clinically significant incidence of febrile neutropenia." The approval letter included the following postmarketing commitment:

PMR 2333-1: Phase 2 trial in 50 pediatric patients 1 month to 16 years of age to evaluate pharmacokinetics, pharmacodynamics, and safety data in patients with solid tumors without bone marrow involvement. Submit the protocol for Agency review and concurrence prior to beginning the trial and in advance of the "final protocol submission" date so that agreement on the essential trial elements can be reached. Important regulatory dates:

Draft Protocol Submission: 02/2013
Final Protocol Submission: 06/2013
Trial Completion: 06/2016
Final Report Submission: 12/2016

The sponsor requested to change the timetable for PMR 2333-1 submitted to Sequence No. 0131 on March 31, 2016. In a letter dated May 11, 2016, FDA agreed to revise the postmarketing requirement milestones for PMR 2333-1:
Draft Protocol Submission: 02/2013

Final Protocol Submission: 06/2013
Trial Completion: 07/2017
Final Report Submission: 12/2017

On 31 May 2017 (IND 103188, Sequence No. 0062), the Sponsor submitted a Proposed Pediatric Study Request to request the Agency to consider study XM02-ONC-201 as the basis for issuing a Written Request. The Written Request issued to the Sponsor on September 21, 2017 confirmed that study XM02-ONC-201conducted to fulfill PMR 2333-1 can be utilized as the basis for the Written Request.

On December 8, 2017, the Sponsor submitted a request to revise the final report submission milestone date for PMR 2333-1 to BLA 125294, Sequence No. 0177. In a letter dated December 29, 2017, the Agency agreed to revise the milestone date for PMR 2333-1. The revised timetable is presented below:

Draft Protocol Submission: 02/2013
Final Protocol Submission: 06/2013
Trial Completion: 07/2017
Final Report Submission: 03/2018

On 31 January 2018, the sponsor submitted a sBLA application and requested Priority Review Designation because the proposed labeling changes are for a pediatric indication. The sponsor is also requesting Pediatric Exclusivity Determination.

Study Background

Study Title/Number: XM02-ONC-201: A multicenter, open-label study to evaluate the safety, tolerability, pharmacokinetics, pharmacodynamics, efficacy, and immunogenicity of daily subcutaneous administration of 5 µg/kg tbo-filgrastim in infants, children and adolescents with solid tumors without bone marrow involvement.

Protocol Design: Single-arm open-label clinical trial (details from SAP)

Objectives: Primary: to determine the safety/tolerability of 5 µg/kg tbo-filgrastim in the pediatric population with solid tumors without bone marrow involvement. The secondary objectives are to assess the pharmacokinetics, pharmacodynamics, efficacy, and immunogenicity of tbo-filgrastim in this patient population.

Planned enrollment: 50
Actual enrollment: 50

Diagnosis and Main Criteria for Inclusion (from synopsis): Patients were included in the study if all of the following main criteria were fulfilled (not inclusive):

- Male or female infants, children, and adolescents aged 1 month to <16 years of age at the time of ICF
- signing.

- Patients with solid tumors without bone marrow involvement (ie, non-myeloid neoplasms), who were
- scheduled to receive myelosuppressive CTX.
- Body weight ≥5 kg.
- Written informed consent provided by parent(s)/legal representative(s) of the pediatric patient and
- patient's assent if able to understand and/or follow study instructions alone or with parental assistance.
- Patients must have an initial diagnosis and histologic proof of their malignancy. Additionally, if the
- patients have a recurrence of their disease, clear radiographic or biopsy evidence is required within
- 4 weeks before study entry.
- All enrolled patients should have signed consent for a CTX regimen that is known to be myelotoxic,
- with counts expected to drop below with ANC of 0.5 × 109/L for at least 3 days. These regimens would include at least 1 of the following:
    - etoposide
    - doxorubicin
    - ifosfamide
    - cyclophosphamide
- ANC and platelet count: Patients must have an ANC >1 × 109/L and a platelet count >100 × 109/L to be eligible for therapy at the start of CTX.
- Normal cardiac, renal, and hepatic function.

Treatment (from synopsis)

Treatment consisted of Tbo-filgrastim subcutaneous administration of 5 μg/kg body weight daily. Treatment duration was until the expected neutrophil nadir was passed and the neutrophil count had recovered to 2.0 × 109/L but not longer than 14 consecutive days.
The maximum study duration for an individual patient (from screening period until the end of the 90-day follow-up period) was approximately 18 weeks.

Monitoring Plan

See table 1 in the protocol for the monitoring plan.

Statistical Analysis

Analysis Population:
The FAS was used for all efficacy analyses. The FAS included all patients in the ITT population who received at least 1 dose of tbo-filgrastim and had at least 1 post baseline efficacy assessment. The FAS analysis set included all 50 enrolled patients.

Primary endpoint: the safety of tbo-filgrastim

Secondary Endpoints: The pharmacokinetic measure for this study was the serum concentration of tbo-filgrastim. The pharmacodynamic measure for this study was the ANC in blood. The

immunogenicity endpoints were the anti-drug antibody (ADA) assessment prior to the first tbo-filgrastim administration, at the end-of-study (EOS) visit, and at 30 days and 3 months after the last tbo-filgrastim administration during the first cycle of CTX.

Analysis of Efficacy:
For continuous variables, descriptive statistics were provided, showing the number of patients (N), number of non-missing observations (n), mean, standard deviation (SD), standard error of the mean (SE), median, minimum and maximum. For categorical variables, frequency tables were provided, showing the number of patients, the number of missing observations (if any), and the number and percentage (based on the number of non-missing observations) of patients falling into each category. In view of the limited number of patients enrolled in the 1 month to <2 years group, use of summary statistics for comparison purpose across all age groups can be misleading. Therefore, min and max values are provided in the 1 month to <2 years age groups

For all variables, other than ANC, imputation of missing values was not foreseen. For the calculation of DSN and time to ANC recovery, missing ANC values during Cycle 1 were imputed as described below. However, imputation of missing ANC values was performed only if at least 3 non-missing ANC values (including the baseline value) were available.

