CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761082Orig1s000

SUMMARY REVIEW

CROSS DISCIPLINE TEAM LEADER REVIEW

Date: Feburary 24, 2022

From: Tanya Wroblewski, M.D.
Clinical Team Leader
Division of Nonmalignant Hematology (DNH)
Office of Cardiology, Hematology, Endocrinology, and Nephrology (OCHEN)/CDER

Subject: Cross Discipline Team Leader (CDTL) Memorandum
BLA 761082, Resubmission after Complete Response (4th resubmission)
Proposed Biosimilar Product Applicant: Kashiv BioSciences, LLC

To: BLA 761082

Product Information

BLA 761082

Proposed Proprietary Name[1]: Releuko

Proposed Non-proprietary Name: filgrastim-ayow

Code Name: Theragrastim

Theragrastim is a proposed biosimilar to US-licensed Neupogen (Filgrastim).

Dosage Forms, Strength, Presentation:

Injection 300 mcg/mL and 480 mcg/1.6 mL in single-dose vials; 300 mcg/0.5 mL and 480 mcg/0.8 mL in single-dose prefilled syringes

Pharmacologic Class: Leukocyte growth factor

Mechanism of Action: Theragrastim (filgrastim-ayow) is a granulocyte colony stimulating factor (G-CSF) manufactured by recombinant DNA technology which has been developed as a biosimilar product to US-licensed Neupogen (filgrastim). The applicant (Kashiv BioSciences, LLC) is seeking approval of Theragrastim for the following indications for which US-licensed Neupogen has been previously approved:

Proposed Indications:

[1] Proposed proprietary and non-proprietary names are conditionally accepted until such time that the application is approved

- To decrease the incidence of infection, as manifested by febrile neutropenia, in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a clinically significant incidence of severe neutropenia with fever.
- Reduce the time to neutrophil recovery and the duration of fever, following induction or consolidation chemotherapy treatment of patients with acute myeloid leukemia (AML).
- Reduce the duration of neutropenia and neutropenia-related clinical sequelae, e.g., febrile neutropenia, in patients with nonmyeloid malignancies undergoing myeloablative chemotherapy followed by bone marrow transplantation (BMT)
- Reduce the incidence and duration of sequelae of severe neutropenia (e.g., fever, infections, oropharyngeal ulcers) in symptomatic patient with congenital neutropenia, cyclic neutropenia, or idiopathic neutropenia.

The applicant is not seeking approval of Theragrastim for the additional indications for which US-licensed Neupogen has been previously approved:

- Mobilize autologous hematopoietic progenitor cells into the peripheral blood for collection by leukapheresis
- Increase survival in patients acutely exposed to myelosuppressive doses of radiation.

Regulatory History

This application was originally submitted in July 2017 by Adello Biologics, LLC and received a Complete Response (CR) action on May 10, 2018 due to Product Quality issues (including deficiencies with regard to comparative analytical assessment, reference standards or materials, drug substance process description and validation, drug substance container closure system, drug product, stability protocols, analytical methods, control strategy, cell banks, shipping validation, drug product container closure system, stability and microbiology) and deficiencies identified during inspection of the Adello Biologics manufacturing facility (FE:3011289655). The applicant responded to the CR Letter with a resubmission on 12/11/2018. Review of the resubmission found deficiencies including facilities and product quality issues that precluded approval (see CDTL review by Sanjeeve Balasubramaniam, 6/6/2019). A second CR letter was issued on 6/11/2019 citing these deficiencies. A replacement CR Letter was reissued on 6/11/2019 to correct errors in the company name and the FEI number of the deficient facility.

The applicant responded to the second CR Letter with a resubmission on 6/24/2020. The Office of Biotechnology Products (OBP)/Office of Pharmaceutical Quality (OPQ), identified several product quality issues that were included in the CR letter. The Office of Pharmaceutical Manufacturing Assessment (OPMA)/OPQ reviewed the BLA from a product quality microbiology perspective and recommend approval, however the manufacturing facility assessment recommendation for the application was withhold. In particular, for the Drug Substance

manufacturing site, Kashiv Biosciences, LLC, FEI#3011289655; all other Drug Substance related facilities were acceptable based on their current CGMP compliance status and recent relevant inspectional coverage. A CR letter was issued on 12/22/2020.

The Sponsor submitted a response to the CRL issued on 12/22/2020 on February 2, 2021. As described above, in previous cycles of review for this BLA, during a pre-BLA inspection in 2019, the Division of Inspectional Assessment (DIA), now called Division of Biotechnology Manufacturing (DBM), in OPMA, identified deficiencies in the manufacture and control of Theragrastim DS, including GMP deficiencies at Kashiv Biosciences, LLC, FEI#3011289655. FDA determined that an inspection of the Kashiv Biosciences LLC DS site (FEI 3011289655), Chicago, Illinois, facility would be required before this application could be approved as the FDA had to assess the ability of that facility to conduct the listed manufacturing operations in compliance with cGMP.

Due to the U.S. Government and/or Agency-wide restrictions on travel, OPQ was unable to conduct an inspection of the Kashiv Biosciences LLC facility during the review cycle, and the application could not be approved until the required FDA inspection was conducted and the findings were assessed with regard to this application.

In addition, review of the data submitted by Kashiv in response to the December 22, 2020 issued CR letter, identified deficiencies in the information provided for the new in-house Theragrastim Working Reference Standard and the revised potency assay method. A Complete Response letter was issued to Kashiv Biosciences, LLC on August 2, 2021.

CMC Review (summarized from OPQ review dated Feb 1, 2022)

On August 27, 2021 the Applicant submitted a response to the CRL (8/2/2021). The Applicant satisfactorily addressed the product quality deficiencies identified in the Agency's CR letter issued on August 2, 2021. A pre-license inspection was conducted from January 10, 2022 through January 14, 2022 at the drug substance manufacturing facility for theragrastim located in Chicago, IL (FEI# 3011289655). The inspection covered the manufacturing process and testing of theragrasim including the following five quality systems: Quality Procedures, Facilities and Equipment, Materials Management, Production Processes and Contamination Prevention, and Laboratory Controls. The facility was assessed to be acceptable.

A compliance inspection of the (b) (4) manufacturing facility for theragrastim drug product in (b) (4) was conducted from (b) (4). The FDA field investigation team conveyed deficiencies to the representative of the facility. The facility's response to these deficiencies was reviewed and found satisfactory. The current status of this facility is compliant since August 10, 2021.

To support a determination that theragrastim (Releuko) is highly similar to U.S.-licensed Neupogen, 28 lots of U.S.-licensed Neuopogen and 27 lots of Theragrastim DP and 3 lots of

Theragrastim DS were evaluated, including lots used in PK/PD similarity and safety clinical studies and lots manufactured by the proposed commercial manufacturing process. The data provided in the BLA support a determination that Releuko is highly similar to U.S. licensed Neuopogen, notwithstanding minor differences in clinically inactive components. The OPQ review of the submission has determined that the methodologies and processes used for drug substance and drug product manufacturing, release and stability testing as submitted in the BLA submission are sufficient to assure a consistent and safe product. The drug substance manufacturing process is robust for inactivation and removal of adventitious agents. The Applicant agreed to a PMC to evaluate the impact of removing kanamycin from the DS manufacturing process to enhance patient safety. The technical assessments for OBP drug substance and drug product quality and immunogenicity assay, OPMA microbiological drug substance and drug product and facilities, OBP labeling, and OBP comparative analytical assessment are located as separate documents in the Panorama informatics platform.

