DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 125294

WRITTEN REQUEST

Teva Branded Pharmaceutical Products R&D, Inc.
Attention: Michael McGraw, PharmD, MS
Senior Director, Regulatory Affairs
41 Moores Road
P.O. Box 4011
Frazer, PA 19355

Dear Mr. McGraw:

Reference is made to your May 31, 2017, Proposed Pediatric Study Request for GRANIX® (tbo-filgrastim).

This study investigates the potential use of tbo-filgrastim to reduce the duration of severe neutropenia in patients with non-myeloid malignancies receiving myelosuppressive anticancer drugs associated with a clinically significant incidence of febrile neutropenia.

Chemotherapy-induced neutropenia occurs in more than 1 out of 3 patients receiving chemotherapy for cancer, and increases the risk of infection, fever, and potentially life-threatening event in these patients. In the pediatric population, chemotherapy -induced neutropenia is the primary dose-limiting toxicity in patients receiving myelosuppressive chemotherapy.

Recombinant granulocyte colony-stimulating factors (GCSFs) are the current standard treatment for prevention of chemotherapy-induced neutropenia in pediatric populations; however, only a limited number of options are available (i.e., filgrastim and its biosimilar, or pegfilgrastim). The addition of tbo-filgrastim to the therapeutic armamentarium would represent a meaningful public health benefit for pediatric patients with non-myeloid cancers.

The efficacy of tbo-filgrastim for the reduction in the duration of severe neutropenia in the pediatric population can be extrapolated from the data from adult trials; however, a trial is required to evaluate the safety in the pediatric population and confirm the validity of the efficacy extrapolation by evaluating the PK and PD in the pediatric population. The trial should be a multicenter, open-label study of subcutaneous (SC) tbo-filgrastim in infants, children, and adolescents up to 16 years of age with solid tumors without bone marrow involvement, who are scheduled to receive myelosuppressive chemotherapy. The conduct of this study was required under PREA.

The requirement for investigating tbo-filgrastim in neonates was waived, because of the rare incidence of non-myeloid cancers requiring myelosuppressive chemotherapy in the neonatal population, which makes it unfeasible or highly impracticable to study this agent in the neonatal population.

To obtain needed pediatric information on tbo-filgrastim, the Food and Drug Administration (FDA) is hereby making a formal Written Request, pursuant to Section 505A of the Federal Food, Drug, and Cosmetic Act (the FD&C Act), as amended by the Food and Drug Administration Amendments Act of 2007, and pursuant to section 351(m) of the Public Health Service Act (the PHS Act), as amended by the Biologics Price Competition and Innovation Act of 2009, that you submit information from the studies described below.

- *Nonclinical study(ies):*

  Based on review of the available non-clinical toxicology, no additional animal studies are required at this time to support the clinical studies described in this written request.

- *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.

  Efficacy of tbo-filgrastim in treatment of severe neutropenia in pediatric patients (in infants, children, and adolescents up to 16 years of age) receiving myelosuppressive chemotherapy for the treatment of non-myeloid cancers can be extrapolated from adult trials because the mechanism of action of post chemotherapy neutrophil reconstitution is the same in adult and pediatric populations. The safety, PK, and PD of tbo-filgrastim for treatment of severe neutropenia in infants, children, and adolescents up to and including 16 years of age cannot be extrapolated and will be determined by the studies outlined in the WR.

- *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.

- *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]).

- *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.

- *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 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$<0.5 \times 10^9$/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 $\geq 1.0 \times 10^9$/L, and time to ANC recovery to $\geq 2.0 \times 10^9$/L from ANC nadir
    - time to ANC recovery to $\geq 1.0 \times 10^9$/L, and time to ANC recovery to $\geq 2.0 \times 10^9$/L from the beginning of tbo-filgrastim administration and from chemotherapy day 1

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 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.

- *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.

- *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.

- *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.

- *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.

  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.

- *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).

- *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, 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/FormsSubmissionRequirements/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.

- *Timeframe for submitting reports of the study(ies):* Reports of the above studies must be submitted to the Agency on or before January 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 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.

Submit protocols for the above study(ies) to an investigational new drug application (IND) and clearly mark your submission "**PEDIATRIC PROTOCOL SUBMITTED FOR PEDIATRIC WRITTEN REQUEST STUDY**" in large font, bolded type at the beginning of the cover letter of the submission.

Reports of the study(ies) must be submitted as a biologics license application (BLA) or as a supplement to your approved BLA with the proposed labeling changes you believe are warranted based on the data derived from these studies. When submitting the reports, please clearly mark your submission "**SUBMISSION OF PEDIATRIC STUDY REPORTS - PEDIATRIC EXCLUSIVITY DETERMINATION REQUESTED**" in large font, bolded type at the beginning of the cover letter of the submission and include a copy of this letter. Please also send a copy of the cover letter of your submission to the Office of New Drugs, Immediate Office, Therapeutic Biologics and Biosimilars Team, 10903 New Hampshire Ave, Building 22, Mail Stop 6411, Silver Spring, MD 20993. If you wish to fax it, the fax number is 301-796-9855.

In accordance with section 505A(k)(1) of the FD&C Act, *Dissemination of Pediatric Information*, FDA must make available to the public the medical, statistical, and clinical pharmacology reviews of the pediatric studies conducted in response to this Written Request within 210 days of submission of your study report(s). These reviews will be posted regardless of the following circumstances:

1. the type of response to the Written Request (i.e., complete or partial response);
2. the status of the application (i.e., withdrawn after the supplement has been filed or pending);
3. the action taken (i.e., approval, complete response); or
4. the exclusivity determination (i.e., granted or denied).

FDA will post the medical, statistical, and clinical pharmacology reviews on the FDA website at http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/UCM049872.

If you wish to discuss any amendments to this Written Request, please submit proposed changes and the reasons for the proposed changes to your application. Submissions of proposed changes to this request should be clearly marked "**PROPOSED CHANGES IN WRITTEN REQUEST FOR PEDIATRIC STUDIES**" in large font, bolded type at the beginning of the cover letter of the submission. You will be notified in writing if any changes to this Written Request are agreed upon by the Agency.

Please note that, if your trial is considered an "applicable clinical trial" under section 402(j)(1)(A)(i) of the PHS Act, you are required to comply with the provisions of section 402(j) of the PHS Act with regard to registration of your trial and submission of trial results. Additional information on submission of such information can be found at www.ClinicalTrials.gov.

If you have any questions, call Suria Yesmin, Regulatory Project Manager, at 301-348-1725.

Sincerely,

{See appended electronic signature page}

Gregory Reaman, MD
Associate Director, Oncology Sciences
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

GREGORY H REAMAN
09/21/2017