- Missing ANC values pre-CTX and pre-tbo-filgrastim dose (baseline) were not imputed.
- Missing ANC values for measurements between baseline and the last scheduled measurement (15 days post dose) that lie between 2 non-missing measurements were imputed using linear (=straight line) interpolation.
- Missing ANC values at the end (i.e., after the last available measurement up to day 15) were imputed using the last observation carried forward (LOCF) method.
- ANC values for days 2, 3, 4, 8, 9, 11, 13, and 14 post dose (no measurements scheduled) were imputed as described before, using linear interpolation or LOCF, as applicable.

Imputed values were presented in the corresponding listings and flagged as such. In the summary statistics for ANC, missing values were not imputed.

The key efficacy variable was the incidence of febrile neutropenia. This was summarized by a frequency table along with 95% exact confidence interval (CI) for the incidence rate, by age group and overall, and by CTX toxicity group and overall. Logistic regression analyses with age class and CTX toxicity group were performed in an exploratory manner using separate models. Out of these logistic regression analyses, pair-wise odds ratios along with 95% CIs for the classes of the explanatory variables were estimated.

The incidence of hospitalization due to febrile neutropenia was descriptively summarized by number and percentage of patients hospitalized. Exact 95% CIs for the proportion hospitalized was presented. In case of hospitalization, the duration of hospitalization and the duration in intensive care units were descriptively analyzed. The administration of systemic antibiotics and antipyretics were summarized by number and percentage of patients along with 95% exact CIs for the proportion of patients experiencing either event.

Summary of Results
Patient Disposition and Demography: All of the 50 patients enrolled received at least 1 dose of tbo-filgrastim and were evaluated for safety, efficacy and pharmacodynamics. Forty-nine patients

were evaluable for pharmacokinetics; 1 patient was excluded from the pharmacokinetic analysis set since serum concentrations of tbo-filgrastim were not obtained (due to a clot in the tube).

All 50 patients completed the treatment period of the study. Forty-nine of the 50 patients (98%) completed the 30 day and 90 follow-up periods: 2 (100%) of infants (1 month to <2 years), 29/30 (97%) of children (2 to < 12 years), and 18/18 (100%) of adolescents (12 to < 16 years). In the 1 month to <2 years age group, 2 patients were enrolled, with an age range of 1.4 to 1.9 years of age. In the 2 to < 12 years age group, there were 30 patients enrolled, with an age range from 2.4 to 11.5 years of age. In the 12 to < 16 years age group, there were 18 patients enrolled with an age range of 12.0 to 15.9 years of age. The average age of the patients overall was 9.17 years (range 1.4 to 15.9 years). The 2 infants (1 month to <2 years) were 1.4 and 1.9 years old. The mean (SD) age of patients enrolled in the 2 to <12 years age group was 6.90 (2.744). The mean (SD) age of patients enrolled in the 12 to <16 years age group was 13.80 (1.014) years. There were 30 males (30/50; 60%) and 20 females (20/50;40%) enrolled in the study. All 50 (100%) patients were White and not Hispanic or Latino

Safety/Derived Efficacy Results:
In total, the incidence of febrile neutropenia was 13/50 (26%). Children in the 2 to < 12 years age group had the highest incidence of febrile neutropenia (30%, [9/30, 95% CI=0.147; 0.494]). The incidence of febrile neutropenia was 17% (3/18 [95% CI=0.036; 0.414]) in the 12 to < 16 years age group and 1/2 in the 1 month to <2 years age group.

Pharmacodynamic results:
Severe neutropenia was defined as any value of ANC $<0.5 \times 10^9$/L at any time. The incidence of severe neutropenia was 26/50 (52%, 95% CI= 0.374, 0.663). The incidence of severe neutropenia was highest in the 2 to < 12 years age group (63%, [19/30, 95% CI=0.439, 0.801]). The incidence of severe neutropenia was 33% in the 12 to < 16 years age group (33% [6/18; 95% CI= [0.133, 0.590]). One of the 2 infants in the 1 month to <2 years age group experienced severe neutropenia.

The time to the ANC nadir from the beginning of tbo-filgrastim administration was similar amongst the 2 to <12 years age group and the 12 to <16 years age group (mean [SD]=6.9 [2.55] days and median [range]=6.0[5,14] versus mean [SD]=7.3 [2.72] and median [range]=6.0[4,14] days).

The mean ANC nadir was similar in the 2 to < 12 years age group as compared to the 12 to < 16 years age group (mean [SD]=0.851 x 10^9/L [1.3633] versus 0.832 x 10^9/L [0.6358]).

The mean (SD) time to ANC recovery to $\geq$1.0 x 10^9/L from tbo-filgrastim administration was 7.3 [4.43] (median [range]=8.0 [0,16]) days in the 2 to < 12 years versus 5.1 (5.3) (median [range]=7.0 [0,15]) days in the 12 to < 16 years age group.

The mean AUC ANC (x 10^9/L x days), which indicates the overall response to tbo-filgrastim was 53.931 (44.8741) in the 2 to < 12 years age group as compared to the 87.098 (61.1857) in the 12 to < 16 years age group.

Similar trends were observed in the time to ANC nadir from the beginning of CTX and the mean times to recovery to ANC thresholds of ≥1.0 x 10^9/L and ≥2.0 x 10^9/L from the beginning of CTX.

Safety Results:
Adverse events: During the treatment period, 45/50 (90%) patients reported at least 1 TEAE; 2/2 in the 1 month to <2 years age group, 28/30 (93%) in the 2 to < 12 years age group, and 15/18 (83%) in the 12 to < 16 years age group. There were no TEAEs leading to death, discontinuation, or withdrawal from the study. Treatment-emergent adverse events considered to be treatment-related were reported in 9/50 (18%) patients in total; 4/30 (13%) of patients in the 2 to < 12 years age group and 5/18 (28%) of patients in the 12 to < 16 years age group. There were no treatment-related TEAEs in the 1 month to <2 years age group.