Nonclinical Pharmacology/Toxicology Review: No additional pharmacology/toxicology information is included in this resubmission. Pharmacology/Toxicology Memorandum (Todd Bourcier, completed 12/3/2020) concluded there remain no outstanding nonclinical issues that would preclude approval of this BLA.

Clinical Pharmacology/Biopharmaceutics Review: There were no new clinical pharmacology information included in this submission.

Clinical/Statistical Review: There was no new clinical information included in this submission. There was no clinical/statistical review for this submission.

Labeling: Please refer to the labeling review by Virginia Kwitowski in DARRTS dated Feb 22, 20222 for details.

Post Marketing Requirements and Commitments: The following post marketing commitment is recommended, " To perform a study to evaluate the impact of the removal of kanamycin from the theragrasim drug substance manufacturing process. If the data support removal of kanamycin, a plan for the removal of kanamycin from the manufacturing process will be provided. The plan should include an evaluation of consistency of the fermentation process and comparability of the theragrastim drug substance manufactured with and without kanamycin. The results will be reported per 21 CFR 601.12". The proposed final report submission is December 31, 2024.

Conclusion and Recommendations: This BLA for theragrastim, a proposed biosimilar product to US-licensed Neupogen, is recommended for approval.

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/s/

TANYA M WROBLEWSKI
02/24/2022 10:11:23 AM

CROSS DISCIPLINE TEAM LEADER REVIEW

Date: July 21, 2021

From: Tanya Wroblewski, M.D.
Clinical Team Leader
Division of Nonmalignant Hematology (DNH)
Office of Cardiology, Hematology, Endocrinology, and Nephrology (OCHEN)/CDER

Subject: Cross Discipline Team Leader (CDTL) Memorandum
BLA 761082, Resubmission after Complete Response (3rd resubmission)
Proposed Biosimilar Product Applicant: Kashiv BioSciences, LLC

To: BLA 761082

1.1 Product Information

BLA 761082

Proposed Proprietary Name[1]: Releuko

Proposed Non-proprietary Name: filgrastim-ayow

Code Name: Theragrastim

Theragrastim is a proposed biosimilar to US-licensed Neupogen (Filgrastim).

Dosage Forms, Strength, Presentation:

Injection 300 mcg/mL and 480 mcg/1.6 mL in single-dose vials; 300 mcg/0.5 mL and 480 mcg/0.8 mL in single-dose prefilled syringes

Pharmacologic Class: Leukocyte growth factor

Mechanism of Action: Theragrastim (filgrastim-ayow) is a granulocyte colony stimulating factor (G-CSF) manufactured by recombinant DNA technology which has been developed as a biosimilar product to US-licensed Neupogen (filgrastim). The applicant (Kashiv BioSciences, LLC) is seeking approval of Theragrastim for the following indications for which US-licensed Neupogen has been previously approved:

Proposed Indications:

[1] Proposed proprietary and non-proprietary names are conditionally accepted until such time that the application is approved

- To decrease the incidence of infection, as manifested by febrile neutropenia, in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a clinically significant incidence of severe neutropenia with fever.
- Reduce the time to neutrophil recovery and the duration of fever, following induction or consolidation chemotherapy treatment of patients with acute myeloid leukemia (AML).
- Reduce the duration of neutropenia and neutropenia-related clinical sequelae, e.g., febrile neutropenia, in patients with nonmyeloid malignancies undergoing myeloablative chemotherapy followed by bone marrow transplantation (BMT)
- Reduce the incidence and duration of sequelae of severe neutropenia (e.g., fever, infections, oropharyngeal ulcers) in symptomatic patient with congenital neutropenia, cyclic neutropenia, or idiopathic neutropenia.

The applicant is not seeking approval of Theragrastim for the additional indications for which US-licensed Neupogen has been previously approved:

- Mobilize autologous hematopoietic progenitor cells into the peripheral blood for collection by leukapheresis
- Increase survival in patients acutely exposed to myelosuppressive doses of radiation.

This application was originally submitted in July 2017 by Adello Biologics, LLC and received a Complete Response (CR) action on May 10, 2018 due to Product Quality issues (including deficiencies with regard to comparative analytical assessment, reference standards or materials, drug substance process description and validation, drug substance container closure system, drug product, stability protocols, analytical methods, control strategy, cell banks, shipping validation, drug product container closure system, stability and microbiology) and deficiencies identified during inspection of the Adello Biologics manufacturing facility (FE:3011289655). The applicant responded to the CR Letter with a resubmission on 12/11/2018. Review of the resubmission found deficiencies including facilities and product quality issues that precluded approval (see CDTL review by Sanjeeve Balasubramaniam, 6/6/2019). A second CR letter was issued on 6/11/2019 citing these deficiencies. A replacement CR Letter was reissued on 6/11/2019 to correct errors in the company name and the FEI number of the deficient facility.

The applicant responded to the second CR Letter with a resubmission on 6/24/2020. The Office of Biotechnology Products (OBP)/Office of Pharmaceutical Quality (OPQ), identified several product quality issues that were included in the CR letter. The Office of Pharmaceutical Manufacturing Assessment (OPMA)/OPQ reviewed the BLA from a product quality microbiology perspective and recommend approval, however the manufacturing facility assessment recommendation for the application was withhold. In particular, for the Drug Substance manufacturing site, Kashiv Biosciences, LLC, FEI#3011289655; all other Drug Substances related facilities were acceptable based on their current CGMP compliance status and recent relevant inspectional coverage. A CR letter was issued on 12/22/2020.

CMC Review (summarized from OPQ review dated June 14, 2021)

The Sponsor submitted a response to the CRL issued on 12/22/2020 on February 2, 2021. As described above, in previous cycles of review for this BLA, during a pre-BLA inspection in 2019, the Division of Inspectional Assessment (DIA), now called Division of Biotechnology Manufacturing (DBM), in OPMA, identified deficiencies in the manufacture and control of Theragrastim DS, including GMP deficiencies at Kashiv Biosciences, LLC, FEI#3011289655. FDA determined that an inspection of the Kashiv Biosciences LLC DS site (FEI 3011289655), Chicago, Illinois, facility will be required before this application may be approved as the FDA must assess the ability of that facility to conduct the listed manufacturing operations in compliance with cGMP.

Due to the U.S. Government and/or Agency-wide restrictions on travel, OPQ is unable to conduct an inspection of the Kashiv Biosciences LLC facility during the current review cycle, and the application cannot be approved until the required FDA inspection is conducted and the findings are assessed with regard to this application. During a recent inspection of the (b) (4) manufacturing facility, FDA field investigation team conveyed deficiencies to the representative of the facility. Satisfactory resolution of these deficiencies is required before this application may be approved.

In addition, review of the data submitted by Kashiv in response to the December 22, 2020 issued CR letter, identified deficiencies in the information provided for the new in-house Theragrastim Working Reference Standard and the revised potency assay method. From a product quality perspective, OPQ, is recommending a Complete Response letter be issued to Kashiv Biosciences, LLC to outline the deficiencies noted below and the information and data that will be required to support approval.

Deficiencies to be Communicated to the Applicant:

Please refer to your biologics license application (BLA) dated and received July 8, 2017submitted under section 351(k) of the Public Health Service Act for Theragrastim.[2]

We acknowledge receipt of your amendment dated February 2, 2021, which constituted a complete response to our December 22, 2020, action letter.