Serious TEAEs were reported in 12/50 (24%) patients in total, 9/30 (30%) of patients in the 2 to < 12 years age group and 3/18 (17%) in the 12 to < 16 years age group. There were no serious adverse events reported in the 1 month to <2 years age group.

The most frequently occurring TEAEs were in the following SOCs: blood and lymphatic system (36/50 [72%]), gastrointestinal disorders (20/50 [40%]), general disorders and administration site conditions (12/50 [24%]), investigations (8/50 [16%]), metabolism and nutrition disorders and skin and subcutaneous tissue disorders (each 6/50 [12%]), infections and infestations (7/50 [14%]), and musculoskeletal and connective tissue disorders SOCs (5/50 [10%]).

Clinical laboratory tests: There were no clinically meaningful changes in mean values for glucose, creatinine, sodium, potassium, calcium, phosphate, and uric acid from baseline to end of study. There were slight decreases from baseline to EOS visit in: hemoglobin (mean [SD]=115.9 g/L [16.14]) at baseline to (mean [SD]=113.1 g/L [.332251]) at EOS visit, ANCs (mean [SD])=5.64 x 109/L [6.035]) at baseline to (mean [SD]=3.93 x 109/L [3.981]) at EOS visit, and hematocrit (mean [SD])=35.72 % [5.284]) at baseline to (mean [SD])=34.44 % [6.776]) at EOS visit. There was a slight decrease in platelets from baseline (mean [SD])=375.6 x 109/L[172.78] to EOS visit (mean [SD])= 324.1 x 109/L [185.81]. Mean ALT enzyme increased from baseline (mean [SD]=21.6U/L [13.55]) to EOS visit (mean [SD]=64.7U/L [149.82]). Mean AST enzyme increased from baseline (mean [SD]=28.1U/L[15.45]) to EOS visit (mean [SD]=68.3U/L [177.25]). Mean GGT increased from baseline (mean [SD]=26.5U/L[44.02]=U/L) to EOS visit (mean [SD]=42.0U/L[57.30]). Mean LDH from baseline (mean [SD]=257.4U/L[86.44]) to EOS visit (mean [SD]=312.7U/L [159.38]). Increases in mean values of alkaline phosphatase, total bilirubin, direct and indirect bilirubin were not observed.

Vital signs: There were no clinically meaningful trends in mean changes from baseline to any time point for any vital signs.

ECG: There were no abnormal clinically significant shifts from baseline to any time point in any of the 3 age groups. There were no instances where the mean QTcF per time point was greater than 450 ms or where the mean increase from baseline was greater than 60 ms.

Physical examination findings: At the baseline visit, there were no patients with normal findings in the head, ears, eyes, nose and throat, heart, chest and lungs, or abdomen with abnormal clinically significant findings at EOS.

Concomitant medication use throughout the study: A total of 49/50 (98%) of patients were taking concomitant medication during the study. Common therapeutic classes of concomitant medications received were antiemetics and antinauseants (36/50 [72%]), antibacterials for systemic use (33/50 [66%] of patients, blood substitutes and perfusion solutions (24/50 [48%]), all other therapeutic products (24/50 [48%]). All other therapeutic products included: MESNA, calcium folinate, and phenibut.

Local tolerability at the injection site: Surface ecchymosis was reported in 11/50 (22%) of patients in total; surface erythema/redness was reported in 4/50 (8%) of patients in total; induration was reported in 1/50 (2%) of patients in total; pain at the injection site was absent in all patients (50/50 [100%]) enrolled in the study.

Spleen sonography assessments: There were no shifts from normal spleen sonography findings at baseline to abnormal clinically significant or abnormal, not clinically significant at the EOS visit.

ADA assessment: There were no patients who developed ADA after administration of tbo-filgrastim in this study.

Survival: All patients were alive at the end of the treatment period, days 30 and 90 of the study.

Pharmacokinetics Results:
A total of 49 pediatric patients had evaluable single dose pharmacokinetic parameter values following administration of 5 ug/kg/ body weight tbo-filgrastim administered sc, 2 patients were in the 1 month to <2 years age group, 29 patients were in the 2 to < 12 years age group, and 18 patients were in the 12 to <16-18 years age group.

The pharmacokinetic parameter values for Cmax and AUC0-12 overlapped in all age groups. For all groups, the median (range) tmax was 4.05 hours (3.9 to 8.0) and there were no apparent differences amongst the 1 month to <2 year, 2 to <12 year, and 12 to <16 year age groups, since the ranges overlapped. When considering in the limited number of patients in the 1 month to <2 years age group, and the overall interpatient variability in serum exposures for tbo-filgrastim across the 2 to < 12 years age group, and the 12 to < 16 years age groups, Cmax, AUC0-12, and tmax parameter values following a single dose of tbo filgrastim 5 ug/kg/body weight administered sc were comparable. For the 23 patients in total, in the 2 to < 12 year age group and the 12 to < 16 years age group, for whom a terminal elimination phase could be characterized, GM (CV%) estimates for t½, AUC0-∞, %AUCext, CL/F and Vz/F were 2.39 hours (22.2%), 152053.68 hr*pg/mL (48.7%), 6.83% (51.8%), 1.02 L/h (64.5%) and 3.51 L (65.0%), respectively.

Tbo filgrastim serum exposure (Cmax, AUC0-12) and tmax were comparable in patients administered CTX of mild, moderate, or severe toxicity since the range of 95% CIs for these parameters overlapped across CTX toxicity groups. A trend of higher exposure with increasing CTX toxicity was observed.

Conclusions:
Safety conclusions: Safety data in this study indicate that a single sc dose tbo-filgrastim 5 µg/kg of body weight was generally safe and well tolerated, up to at least 21 days post-administration, in 50 patients from 1.4 years of age to 15.9 years, with solid tumors without bone marrow involvement.

Review: There were no unexpected safety or efficacy findings. There were no allergic reactions or anaphylaxis. Local reactions and anaphylaxis have been reported in the adult breast cancer population.