We have completed our review of this application, as amended, and have determined that we cannot approve this application in its present form. We have described our reasons for this action below and, where possible, our recommendations to address these issues.

Facilities Inspections

[2] Your proposed proprietary name, Releuko, and proposed proper name, filgrastim-ayow, are conditionally accepted until such time that the application is approved. In this document, we refer to your proposed biosimilar product by using the descriptor Theragrastim, a developmental code name.

1. An inspection of the Kashiv Biosciences LLC DS manufacture facility (FEI 3011289655), Chicago, Illinois, is required before this application can be approved as the FDA must assess the ability of that facility to conduct the listed manufacturing operations in compliance with CGMP. Due to U.S. Government and/or Agency-wide restrictions on travel, we were unable to conduct an inspection of the Kashiv Biosciences LLC facility during the current review cycle, and the application cannot be approved until the required FDA inspection is conducted and the findings are assessed with regard to this application. We will continue to monitor the public health situation as well as travel restrictions.

Please see the FDA's "Resiliency Roadmap for FDA Inspectional Oversight" for more information on FDA's plan to resume inspections (https://www.fda.gov/media/148197/download). Please also see the FDA guidances related to COVID 19. These guidances can be found at https://www.fda.gov/emergency-preparedness-and-response/coronavirus-disease-2019-covid-19/covid-19-related-guidance-documents-industry-fda-staff-and-other-stakeholders.

2. During inspection of the (b) (4) **manufacturing facility from** (b) (4) **the FDA field investigation team conveyed deficiencies to the representative of the facility. Satisfactory resolution of these deficiencies is required before this application may be approved.**

Product Quality

3. In-House Reference Standards

a. In response to FDA Item #4, you updated the stability protocols PTL-1981 "Stability Protocol for Theragrastim Primary Reference Standard (b) (4) **"Stability Protocol for Theragrastim Working Reference Standard" for the working reference standards** (b) (4) **to include a trending strategy and the acceptance criterion to control for EC50 values in the potency testing. However, there are deficiencies in both stability protocols.**

(b) (4)

(b) (4)

b. You provided PTL-2306-R "Summary Report for Qualification of Theragrastim In-House Working Reference Standard Lot (b) (4)" as an update to the information request response #3 dated October 08, 2020 (BLA 761082/0053). However, the Agency noted multiple out of specification results (OOS) in this report. Specifically,

(b) (4)

Because of the above OOS results, we do not agree that the current in-house (b) (4) has been qualified appropriately. To address the above issues, update the stability protocols for the in-house primary and working reference standards to

i. **Provide adequate trending analysis strategies for the EC50 values of the RSs. You should evaluate whether there is a EC50 value drift based on the absolute values generated in the potency assay.**
ii. **ii. Provide an updated qualification report for the adequately qualified in-house WRS. You should use an adequately qualified WRS as the standard in the stability testing for the PRS.**
iii. **iii. Establish a stability acceptance criterion for the EC50 for the WRS based on a trend analysis of the EC50 values of the WRS obtained during routing release and stability testing.**

4. Analytical methods

In section "Additional information related to Module 3", you revised the potency method (STM-0118) based on the change control CC-20-036. However, the summary information you provided to justify the changes made to the potency assay was inadequate because no supporting data were provided to allow assessment of the appropriateness of the proposed change. To ensure that the proposed change has no impact on the potency assay method validation and test article data, provide adequate information to support the proposed change.

Additional Comments

In addition, there are several deficiencies that are not approvability issues, but need to be addressed.

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(b) (4)

3. You have not provided stability data for deliverable volume to support the proposed shelf life of 24 months (accelerated or real time) for your drug product. As stated in our February 7, 2017 BPD Type 4 meeting to discuss the content of format of the BLA, we stated that you should include expellable volume testing at the end of your proposed shelf life. We recommend that you provide results for this essential performance requirement testing to support the proposed 24-month shelf life for your drug product.

Nonclinical Pharmacology/Toxicology Review: No additional pharmacology/toxicology information is included in this resubmission. Pharmacology/Toxicology Memorandum (Todd Bourcier, completed 12/3/2020) concluded there remain no outstanding nonclinical issues that would preclude approval of this BLA.

Clinical Pharmacology/Biopharmaceutics Review: There were no new clinical pharmacology information included in this submission.

Clinical/Statistical Review: There was no new clinical information included in this submission. There was no clinical/statistical review for this submission.

Labeling: The proposed labeling for this resubmission is deferred until the next review cycle.

Conclusion and Recommendations: This BLA for a proposed biosimilar product to US-licensed Neupogen is not recommended for approval due to CMC and facility issues as stated under the CMC Review section above.

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/s/

TANYA M WROBLEWSKI
08/02/2021 09:44:59 AM

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

Date: December 18, 2020

From: Kathy M. Robie-Suh, M.D., Ph.D.
Clinical Team Leader
Division of Nonmalignant Hematology (DNH)
Office of Cardiology, Hematology, Endocrinology, and Nephrology (OCHEN)/ CDER

Subject: Cross-Discipline Team Leader (CDTL) Memorandum
BLA 761082, Resubmission After Complete Response [2nd resubmission]
Proposed Biosimilar Product
Theragrastim (Releuko, filgrastim-ayow[1]), submitted 6/24/2020

Sponsor: Kashiv BioSciences, LLC

To: BLA 761082

Background:
Theragrastim (filgrastim-ayow) is a granulocyte colony stimulating factor (G-CSF) manufactured by recombinant DNA technology which has been developed as a biosimilar product to US-licensed Neupogen (filgrastim). The applicant (Kashiv BioSciences, LLC) is seeking approval of Theragrastim for the following indications for which US-licensed Neupogen has been previously approved[2]:

- Decrease the incidence of infection, as manifested by febrile neutropenia, in patients with nonmyeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a significant incidence of severe neutropenia with fever;
- Reduce the time to neutrophil recovery and the duration of fever, following induction or consolidation chemotherapy treatment of patients with acute myeloid leukemia (AML)
- Reduce the duration of neutropenia and neutropenia-related clinical sequelae, e.g., febrile neutropenia, in patients with nonmyeloid malignancies undergoing myeloablative chemotherapy followed by bone marrow transplantation (BMT)
- Reduce the incidence and duration of sequelae of severe neutropenia, (e.g., fever, infections, oropharyngeal ulcers) in symptomatic patients with congenital neutropenia, cyclic neutropenia, or idiopathic neutropenia

[1] The proposed proprietary name, Releuko, and the proposed nonproprietary name, filgrastim-ayow, are conditionally accepted until such time that the application is approved. This document also uses the name, Theragrastim, a developmental code name, to refer to the proposed product.
[2] FDA-approved Neupogen labeling.