Terms of Written Request (January 19, 2018)	**Sponsor's Position on fulfillment of the terms of WR**	**Review**
Clinical *Studies: Study 1* *Study XM02-ONC-201:* A multicenter, open-label study to evaluate the safety, tolerability, pharmacokinetics, pharmacodynamics, efficacy, and immunogenicity of tbo- filgrastim at a dose of 5mcg/kg/day in infants, children, and adolescents with solid tumors without bone marrow involvement scheduled to receive at least 1 cycle of chemotherapy.	Study XM02-ONC-201 was conducted according to the terms provided in this section of the Written Request Section 9.1 Overall study design and Plan of Clinical Study Report (CSR) XM02-ONC-201: This was a Phase 2, multicenter, open-label study to evaluate the safety, tolerability, pharmacokinetics, pharmacodynamics, efficacy, and immunogenicity of tbo-filgrastim at a dose of 5 µg/kg/day of body weight in infants, children, and adolescents with solid tumors without bone marrow involvement scheduled to receive at least 1 cycle of CTX.	Ok with us.
Objective of the study: The primary objective of this study is to assess the safety and tolerability of 5 mcg/kg tbo-filgrastim in the pediatric population with solid tumors without bone marrow involvement. The secondary objectives are to assess the pharmacokinetics using sparse sampling strategy, pharmacodynamics, efficacy, and immunogenicity of tbo-filgrastim in this patient population.	Study XM02-ONC-201 was conducted according to the terms provided in this section of the Written Request, Section 8.1 Primary Objective and Endpoint of CSR: The primary objective of the study was to assess the safety and tolerability of 5 µg/kg of tbo-filgrastim in the pediatric population with solid tumors without bone marrow involvement. The primary endpoint was the safety of tbo-filgrastim. Section 8.2 Secondary Objectives and Endpoints of CSR: The secondary objectives were to assess the pharmacokinetics using sparse sampling strategy, pharmacodynamics, efficacy, and immunogenicity of tbo-filgrastim in this patient population. The pharmacokinetic measure for	Ok with us.

	this study was the serum concentration of tbo-filgrastim. The pharmacodynamic measure for this study was the ANC in blood. The immunogenicity endpoints were the anti-drug antibody (ADA) assessment prior to the first tbo-filgrastim administration, at the end-of-study (EOS) visit, and at 30 days and 3 months after the last tbo-filgrastim administration during the first cycle of CTX.	
Terms of Written Request (January 19, 2018)	**Sponsor's Position on fulfillment of the terms of WR**	**Review**
Patients to be studied: 1. Infants (1 month to < 2 years) 2. Children (2 to < 12 years) 3. Adolescents (12 to < 17 years). Approximately 50 patients; at least 2 infants, at least 12 in the children group [2 to <12 years], and at least 12 in the adolescents group [12 to <17 years]).	Patients numbers for each pediatric subset were respected (See Section 10. Study Patients of the CSR) Additionally, age brackets for Infants and Children were also respected as presented in Section 10, Study Patients: In this study, 2 infants (ages 1.4 and 1.9 years), 30 children (2 to <12 years), and 18 adolescents (12 to <16 years) with solid tumors without bone marrow involvement were enrolled. All 50 (100%) patients received at least 1 dose of tbo-filgrastim and were evaluable for safety and efficacy in the treatment period. Forty-nine (98%) of 50 patients completed the follow-up period. The average age of the patients overall was 9.17 years (range 1.4 to 15.9 years). The 2 infants (1 month to <2 years) were 1.4 and 1.9 years old. The mean (SD) age of patients enrolled in the 2 to <12 years age group was 6.90 (2.744). The mean (SD) age of patients enrolled in the 12 to <16 years age group was 13.80 (1.014) years. All 50 (100%) patients enrolled were White and not Hispanic or Latino. The percentages of male and female patients overall were 60% and 40%, respectively (Table 10). One minor difference in the adolescent age bracket exists. Adolescent were indeed defined in the study as aged 12 to <16 years. However, the Sponsor believed it has fairly responded to this term of the written request as detailed in Section 2.	Ok with us.
Terms of Written Request (January 19, 2018)	**Sponsor's Position on fulfillment of the terms of WR**	**Review**

Representation of Ethnic and Racial Minorities: The studies must take into account adequate (e.g., proportionate to disease population) representation of children of ethnic and racial minorities. If you are not able to enroll an adequate number of these patients, provide a description of your efforts to do so and an explanation for why they were unsuccessful.	At the time of issuance of the Written Request, study XM02-ONC-201 was already completed. Section 10.3. Patient Characteristics presents the Ethnic and Racial Minorities. Demographic Characteristics by Age Group. The demographic characteristics of patients in each age group are presented in Table 10. In the 1 month to <2 years age group, 2 patients were enrolled; 1 infant was 1.4 years of age and 1 infant was 1.9 years of age. In the 2 to <12 years age group, there were 30 patients enrolled, with an age range from 2.4 to 11.5 years of age. In the 12 to <16 years age group, there were 18 patients enrolled with an age range of 12.0 to 15.9 years of age. Although no children of ethnic and racial minorities were recruited, the protocol allowed recruitment of children from all ethnic or racial origins as presented in section 4.1 Patient Inclusion Criteria of the protocol. The Sponsor faced issues with the recruitment in this study This led to the submission of a request for a deferral extension for trial completion, including a request to close the study recruitment when a total of 50 pediatric patients completed the study. This was agreed with FDA on May 11, 2016. On this basis, the Sponsor believed it has fairly responded to the terms of this section of the Written Request	Ok with us. 5 patients were screen failures and they were all Caucasian.
Study endpoints: Pharmacokinetic/Pharmacodynamic Endpoints: The pharmacokinetic endpoints for Study XM02-ONC-201 must include serum concentration of tbo-filgrastim. • Blood samples for pharmacokinetics should be obtained on study day 1 within 1 hour prior to tbo-filgrastim administration (pre-dose) and at 2, 4, 6, 8, and 12 hours thereafter. The pharmacodynamic endpoint for Study XM02-ONC-201must be ANC in blood. • Blood samples for ANC measurement should be obtained within 1 hour prior to tbo-filgrastim administration on study day 1	Study XM02-ONC-201 was conducted according to the terms provided in this section of the Written Request- Section 9.6.4.1. Methods and Timing of Pharmacokinetic Sampling of the CSR: Blood samples for pharmacokinetic profiling were collected before tbo-filgrastim administration, and up to 12 hours after the first dose of tbo-filgrastim. Details of the methods and timing of pharmacokinetic sampling presented in Section 9.6.4.1 (above). The pharmacokinetic parameters determined for each patient, when possible, from the serum tbo-filgrastim concentrations are presented in Section 9.6.4.2. The serum pharmacokinetic	Ok