The applicant is not seeking approval of Theragrastim for the additional indications for which US-licensed Neupogen has been previously approved:

- Mobilize autologous hematopoietic progenitor cells into the peripheral blood for collection by leukapheresis;
- Increase survival in patients acutely exposed to myelosuppressive doses of radiation (Hematopoietic Syndrome of Acute Radiation Syndrome)

This application was originally submitted in July 2017 by Adello Biologics, LLC and received a Complete Response (CR) action on May 10, 2018 due to Product Quality issues (including deficiencies with regard to comparative analytical assessment, reference standards or materials, drug substance process description and validation, drug substance container closure system, drug product, stability protocols, analytical methods, control strategy, cell banks, shipping validation, drug product container closure system, stability and microbiology) and deficiencies identified during inspection of the Adello Biologics manufacturing facility (FEI: 3011289655). The CR Letter also included comments and recommendations that were not approvability issues regarding application organization, reference standard or materials, drug substance manufacturing, drug product manufacturing, analytical methods, control strategy, cell banks, stability, comparative analytical assessment, and microbiology. The applicant responded to the CR Letter with a resubmission on 12/11/2018. Review of the Resubmission found deficiencies including facilities and product quality issues that precluded approval (See CDTL Review by Sanjeeve Balasubramaniam, 6/6/2019 (Attachment A). A second CR Letter was issued on 6/11/2019 citing these deficiencies. A replacement CR Letter was issued on 6/11/2019 to correct errors in the company name and the FEI number of the deficient facility. (See Attachment B).

In the current resubmission (submitted 6/24/2020) the applicant responds to the deficiencies in the 6/11/2019 CR letter.

Review of 6/24/2020 Resubmission:
Theragrastim (filgrastim-ayow) has been developed as a proposed biosimilar product to US-licensed Neupogen (filgrastim) for indications listed above that have been previously approved for US-licensed Neupogen. The CDTL Review for the first cycle review (Sanjeeve Balasubramaniam, 5/9/2018) describes Theragrastim as follows: "The therapeutic protein Theragrastim (rHu-met-G-CSF) is a 175 amino acid protein produced in *E. coli.* The primary sequence of Theragrastim is identical to natural G-CSF, except for an additional methionine residue at the N-terminus as a consequence of production in bacterial culture; for the same reason, the therapeutic protein product is non-glycosylated. It was developed to have the same formulation and presentations as described in the product labeling for US-Neupogen, namely a prefilled syringe with strengths of 300 mcg/0.5ml and 480 mcg/0.8 ml, and vials with solution for injection at strengths of 300 mcg/1.0 ml and 480 mcg/1.6 ml."

During the first review cycle Product Quality issues were identified which precluded approval of Theragrastim. There were no clinical issues identified during that review cycle that would affect approvability of the application. As stated in the Clinical Review (Michael Brave, 4/19/2018): "The findings of this review of the clinical data support the demonstration of no

clinically meaningful differences between Theragrastim and the referenced product, US-licensed Neupogen, in support of the biosimilarity of Theragrastim to US-licensed Neupogen. This reviewer recommends approval of Theragrastim for the four indications under review." The first Resubmission did not include any new clinical data. (See Attachment A, CDTL Review signed 6/6/2019).

The current submission includes the following:

- Section 1.1 Administrative forms
- Section 1.2 cover letter
- Section 1.6 meetings (correspondence and meeting minutes)
- Section 1.11.1 *Quality Information Amendment* (includes Facility Inspections – CRL Item #1 and Additional Comments - CRL Items #4 and #5)
- Section 1.18 Proprietary Names
- Section 2.3 Quality Overall Summary (for drug substance and drug product and regional information)
- Section 3.2 Quality – Body of Data (for drug substance and drug product and regional information)
- Section 3.3 Literature references

Draft labeling was provided in submission SD-052, submitted 9/11/2020.

CMC Review:

The primary CMC Review of this resubmission was conducted by Rong Wang, Ph.D. Office of Biotechnology Products (OBP) (final signature, 12/1/2020). The Review recommended against approval of this application and stated the following regarding deficiencies:

> I. Primary Reviewer Summary Recommendation
>
> I do not recommend approval of 351(k) BLA application 761082/0049 for theragrastim (Releuko) as a proposed biosimilar to US-licensed Neupogen for the deficiencies listed below.
>
> II. List of Deficiencies (final comments may be found in the CR letter)

Deficiencies not to be communicated to the Applicant that will be investigated during a pre-license inspection:

(b) (5)

Deficiencies to be communicated to the Applicant:

The Agency issued a Complete Response (CR) letter on June 11, 2019 that included product quality deficiencies identified in the previous review cycle of 351(k) BLA 761082/0038 for theragrastim manufactured by Kashiv Biosciences, LLC (drug substance manufacture facility) and (b) (4) (drug product manufacture facility, a CMO for Kashiv), as a proposed biosimilar to US-licensed Neupogen. Kashiv submitted a Complete Response (CR) to Agency's CR letter on June 25, 2020. Kashiv's response to deficiencies presented in the CR letter issued by FDA on June 11, 2019 was reviewed and the deficiencies identified in Kashiv's response are summarized below.

An inspection of the Kashiv Biosciences LLC DS site (FEI 3011289655), Chicago, Illinois, facility is required before this application can be approved as the FDA must assess the ability of that facility to conduct the listed manufacturing operations in compliance with CGMP. Due to U.S. Government and/or Agency-wide restrictions on travel, we were unable to conduct an inspection of the Kashiv Biosciences LLC facility during the current review cycle, and the application cannot be approved until the required FDA inspection is conducted and the findings are assessed with regard to this application.

1. Audit Completeness and Data Traceability
   It is unclear whether the (b) (4) audit reviewed all the quality data submitted in the BLA because the (b) (4) audit covered data mainly generated during the years 2015-2017 and also, it is not clear whether there were source data traceability issues in the comparative analytical assessment including lots used in clinical studies submitted in the BLA. The audit team reported (see pages 596-7 of "Response to Retrospective Review of the GMP Systems and Product Quality Data of Theragrastim by (b) (4)):
   - some HPLC raw data and UV data were not traceable to the source, and
   - SDS-PAGE data for the clinical lot 45-14042 were not available for review during the audit.

   The theragrastim lots for which source data are not traceable should not be included in the comparative analytical assessment. To address this concern,
   - Provide a table listing all lots, tests performed with those lots, and the dates of testing that were retrospectively reviewed during the audit.
   - Identify results for which data cannot be traced back to the source that were included in the comparative analytical assessment.
   - Remove untraceable data from the comparative analytical assessment.

   Depending on the impact of removing untraceable data from the comparative analytical assessment Kashiv may need to conduct additional comparative analytical studies, repeat clinical studies, or both.

2. Sequence Variants
   Kashiv reported the detection of two sequence variants, S77-R77 and G101-R101. However, Kashiv did not provide an explanation for the etiology of the sequence variants or whether the variants impact conclusions Kashiv reached from the comparative analytical assessment. To address this concern, provide an explanation for the sequence variants, and whether the variants impact a determination that theragrastim is highly similar to US-licensed Neupogen. Depending on the etiology of the sequence variants and their impact on a determination that theragrastim is highly similar to US-licensed Neupogen, Kashiv may need to develop a strategy to control or eliminate these sequence variants in theragrastim.

3. In-House Reference Standards
   The stability protocols for the in-house primary and working reference standards are deficient because there are no acceptance criteria established to control for EC50. To address this concern, update the stability protocols for in-house primary and working reference standards to provide for adequate control over EC50.

4. Post-Approval Stability Protocol
   The post-approval stability protocol for the drug product (DP) is deficient because it does not include container closure integrity (CCI) testing at the 24-month time-point and specifications for syringe break loose and glide force. To address this concern, update the stability specifications to assess for syringe break loose and glide force and modify the stability protocol to include CCI testing at the 24-month time-point.

5. Shipping Validation Protocol
   The shipping validation protocols for the drug product in vials and pre-filled syringes are deficient because
   - Kashiv proposed to use the lower filling volumes in the shipping validation studies without providing adequate justification that the lower filling volumes represent worst-case scenarios, and
   - there is no test to examine the primary and secondary packaging systems to ensure no physical damage to the packaging systems after shipment.