and on days 5, 6, 7, 10, 12, and 15 (optional if day 15 coincides with chemotherapy day 21). The pharmacodynamic variables must include: • incidence and duration of severe neutropenia (DSN, ANC<0.5×10^9/L) • area under the curve of ANC (AUCANC) • ANC nadir (measured in 10^9/L), which is the lowest ANC recorded • time to ANC nadir from the beginning of tbo-filgrastim administration to the occurrence of the ANC nadir • time to ANC nadir from the beginning of chemotherapy to the occurrence of the ANC nadir • time to ANC recovery to ≥1.0×10^9/L, and time to ANC recovery to ≥2.0×10^9/L from ANC nadir • time to ANC recovery to ≥1.0×10^9/L, and time to ANC recovery to ≥2.0×10^9/L from the beginning of tbo-filgrastim administration and from chemotherapy day 1	parameters were estimated from the concentration-time profiles for all patients in the pharmacokinetic analyses set using standard noncompartmental methods as described in the statistical analysis plan. In estimating the pharmacokinetic parameters, below the quantifiable limit (BQL) values at the beginning of the profile were set to 0. Values below the quantifiable limit that occur after the first quantifiable point were considered missing. Values that were embedded between BQLs, or quantifiable values that occurred after 2 or more BQLs, were set to missing at the discretion of the pharmacokineticist. Actual sampling times, rather than scheduled sampling times, were used in all computations involving sampling times. If the actual time or dose time was missing; the scheduled time was substituted in order to calculate the pharmacokinetic parameter. All pharmacokinetic exposure-related parameters (Cmax, area under the serum drug concentration by time curve from time 0 to the last measurable concentration [AUClast], AUC0-12, AUC0-inf, %AUCex, t½, λz, CL/F and Vz/F) were summarized by age group and in addition by CTX toxicity group using the standard summary statistics including the mean, SD, GM, CV for the GM, minimum and maximum values, and the 95% CI for the GM. All tmax values were summarized by age group using mean, SD, median, and minimum and maximum values. Section 9.6.1.3.1. Methods and Timing of Pharmacodynamic Sampling of the CSR: All pharmacodynamic samples for ANC were sent to the local laboratory for evaluation and were determined using a standardized method at the local laboratories. Details of blood sample handling, storage, and shipment were described in a study specific clinical laboratory manual. Blood samples (0.5 mL) were collected via venipuncture or indwelling catheter (at the discretion	

	of the investigator) for the assessment of the pharmacodynamics of tbo-filgrastim. Samples were collected within 1 hour before the tbo-filgrastim dose on day 1, and on days 5, 6, 7, 10, 12, and 15 (optional if day 15 coincided with CTX-day 21). Section 9.6.1.4. Pharmacodynamic Parameters of the CSR: The pharmacodynamic parameters were as follows: incidence and duration of severe neutropenia (DSN, ANC<0.5 × 109/L) area under the curve of ANC (area under the curve of absolute neutrophil count [AUCANC]), ANC nadir (measured in 109/L), which is the lowest ANC recorded, time to ANC nadir from the beginning of tbo-filgrastim administration up to the occurrence of the ANC nadir time to ANC nadir from the beginning of CTX up to the occurrence of the ANC nadir time to ANC recovery to ≥1.0 × 109/L, and time to ANC recovery to ≥2.0 × 109/L from ANC nadir time to ANC recovery to ≥1.0 × 109/L, and time to ANC recovery to ≥2.0 × 109/L from the beginning of tbo-filgrastim administration and from CTX-day 1.	
Terms of Written Request (January 19, 2018)	**Sponsor's Position on fulfillment of the terms of WR**	**Review**
Safety Endpoints: Safety outcomes should include: • adverse event reports throughout the study • clinical laboratory test results at screening and at the end-of-study visit • vital signs measurements (blood pressure, pulse rate, respiration rate, and body temperature) at screening, throughout the study treatment, and at the end-of-study visit • Electrocardiography (ECG) findings at screening, pre-dose, and 4 and 6 hours after the first tbo-filgrastim administration, and at the end-of-study visit • physical examination results at screening and at the end-of-study visit • concomitant medication usage throughout the study • local tolerability at the injection site at 1	Study XM02-ONC-201 was conducted according to the terms provided in this section of the Written Request- Section 9.6.2.1. Adverse Events of the CSR: An adverse event was defined in the protocol as any untoward medical occurrence in a patient administered a pharmaceutical product, regardless of whether it had a causal relationship with this treatment. Any adverse event occurring after the clinical study patient signed informed consent and throughout the study treatment period and until 30 days from the last tbo-filgrastim administration was recorded and reported as an adverse event. An adverse event could, therefore, be any unfavorable and unintended physical sign, symptom, or laboratory parameter that developed or worsened in severity during the course of the study, or significant	Ok