   To address these concerns, update the protocol to
   - provide adequate justification that the lower filling volumes represent worst-case scenarios,
   - update the protocol to include examination of the primary and secondary packaging systems for physical damage.

In addition, there are several deficiencies that are not approvability issues, but need to be addressed by Kashiv.

6. In-House Reference Standards
   The stability protocol for the in-house primary reference standard is deficient because of inadequate replicate runs to robustly test potency. To address this concern, update the stability protocol to include sufficient replicates for potency testing.

7. Cell Banks
   a. The protocol for generation and characterization of new master and working cell banks is deficient because it does not include:
      - adequate acceptance criteria for cell growth kinetics, and
      - alert limits, action limits, or acceptance criteria for trend analysis.

      To address these concerns, update the protocol to include acceptance criteria to ensure that new working cell banks perform comparably to previous working cell banks.

(b) (4)

8. Methods

> Kashiv provided inadequate information to support that there is no impact on the RP-HPLC and CEX-HPLC method validations and test article data generated after replacing the United States Pharmacopeia reference standard, FOL526, with the in-house (b) (4) (b) (4) as a reference standard for the method. To address this concern, provide information supporting the suitable performance of in-house (b) (4) in these methods.

There were no recommendations for postmarketing requirements or commitments.

The Office of Pharmaceutical Quality (OPQ), Office of Pharmaceutical Manufacturing Assessment (OPMA) reviewed the BLA from a product quality microbiology perspective (Product Quality Microbiology/Facility Assessment Review Memorandum, Michael Shanks, final signature 11/3/2020) and recommended for Approval. However, the Manufacturing Facility Assessment Recommendation for the application was Withhold. The review summarized:

> Overall, the process is under adequate microbial control. Microbial quality is controlled at each step of the manufacturing process (b) (4) (b) (4) (b) (4) Adequate controls are in place to maintain microbiological product quality during maximum hold periods and throughout the manufacturing process. All Drug Substance deficiencies from a microbial control and microbiology product quality perspective were resolved and found approvable in second round of application review, BLA 761082-ORIG-1-RESUB-38 (Sequence 0038). New Drug Substance batches were evaluated in the Batch Analysis section and found satisfactory.
>
> Adequate descriptions of the facilities, equipment, environmental controls, cleaning and contamination control strategy were provided for Kashiv Biosciences LLC (FEI 3011289655), proposed for Drug Substance manufacture. With the exception of the Drug Substance manufacturing site, Kashiv Biosciences LLC, all other Drug Substance related facilities are acceptable based on their current CGMP compliance status and recent relevant inspectional coverage.

Nonclinical Pharmacology/Toxicology Review:
No additional pharmacology/toxicology information is included in this resubmission. Pharmacology/Toxicology Memorandum (Todd Bourcier, completed 12/3/2020) concluded there remain no outstanding nonclinical issues that would preclude approval of this BLA.

Clinical Pharmacology/Biopharmaceutics Review: There was no new clinical pharmacology information included in this submission. There was no Clinical Pharmacology review for this resubmission.

Clinical/Statistical Review: There was no new clinical information included in this submission. There was no Clinical/Statistical review for this resubmission.

Consults:
Nonproprietary Name Suffix Review (Carlos Mena-Grillasca, Division of Medication Error Prevention and Analysis (DMEPA), final signature 8/13/2020) found the suffix -ayow conditionally acceptable and recommended use of the nonproprietary name filgrastim-ayow throughout the labels and labeling.

Proprietary Name Review (Stephanie DeGraw, DMEPA, final signature 9/18/2020) found the proposed proprietary name, Releuko, conditionally acceptable.

Labeling:
The proposed labeling for this resubmission was submitted on 9/11/2020. Review of the labeling is deferred until the next review cycle.

Conclusion and Recommendations:
This BLA for a proposed biosimilar product to US-licensed Neupogen is not recommended for approval due to CMC and facility issues as stated under CMC Review section above.

ATTACHMENT A

27 Page(s) have been Withheld in Full as duplicates of Cross discipline review document dated 6.6.19 (9pgs) and Complete Response letter dated 6.11.19 (18pgs) immediately following this page. The 6.6.19 CDTL document can be found within the larger Cross Discipline Team Leader Review(s) document and the 6.11.19 Complete Response Letter can be found in the OtherActionLtrs document of the posted Approval Package on Drugs@FDA.com.

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/s/

KATHY M ROBIE SUH
12/18/2020 09:27:52 AM

Summary Review of Associate Division Director, DHP

Date	*Electronic Stamp Date*
From	Albert Deisseroth, M.D., Ph.D. (Supervisory Associate Division Director)
Subject	Summary Review of Associate Division Director
NDA/BLA #	BLA 761082
Applicant	Kashiv BioSciences, LLC
Date of Reubmission	December 11, 2018
BsUFA Goal Date	June 11, 2019
Proprietary Name/ nonproprietary Name	Releuko (proposed)[1]/ Theragrastim,filgrastim-ayow (proposed) [1]
Dosage forms / Strength	300 µg/mL single-dose vial 480 µg/1.6 mL single-dose vial 300 µg/0.5 mL single-dose pre-filled syringe (PFS) 480 µg/0.8 mL single-dose PFS
Proposed Indication(s)	1. Decrease the incidence of infection, as manifested by febrile neutropenia, in patients with nonmyeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a significant incidence of severe neutropenia with fever. 2. Reduce the time to neutrophil recovery and the duration of fever, following induction or consolidation chemotherapy treatment of patients with acute myeloid leukemia (AML). 3. Reduce the duration of neutropenia and neutropenia-related clinical sequelae, e.g., febrile neutropenia, in patients with nonmyeloid malignancies undergoing myeloablative chemotherapy followed by bone marrow transplantation (BMT). 4. Reduce the incidence and duration of sequelae of severe neutropenia (e.g., fever, infections, oropharyngeal ulcers) in symptomatic patients with congenital neutropenia, cyclic neutropenia, or idiopathic neutropenia.
Recommended:	*Complete Response*

Sources Utilized	Name
Cross-Discipline Team Leader Review	Sanjeeve Balasubramaniam, MD, MPH

[1] The names Releuko and filgrastim-ayow are conditionally accepted until such time that the application is approved. In this document, we refer to Kashiv's proposed product as Theragrastim, which was the name the applicant used to refer to this product during development.

Symmary Review of the Supervisory Associate Division Director

(This section was derived in part from the CDTL Review of Dr. Sanjeeve Balasubramaniam).

On July 8, 2017, Adello Biologics, LLC submitted BLA 761082 requesting licensure of Theragrastim as a biosimilar for US-licensed Neupogen for the following indications for which US-licensed Neupogen is approved:

1. Decrease the incidence of infection, as manifested by febrile neutropenia, in patients with nonmyeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a significant incidence of severe neutropenia with fever.
2. Reduce the time to neutrophil recovery and the duration of fever, following induction or consolidation chemotherapy treatment of patients with acute myeloid leukemia (AML).
3. Reduce the duration of neutropenia and neutropenia-related clinical sequelae, e.g., febrile neutropenia, in patients with nonmyeloid malignancies undergoing myeloablative chemotherapy followed by bone marrow transplantation (BMT).
4. Reduce the incidence and duration of sequelae of severe neutropenia (e.g., fever, infections, oropharyngeal ulcers) in symptomatic patients with congenital neutropenia, cyclic neutropenia, or idiopathic neutropenia.