hour (±30 min) after each study drug injection • spleen sonography assessments at screening, on day 4 of tbo-filgrastim treatment, at the end-of-study visit, and if the patient reports left upper abdominal and/or shoulder tip pain • Anti-Drug Antibody (ADA) assessment prior to the first tbo-filgrastim administration, at the end-of-study visit, and at 30 days and 3 months after the last tbo-filgrastim study drug treatment in the first cycle. • Survival at 90-day follow-up.	worsening of the disease under study or any concurrent disease, whether or not considered related to tbo-filgrastim. A new condition or the worsening of a pre-existing condition was considered an adverse event. Stable chronic conditions (such as arthritis) that were present prior to study entry and did not worsen during the study were not considered adverse events. Worsening of the disease under study was recorded as an adverse event only if the presentation and/or outcome were more severe than would normally be expected from the normal course of the disease in a particular patient. Accordingly, an adverse event included any of the following: intercurrent illnesses, physical injuries, events possibly related to concomitant medication, significant worsening (change in nature, severity, or frequency) of the disease under study or other pre-existing conditions. (NOTE: A condition, recorded as pre-existing, that was intermittently symptomatic [e.g., headache] and which occurred during the study was recorded as an adverse event), drug interactions, events that occurred during diagnostic procedures or during any washout phase of the study, laboratory or diagnostic test abnormalities that resulted in the withdrawal of the patient from the study, were associated with clinical signs and symptoms or a serious adverse event, or required medical treatment or further diagnostic work-up, or were considered by the study investigator to be clinically significant. NOTE: Abnormal laboratory test results at the screening visit that precluded a patient from entering the study or receiving study treatment were not considered adverse events, but were to be recorded to monitor data from patients who did not meet screening criteria. All events of possible drug-induced liver injury with hyperbilirubinemia (defined as aspartate aminotransferase [AST] or alanine aminotransferase [ALT] ≥3	

	times the upper limit of the normal range [ULN], plus either bilirubin ≥2 times the ULN or international normalized ratio >1.5) or Hy's Law events required immediate study treatment cessation and reporting as a serious adverse event. Section 9.6.2.2. Clinical Laboratory Tests: Clinical laboratory tests (serum chemistry and hematology) were conducted at the screening visit, at the EOS visit at CTX day 21 (±2) days, and before the next CTX cycle) or the EOS visit. Clinical laboratory tests were performed by a central laboratory. In case the results from the central laboratory were not available on day 1 before start of CTX, the investigator was permitted to use test results from local laboratories in order to initiate CTX. All clinical laboratory test results that were outside of the reference range were interpreted by the investigator as 1 of the following categories: abnormal but not a clinically significant worsening from baseline abnormal and a clinically significant worsening from baseline. A laboratory test result that had significantly worsened (according to medical judgment) from the baseline result was recorded onto the CRF as an adverse event and monitored as described in Section 9.6.2.1.1. An adverse event includes a laboratory or diagnostic test abnormality (once confirmed by repeat testing) that resulted in the withdrawal of the patient from the study, the temporary or permanent cessation of treatment with tbo-filgrastim, or required medical treatment or further diagnostic work-up. In addition, potentially clinically significant values were predefined by the sponsor for select laboratory parameters (see Section 9.6.2.2) and were detailed in the statistical analysis plan. Laboratory tests that were performed are listed in Table 4. Section 9.6.2.4. Electrocardiography of the CSR: A 12-lead ECG was conducted at the screening visit, pre-dose, 4 and 6	

	hours post-dose on day 1 of tbo-filgrastim administration, and at the EOS visit. A qualified physician at a central diagnostic center identified in Section 6 was responsible for providing interpretation of the ECG. Any ECG finding that was judged by the investigator as a clinically significant change (worsening) compared with a baseline value was considered an adverse event, recorded on the CRF, and monitored as described in Section 9.6.2.1.1. Section 9.6.2.5. Physical Examination of the CSR: Physical examinations (including height and weight to be obtained at the screening visit only) were performed at screening and at the EOS visit. Any physical examination finding that was judged by the investigator as a clinically significant change (worsening) from a baseline value was considered an adverse event, recorded on the CRF, and monitored as described in Section 9.6.2.1.1. Section 9.6.2.7. Concomitant Therapy of the CSR: Concomitant therapy was recorded after the informed consent was signed throughout the treatment period and until 30 days from the last tbo-filgrastim administration. Commercially available G-CSFs such as filgrastim, pegfilgrastim, or lenograstim, or their biosimilars were prohibited during the treatment period. At the follow-up visits at 30 (±3) and 90 (±6) days from the last tbo-filgrastim administration in CTX Cycle 1, use of the following concomitant medications was documented: filgrastim, pegfilgrastim, lenograstim, biosimilars to G-CSFs, or other investigational white blood cell (WBC) growth factors. Section 9.6.2.8. Local Tolerability at the Injection Site of the CSR: Local tolerability at the tbo-filgrastim injection site was assessed at 1 hour (±30 minutes) following tbo-filgrastim administration. The injection site was assessed for the presence and severity of pain,	

	erythema/redness, ecchymosis, and induration. Severity of injection site reactions was assessed as described in Table 5 at the discretion of the investigator. Severe cases were recorded as an adverse event Section 9.6.2.9. Spleen Sonography of the CSR: A sonographic examination of the spleen was performed at screening, on day 4 of tbo-filgrastim treatment, at the EOS visit, and if the patient reported left upper abdominal and/or shoulder tip pain. Any abnormal findings or changes (worsening) compared to a baseline value assessed by the investigator as clinically significant was recorded in the relevant CRF modules (e.g., adverse event, medical history). Section 9.6.2.10. Immunogenicity Assessment of the CSR: Blood specimens (1.2 mL for 0.6 mL of serum) were collected via venipuncture or indwelling catheter (at the discretion of the investigator) for ADA analysis at screening (prior to the first tbo-filgrastim administration), at day 21±2 after the first tbo-filgrastim treatment, and at 30 and 90 days after the last tbo-filgrastim treatment.	
Terms of Written Request (January 19, 2018)	**Sponsor's Position on fulfillment of the terms of WR**	
Known safety concerns and monitoring: The most common adverse reaction to tbo-filgrastim is bone pain. Other potential serious adverse reactions include splenic rupture, acute respiratory distress syndrome, serious allergic reactions, increased vaso-occlusive complications in patients with sickle cell disorders, glomerulonephritis, capillary leak syndrome and potential for tumor growth stimulatory effects on malignant cells. Adverse reactions reported during post-approval use of tbo-filgrastim include Sweet's syndrome (acute febrile neutrophilic dermatosis), asthenia, diarrhea, and fatigue. Spleen sonography assessments will occur at screening, on day 4 of tbo-filgrastim treatment, at the end-of-study visit, and if the patient reports left upper abdominal and/or shoulder tip pain.	All events presented in the known safety concerns and monitoring were included in Appendix A - reference safety information of the Investigator's Brochure, Edition 09, dated 13 September 2016 (IND 103188, Sequence 0050). Section 9.6.2.9. Spleen Sonography of the CSR: A sonographic examination of the spleen was performed at screening, on day 4 of tbo-filgrastim treatment, at the EOS visit, and if the patient reported left upper abdominal and/or shoulder tip pain. Any abnormal findings or changes (worsening) compared to a baseline value assessed by the investigator as clinically significant was recorded in the relevant CRF modules (e.g., adverse event, medical history).	Ok

Extraordinary results: In the course of conducting these studies, you may discover evidence to indicate that there are unexpected safety concerns, unexpected findings of benefit in a smaller sample size, or other unexpected results. In the event of such findings, there may be a need to deviate from the requirements of this Written Request. If you believe this is the case, you must contact the Agency to seek an amendment. It is solely within the Agency's discretion to decide whether it is appropriate to issue an amendment	Not Applicable At time of issuance of the Written Request, study XM02-ONC-201 was completed. All results are reported within this sBLA and no amendment were sought based on the findings	Ok
Terms of Written Request (January 19, 2018)	**Sponsor's Position on fulfillment of the terms of WR**	
Biological product information: Dosage form: The product is a sterile, clear, colorless, preservative-free solution containing tbo-filgrastim (300 µg/mL), glacial acetic acid (0.60 mg/mL), sorbitol (50.0 mg/mL), polysorbate 80 (0.055 mg/mL), sodium hydroxide (q.s. to pH 4.20), and water for injection (q.s. to 1.00 mL). Route of administration: Tbo-filgrastim must be administered subcutaneously (SC). Regimen: Patients should receive SC doses of tbo-filgrastim 5 mcg/kg body weight daily. The first dose of tbo-filgrastim should be administered not earlier than 24 hours (±3 hours) following the end of myelosuppressive chemotherapy in week 1 of the cycle. Daily dosing with tbo-filgrastim should continue until the expected neutrophil nadir is passed and the neutrophil count has recovered to 2.0×10^9 /L but not longer than on 14 consecutive days. The current age-appropriate formulation will be used in the study described above.	Study XM02-ONC-201 was conducted according to the terms provided in this section of the Written Request- Section 9.4.2.1. Formulation of the CSR: The product was a sterile, clear, colorless, preservative-free solution containing 5-10g tbo-filgrastim (300 µg/mL), glacial acetic acid (0.60 mg/mL), sorbitol (50.0 mg/mL), polysorbate 80 (0.055 mg/mL), sodium hydroxide (q.s. to pH 4.20), and water for injection (q.s. to 1.00 mL). Packaging, Labeling, Preparation, and Storage: Storage: Tbo-filgrastim was supplied in vials containing 300 µg/mL. All drug product was to be stored and maintained in a temperature-controlled environment according to the labeled storage conditions. Any temperature excursion outside of the labeled storage conditions should have been communicated to Teva. Teva evaluated each excursion and communicated the material disposition back to the notifying site. It was required that the tbo-filgrastim be protected from light. It was recommended that the vial not be shaken. The solution was visually inspected before use. Only clear solutions without particles were used. Packaging: The secondary packaging and labeling was performed in accordance with Good Manufacturing Practice (GMP) and local regulatory requirements. The label text was translated into the local language. Data for patients receiving XM02 from specific batches is collected in the interactive response	Ok

	technology (IRT) system. The information is available upon request. Section 9.4.4 Selection of Doses of Tbo-filgrastim of the CSR: The dosage of tbo-filgrastim evaluated in this open-label study was 5 µg/kg of body weight daily administered subcutaneously (sc). This dosage is the only approved dosage for tbo-filgrastim in the US. Section 9.4.2.2. Investigational Product and Dosage of the CSR: Patients received tbo-filgrastim 5 µg/kg body weight daily; administered via the sc route. Each daily dose, was administered at the site, and was taken from a vial containing 300 µg/mL tbo-filgrastim. Injection of tbo-filgrastim was performed using a fine-graded syringe (gradations of 0.01 mL). After the syringe had been filled with tbo-filgrastim, the needle was changed. Injection was carried out using a new 29 gauge (G) × ½ inch injection needle. The abdomen was the preferred location for injection. The first dose of tbo-filgrastim was administered not earlier than 24 hours (±3 hours) following the end of myelosuppressive CTX in week 1 of the cycle. Daily dosing with tbo-filgrastim continued until the expected neutrophil nadir was passed and the neutrophil count had recovered to 2.0 × 109/L but not longer than on 14 consecutive days. A transient increase in neutrophil counts is typically seen 1 to 2 days after initiation of tbo-filgrastim therapy followed by the CTX-induced nadir. The lot numbers for each dose of tbo-filgrastim administered is available upon request.	
Terms of Written Request (January 19, 2018)	**Sponsor's Position on fulfillment of the terms of WR**	**Review**
Statistical information, including power of study(ies) and statistical assessments: The study does not need to be statistically powered but must include at least 2 in the infant group, at least 12 in the children group and 12 in the adolescents group.	Study XM02-ONC-201 was conducted according to the terms provided in this section of the Written Request- Patient numbers for each pediatric subsets were respected (See Section 10- Study Patients of the CSR): In this study, 2 infants (ages 1.4 and	ok