.

Because of deficiencies discovered at the manufacturing facility that was used by Adello to produce Theragrastim as well as analytical similarity and product quality deficiencies, the FDA issued a Complete Response letter on May 10, 2018.

On December 11, 2018, Kashiv Biologics LLC (which succeeded Adello as the Applicant sponsoring company for BLA 761082) submitted a Complete Response. In this resubmission, Kashiv is seeking approval for the same indications (see above) included in the initial BLA submitted on July 8, 2017 .

Following a review of this Complete Response submitted by Kashiv, and a pre-license inspection (PLI) of the facility used by Kashiv to manufacture Theragrastim drug substance and to test Theragrastim drug substance and drug product, it was concluded that a determination that Theragrastim and US-licensed Neupogen are highly similar is not possible due to deficiencies identified during the inspection of the manufacturing and testing facility used by Kashiv.

Other deficiencies identified by the review team included deficiencies in the in-house reference standard, deficiencies in the control strategy for purity and potency of Theragrastim, deficiencies in the manufacturer's cell bank, deficiencies in the determination of the impurity profile, deficiencies in the microbial control and in the sterility assurance of drug product.

Regulatory Recommendation: The Supervisory Associate Division Director, DHP agrees with the recommendation of the CDTL and the review divisions to issue a Complete Response for the application (BLA 761082) submitted on December 11, 2018.

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/s/

KRISTOPHER KOLIBAB
06/07/2019 08:00:06 AM

ALBERT B DEISSEROTH
06/07/2019 08:19:40 AM

Cross-Discipline Team Leader Review

Date	*Electronic Stamp Date*
From	Sanjeeve Balasubramaniam, M.D., M.P.H. (CDTL) Albert Deisseroth, M.D., Ph.D. (Deputy Division Director)
Subject	Cross-Discipline Team Leader Review
NDA/BLA #	BLA 761082
Applicant	Kashiv BioSciences, LLC
Date of Reubmission	December 11, 2018
BsUFA Goal Date	June 11, 2019
Proprietary Name/ nonproprietary name	Releuko (proposed)/ Theragrastim, filgrastim-ayow (proposed) [1]
Dosage forms / Strength	300 µg/mL single-dose vial 480 µg/1.6 mL single-dose vial 300 µg/0.5 mL single-dose pre-filled syringe (PFS) 480 µg/0.8 mL single-dose PFS
Proposed Indication(s)	1. Decrease the incidence of infection, as manifested by febrile neutropenia, in patients with nonmyeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a significant incidence of severe neutropenia with fever. 2. Reduce the time to neutrophil recovery and the duration of fever, following induction or consolidation chemotherapy treatment of patients with acute myeloid leukemia (AML). 3. Reduce the duration of neutropenia and neutropenia-related clinical sequelae, e.g., febrile neutropenia, in patients with nonmyeloid malignancies undergoing myeloablative chemotherapy followed by bone marrow transplantation (BMT). 4. Reduce the incidence and duration of sequelae of severe neutropenia (e.g., fever, infections, oropharyngeal ulcers) in symptomatic patients with congenital neutropenia, cyclic neutropenia, or idiopathic neutropenia.
Recommended:	*Complete Response*
Recommended Indication (if applicable)	Not applicable

[1] The proposed proprietary name, Releuko, and proposed nonproprietary name, filgrastim-ayow, are conditionally accepted until such time that the application is approved. In this document, we refer to Kashiv's proposed product by descriptor Theragrastim, which was the name the applicant used to refer to this product during development.

REVIEW TEAM

Product Quality (CMC) Review Team:

Product Quality/Drug Substance/Drug Product: Rong Wang
Analytical Similarity: Rong Wang
Microbiology: Monica Commerford/ Maria Reyes Candau-Chacon (TL)
Facilities: Steve Fong, Peter Qiu (TL)
Labeling: Vicky Borders-Hemphill
RBPM: Kelly Ballard
Application Technical Lead: Ramesh Potla
Tertiary Reviewer: Susan Kirshner

Statistics: Tianhua Wang, Tianjiao DaiMeiyu Shen (TL)

Pharm/Tox: Emily Place, Chris Sheth (TL)

Clinical Pharmacology: Xianhua (Walter) Cao, Sarah Schrieber (TL)

Medical Reviewers: Michael Brave, Sanjeeve Balasubramaniam (TL)

OSE/DMEPA: Carlos M Mena-Grillasca, Danielle Harris

OPDP: Robert Nguyen

DMPP: Sharon Mills, LaShawn Griffiths

RPM: Kris Kolibab

CDTL: Sanjeeve Balasubramaniam

DHP Deputy Division Director: Albert Deisseroth

1. Introduction

On July 8, 2017, the applicant submitted a biologics license application (BLA) under section 351(k) of the Public Health Service Act (PHS Act) for Theragrastim, a proposed biosimilar to US-licensed Neupogen[2] (filgrastim). Because of the drug substance manufacturing facility inspection classification (i.e., withhold) as well as the product quality and analytical similarity deficiencies identified by the Office of Pharmaceutical Quality (OPQ) during that initial review, as summarized in the CDTL review dated May 9, 2018, BLA 761082 for Theragrastim was not recommended for approval. Specifically, the data submitted in that application were not found to be sufficient to support a conclusion that the manufacture of Theragrastim is well controlled and would lead to a product that is safe, pure, and potent for the duration of the shelf-life. Theragrastim was evaluated and compared to US-licensed Neupogen (hereafter US-Neupogen) using multiple orthogonal physicochemical and functional methods, and a determination that the two products are highly similar was not possible due to a number of deficiencies identified during the manufacturing and analytical assessment of Theragrastim by the OPQ review teams. A Complete Response letter dated May 10, 2018 was forwarded to the company detailing the deficiencies from that application. On December 11, 2018, Kashiv provided a complete response to the deficiencies listed in the CR letter and resubmitted the application for marketing approval.

The Applicant is seeking licensure of Theragrastim for the following indications for which US-Neupogen is licensed:

1. Decrease the incidence of infection, as manifested by febrile neutropenia, in patients with nonmyeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a significant incidence of severe neutropenia with fever.
2. Reduce the time to neutrophil recovery and the duration of fever, following induction or consolidation chemotherapy treatment of patients with acute myeloid leukemia (AML).
3. Reduce the duration of neutropenia and neutropenia-related clinical sequelae, e.g., febrile neutropenia, in patients with nonmyeloid malignancies undergoing myeloablative chemotherapy followed by bone marrow transplantation (BMT).
4. Reduce the incidence and duration of sequelae of severe neutropenia (e.g., fever, infections, oropharyngeal ulcers) in symptomatic patients with congenital neutropenia, cyclic neutropenia, or idiopathic neutropenia.

Section 351(i) of the PHS Act defines the terms “biosimilar” or “biosimilarity” to mean that “the biological product is highly similar to the reference product notwithstanding minor differences in clinically inactive components” and that “there are no clinically meaningful differences between the proposed biosimilar and the reference product in terms of the safety, purity, and potency of the product.”

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[2] In this document, any reference to “Neupogen” should be considered a reference to US-licensed Neupogen, also referred to as “US-Neupogen.” References to unknown sources of filgrastim (e.g., based on historical studies) will use the term “filgrastim.”

The OPQ review team completed review of this resubmission and determined that the data submitted are not sufficient to support a conclusion that the manufacture of Theragrastim is well-controlled and would lead to a product that is pure and potent for the duration of the shelf-life. There are deficiencies in the accuracy and reliability of the analytical similarity data and other product quality data, in the control strategy for purity, potency, and protein concentration, in the qualification and requalification program for cell banks, and in shipping validation. The Division of Microbiology identified deficiencies in the sterility assurance of the drug product. The Division of Inspectional Assessment identified deficiencies in the manufacture and control of the Theragrastim drug substance (DS), including Good Manufacturing Practices deficiencies at Kashiv Biosciences, LLC. As a result, from a product quality standpoint, OPQ is recommending a Complete Response (CR) letter be issued to Kashiv Biosciences, LLC, to outline the deficiencies identified during the review, as well as the additional information and data that would be required to support approval. Refer also to the OPQ Executive Summary memorandum dated May 24, 2019, for additional details.

Additionally, the statistical reviewers were unable to complete an analysis of relative potency because of inconsistencies in reported potency of specific Theragrastim drug product lots between the original submission and the resubmission. For details, refer to the Analytical Similarity Evaluation for Tier 1 Attributes from the Division of Biometrics VI, dated May 24, 2019.

2. CMC

Source: CMC/Quality/Micro/Facilities Review dated May 14, 2019; CMC Executive Summary dated May 23, 2019; additional information from the CMC executive summary of the initial submission, dated April 2, 2018.

Final Product Quality Team Recommendation: Complete Response

General product quality considerations

Refer to the CDTL Review for the initial application, dated May 9, 2018, for a general description of Theragrastim.

The Office of Biotechnology Products (OBP), OPQ, CDER, has completed review of the resubmission of BLA 761082 for Theragrastim manufactured by Kashiv Biosciences, LLC (drug substance manufacture) and (b) (4) (drug product, a CMO for Kashiv), as a proposed biosimilar to US-Neupogen. The data submitted in this application are not sufficient to support a conclusion that the manufacture of Theragrastim is well-controlled and would lead to a product that is pure and potent for the duration of the shelf-life. There are deficiencies in the accuracy and reliability of the analytical similarity and other product quality data, in the control strategy for purity, potency and protein concentration, in the qualification and requalification program for cell banks, and in shipping validation.

Thus, overall, the data submitted in this application are not sufficient to support a conclusion that the manufacture of Theragrastim DS and DP is well-controlled and would lead to a product that is pure and potent for the duration of the shelf-life. Therefore, OBP is recommending a Complete Response. Additional deficiencies were identified. Refer to the Complete Response letter for a complete list of deficiencies.

Microbiology reviews

Reviews from the Division of Microbiology Assessment, Office of Process and Facilities (OPF), OPQ have identified deficiencies in the sterility assurance of drug product. The application referenced Drug Master File (DMF) (b) (4). This DMF was found inadequate to support the resubmission and a deficiency letter was sent to the DMF holder on May 16, 2019. Refer also to the Complete Response letter for a complete list of deficiencies and additional comments.

Facilities review/inspection

A pre-license inspection was conducted from March 4, 2019 through March 12, 2019 at the drug substance facility for Theragrastim: Kashiv BioSciences, LLC, in Chicago, IL. The inspection covered the manufacturing of drug substance and testing of Theragrastim for the following five quality systems: Facilities and Equipment, Materials Management, Production System, Packaging and Labeling System, and Laboratory Controls. The FDA inspection team identified serious deficiencies that lead to the conclusion that the process validation as well as the QC release, stability, and analytical similarity data provided in the BLA submission may not be accurate and reliable. Satisfactory resolution of these deficiencies would be required in order to determine the approvability of the BLA application for Theragrastim. A 7-item Form FDA-483 was issued. See the FDA-483 dated March 12, 2019. The initial field recommendation for the inspection was WITHHOLD. The status of the facility is reviewed by Steve Fong, Division of Inspectional Assessment/Office of Process and Facilities/ (DIA/OPF).

A pre-license inspection of the drug product manufacturing site at (b) (4) was conducted from (b) (4) 2019. The initial field recommendation for the inspection is "acceptable" after the firm was found to have adequately addressed issues from an FDA Form-483 regarding deviation investigations, shipping validation, and clean hold time validation.

Analytical similarity assessment

The analytical similarity assessment was performed to demonstrate that Theragrastim and US-Neupogen are highly similar, notwithstanding minor differences in clinically inactive components.

Inspectional findings lead to the conclusion that analytical similarity data provided in the BLA submission may not be accurate and reliable. Other deficiencies were identified during the evaluation of analytical similarity. Refer to the CMC review dated May 14, 2019 for details.

Reviewer Comment: I concur with the OBP/OPQ review team's conclusion that the analytical similarity data do not support a determination that Theragrastim is highly similar to US-Neupogen. Thus, because of this conclusion, as well as outstanding manufacturing and control issues, this application is not recommended for approval. Refer to the Complete Response Letter for the deficiencies.

Immunogenicity

There were no additional immunogenicity data submitted for review during this resubmission. Refer to the CDTL Review for the initial application, dated May 9, 2018, for additional details of the immunogenicity data review for Theragrastim. See also the CMC executive summary of the initial submission, dated April 2, 2018.

CMC Statistical Review

Source: CMC Statistical Review dated May 24, 2019 (Tianhua Wang, Tianjiao Dai, and Meiyu Shen) and additional information from the CMC Statistical Review of the initial submission dated March 30, 2018 (Tianhua Wang and Meiyu Shen)

The CMC statistical reviewers were unable to complete an analysis of relative potency because of inconsistencies in reported potency of some Theragrastim drug product lots between the original submission and the resubmission. Refer also to the Complete Response letter for a detailed description of this deficiency.

3. Nonclinical Pharmacology/Toxicology

There were no additional nonclinical data submitted for review during this resubmission. Refer to the CDTL Review for the initial application, dated May 9, 2018, for additional details of the nonclinical pharmacology/toxicology review for Theragrastim. See also the Nonclinical Pharmacology and Toxicology Primary Review for the initial application dated April 12, 2018, 2018 (prepared by Emily Place and Christopher Sheth).

4. Clinical Pharmacology

There were no additional clinical pharmacology data submitted for review during this resubmission. Refer to the CDTL Review for the initial application, dated May 9, 2018, for additional details of the clinical pharmacology review for Theragrastim. See also the Clinical Pharmacology Review dated April 4, 2018 (prepared by Xianhua (Walt) Cao, Sarah J. Schrieber and Nam Atiqur Rahman).

5. Clinical Microbiology

Not applicable.

6. Clinical/Statistical- Efficacy

There were no additional clinical efficacy data submitted for review during this resubmission. Refer to the CDTL Review for the initial application, dated May 9, 2018, for additional details of the clinical review for Theragrastim. See also the Clinical Review dated April 19, 2018 (prepared by Michael Brave and Sanjeeve Balasubramaniam) and Clinical Pharmacology Review dated April 4, 2018 (Xianhua (Walt) Cao, Sarah Schrieber, and Nam Atiqur Rahman).

7. Safety

There were no additional clinical efficacy data submitted for review during this resubmission. Refer to the CDTL Review for the initial application, dated May 9, 2018, for additional details of the clinical review for Theragrastim. See also the Clinical Review dated April 19, 2018 (prepared by Michael Brave and Sanjeeve Balasubramaniam) and and Statistical Review dated April 2, 2018 (prepared by Haiyan Chen, Lei Nie, and Thomas Gwise).