The descriptive statistical analyses that will be performed with respect to the study endpoint(s) must be described. The study data should be evaluated using statistical approaches for exploratory data analyses.	1.9 years), 30 children (2 to <12 years), and 18 adolescents (12 to <16 years) with solid tumors without bone marrow involvement were enrolled. All 50 (100%) patients received at least 1 dose of tbo-filgrastim and were evaluable for safety and efficacy in the treatment period. Forty-nine (98%) of 50 patients completed the follow-up period. The average age of the patients overall was 9.17 years (range 1.4 to 15.9 years). The 2 infants (1 month to <2 years) were 1.4 and 1.9 years old. The mean (SD) age of patients enrolled in the 2 to <12 years age group was 6.90 (2.744). The mean (SD) age of patients enrolled in the 12 to <16 years age group was 13.80 (1.014) years. All 50 (100%) patients enrolled were White and not Hispanic or Latino. The percentages of male and female patients overall were 60% and 40%, respectively (Table 10). Section 16.1.9. Statistical Analyses plan of the CSR:	
Terms of Written Request (January 19, 2018)	**Sponsor's Position on fulfillment of the terms of WR**	**Review**
Labeling that may result from the study(ies): You must submit proposed pediatric labeling to incorporate the findings of the study(ies). Under section 505A(j) of the FD&C Act, regardless of whether the study(ies) demonstrate that tbo-filgrastim is safe, pure, and potent, or whether such study results are inconclusive in the studied pediatric population(s) or subpopulation(s), the labeling must include information about the results of the study(ies). Under section 505A(k)(2) of the FD&C Act, you must distribute to physicians and other health care providers at least annually (or more frequently if FDA determines that it would be beneficial to the public health), information regarding such labeling changes that are approved as a result of the study(ies).	The Sponsor has proposed revisions to the Prescribing Information and Patient Information leaflet in light of the results from study XM02-ONC-201 (See Section 1.14.1.3. Draft labeling Text – USPI and Section 1.14.1.3. Draft labeling Text – Patient Information leaflet)	Ok
Format and types of reports to be submitted: You must submit full study reports (which have not been previously submitted to the Agency) that address the issues outlined in this request, with full analysis, assessment, and interpretation. In addition, the reports must include information on the representation of pediatric patients of ethnic and racial minorities. All pediatric patients enrolled in the study(ies) should be categorized using one of the following designations for race: American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or other Pacific Islander or White. For ethnicity, you should use one of the following designations: Hispanic/Latino or Not Hispanic/Latino. If you choose to use other categories,	Study XM02-ONC-201 was conducted according to the terms provided in this section of the Written Request- Full CSR for Study XM02-ONC-201 is provided in Module 5.3.5.2 Study reports and related information of uncontrolled clinical studies: Race and Ethnicity convention were respected as presented in Section 10.3. Patient Characteristics. All periodic post-marketing adverse events reports were provided as either a leaf or actual report in Module	Ok

you should obtain agency agreement. Under section 505A(d)(2)(B) of the FD&C Act, when you submit the study reports, you must submit all postmarketing adverse event reports regarding this drug that are available to you at that time. All post-market reports that would be reportable under section 21 CFR 600.80 should include adverse events occurring in an adult or a pediatric patient. In general, the format of the post-market adverse event report should follow the model for a periodic safety update report described in the Guidance for Industry *E2C Clinical Safety Data Management: Periodic Safety Update Reports for Marketed Drugs* and the Guidance addendum. You are encouraged to contact the reviewing Division for further guidance. Although not currently required, we request that study data be submitted electronically according to the Study Data Tabulation (SDTM) standard published by the Clinical Data Interchange Standards Consortium (CDISC) provided in the document "Study Data Specifications," which is posted on the http://www fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmission Requirements/ElectronicSubmissions/UCM199759.pdf and referenced in the FDA Guidance for Industry, *Providing Regulatory Submissions in Electronic Format - Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications* at http://www fda.gov/Cder/guidance/7087rev htm.	5.3.6. Reports of Post-Marketing Experience. Study Data are submitted according to SDTM standards as requested by the Agency.	
Terms of Written Request (January 19, 2018)	**Sponsor's Position on fulfillment of the terms of WR**	
Timeframe for submitting reports of the study(ies): Reports of the above studies must be submitted to the Agency on or before March 31, 2018. Please keep in mind that pediatric exclusivity can attach only to existing exclusivity, if any, that would otherwise expire nine (9) months or more after pediatric exclusivity is granted, and FDA has 180 days from the date that the study reports are submitted to make a pediatric exclusivity determination. Therefore, if there is unexpired exclusivity that is eligible for pediatric exclusivity to attach, you are advised to submit the reports of the studies at least 15 months (9 months plus 6 months/180 days for determination) before such exclusivity is otherwise due to expire. If FDA has not determined whether tbo-filgrastim is eligible for reference product exclusivity under section 351(k)(7) of the PHS Act, you may submit a request for reference product exclusivity with supporting data and information to the Agency. Note that neither the issuance of this formal pediatric Written Request, nor any request for exclusivity made	The sBLA is being submitted on January 31, 2018 ahead of the March 2018 deadline.	ok

by you confers or otherwise implies that you are eligible for reference product exclusivity under section 351(k)(7) of the PHS Act.		
Response to Written Request: Under section 505A(d)(2)(A)(i), within 180 days of receipt of this Written Request you must notify the Agency whether or not you agree to the Written Request. If you agree to the request, you must indicate when the pediatric studies will be initiated. If you do not agree to the request, you must indicate why you are declining to conduct the study(ies). If you decline on the grounds that it is not possible to develop the appropriate pediatric formulation, you must submit to us the reasons it cannot be developed.	The Sponsor notified the Agency that it agreed to the Written Request on November 28, 2017 (IND 103188; Sequence 0073).	ok

Recommendation: Consider the PMR and WR fulfilled.

We recommend the indication be changed to include pediatric patients 1 month and older with nonmyeloid malignancies receiving myelosuppressive anticancer drugs associated with a clinically significant incidence of febrile neutropenia.

We recommend the label be updated to state that the safety and effectiveness of GRANIX have been established for pediatric patients 1 month to < 17 years old (no data for the age group < 1 month old).

Comment to Sponsor: None.

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/

LEA C CUNNINGHAM
06/29/2018

YAPING WANG
06/29/2018

DONNA PRZEPIORKA
06/29/2018

YUAN L SHEN
07/02/2018

THOMAS E GWISE
07/03/2018