8. Considerations for Extrapolation of Biosimilarity

Not applicable.

9. Advisory Committee Meeting

An advisory committee meeting was not held for this application.

10. Pediatrics

Not applicable.

11. Other Relevant Regulatory Issues

Not applicable.

12. Labeling

Patient labeling in the Division of Medical Policy Programs and the Office of Prescription Drug Promotion deferred review of this submission due to outstanding deficiencies. No additional labeling review was performed. Rereview performed by the Division of Medication Error Prevention and Analysis again found the suffix -ayow acceptable and averred that the nonproprietary name filgrastim-ayow should be used throughout the draft labels and labeling.

13. Recommendations

Recommended Regulatory Action

Because of the drug substance manufacturing facility inspection classification (i.e., withhold) as well as the product quality and analytical similarity deficiencies identified by OPQ, as summarized in section 2 of this review, the BLA 761082 resubmission for Theragrastim is not recommended for approval. Specifically, the data submitted in this application were not found to be sufficient to support a conclusion that the manufacture of Theragrastim is well controlled and would lead to a product that is safe, pure, and potent for the duration of the shelf-life, and that Theragrastim is highly similar to US-Neupogen.

Because the applicant has not adequately demonstrated that Theragrastim is highly similar to US-Neupogen, we cannot conclude that the totality of the evidence supports a demonstration of biosimilarity of Theragrastim to US-Neupogen.

Recommendation for Postmarketing Risk Evaluation and Management Strategies

None.

Recommendation for other Postmarketing Requirements and Commitments

None.

Recommended Comments to Applicant

See Complete Response letter.

Recommended Regulatory Action

Complete Response.

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/s/

SANJEEVE BALASUBRAMANIAM
06/06/2019 01:29:18 PM

ALBERT B DEISSEROTH
06/06/2019 05:11:27 PM

Cross-Discipline Team Leader Review

Date	*Electronic Stamp Date*
From	Sanjeeve Balasubramaniam, M.D., M.P.H. (CDTL) Albert Deisseroth, M.D., Ph.D. (Deputy Division Director)
Subject	Cross-Discipline Team Leader Review
NDA/BLA #	351(k) BLA 761082
Applicant	Adello Biologics, LLC
Date of Submission	July 8, 2017
BsUFA Goal Date	May 10, 2018
Proprietary Name/ Established (USAN) Name	Releuko (proposed)/ Theragrastim, filgrastim-ayow (proposed) [1]
Dosage forms / Strength	300 µg/mL single-use vial 480 µg/1.6 mL single-use vial 300 µg/0.5 mL single-use PFS 480 µg/0.8 mL single-use PFS
Proposed Indication(s)	1. Decrease the incidence of infection, as manifested by febrile neutropenia, in patients with nonmyeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a significant incidence of severe neutropenia with fever. 2. Reduce the time to neutrophil recovery and the duration of fever, following induction or consolidation chemotherapy treatment of patients with acute myeloid leukemia (AML). 3. Reduce the duration of neutropenia and neutropenia-related clinical sequelae, e.g., febrile neutropenia, in patients with nonmyeloid malignancies undergoing myeloablative chemotherapy followed by bone marrow transplantation (BMT). 4. Reduce the incidence and duration of sequelae of severe neutropenia (e.g., fever, infections, oropharyngeal ulcers) in symptomatic patients with congenital neutropenia, cyclic neutropenia, or idiopathic neutropenia.
Recommended:	*Complete Response*
Recommended Indication (if applicable)	Not applicable

[1] The proposed proprietary name, Releuko, and proposed proper name, filgrastim-ayow, are conditionally accepted until such time that the application is approved. In this document, we refer to Adello's proposed product by descriptor Theragrastim, which was the name Adello used to refer to this product during development.

REVIEW TEAM

Product Quality (CMC) Review Team:

Drug Substance: Tracy Denison, and Fabiola Gomez, Joao Pedras Vasconcelos
Drug Product: Fabiola Gomez
Analytical Similarity: Tracy Denison
Immunogenicity: Joao Pedras Vasconcelos, Maria Cecilia Tami, and Susan Kirshner
Labeling: Vicky Borders-Hemphill
Facilities: Laura Fontan, Peter Qiu (TL)
Microbiology: Kathleen Jones (DS), Monica Commerford (DP), Reyes Candau-Chacon (TL)
RBPM: Kelly Ballard
Application Technical Lead: Maria Cecilia Tami
Tertiary Reviewer: Maria Teresa Gutierrez-Lugo

CMC Statistics: Tianhua Wang, Meiyu Shen (TL)

Statistics: Haiyan Chen, Lei Nie (TL)

Pharm/Tox: Emily Place, Chris Sheth (TL)

Clinical Pharmacology: Xianhua (Walter) Cao, Sarah Schrieber (TL)

Medical Reviewers: Michael Brave, Sanjeeve Balasubramaniam (TL)

OSE/DMEPA: Nicole Garrison, Hina Mehta (TL)

OPDP: Robert Nguyen

DMPP: Shawna Hutchins, Barbara Fuller (TL)

TBBS: Carla Lankford, Michele Dougherty, Sue Lim (TL)

RPM: Kris Kolibab

CDTL: Sanjeeve Balasubramaniam

DHP Deputy Division Director: Albert Deisseroth

1. Introduction

On July 8, 2017, the applicant submitted a biologics license application (BLA) under Section 351(k) of the Public Health Service Act (PHS Act) for Theragrastim, a proposed biosimilar to US-licensed Neupogen[2](filgrastim). The Applicant is seeking licensure of Theragrastim for the following indications for which US-Neupogen is licensed:

1. Decrease the incidence of infection, as manifested by febrile neutropenia, in patients with nonmyeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a significant incidence of severe neutropenia with fever.
2. Reduce the time to neutrophil recovery and the duration of fever, following induction or consolidation chemotherapy treatment of patients with acute myeloid leukemia (AML).
3. Reduce the duration of neutropenia and neutropenia-related clinical sequelae, e.g., febrile neutropenia, in patients with nonmyeloid malignancies undergoing myeloablative chemotherapy followed by bone marrow transplantation (BMT).
4. Reduce the incidence and duration of sequelae of severe neutropenia (e.g., fever, infections, oropharyngeal ulcers) in symptomatic patients with congenital neutropenia, cyclic neutropenia, or idiopathic neutropenia.

The applicant is not seeking licensure for the following two additional indications approved for US-licensed Neupogen. Because of the requirement for additional clinical CD34+ cell evaluations, the following indication is not being sought:

1. Mobilize autologous hematopoietic progenitor cells into the peripheral blood for collection by leukapheresis

Due to orphan exclusivity, the applicant is not seeking the following indications for which US-Neupogen has been previously approved:

1. Increase survival in patients acutely exposed to myelosuppressive doses of radiation[3].

Section 351(i) of the PHS Act defines the terms “biosimilar” or “biosimilarity” to mean that “the biological product is highly similar to the reference product notwithstanding minor differences in clinically inactive components” and that “there are no clinically meaningful differences between the proposed biosimilar and the reference product in terms of the safety, purity, and potency of the product.” Both parts of the statutory definition must be met to demonstrate biosimilarity, but the foundation of the data demonstrating biosimilarity is extensive structural and functional characterization to support a determination that the products are highly similar.

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[2] In this document, any reference to “Neupogen” should be considered a reference to US-licensed Neupogen. References to unknown sources of filgrastim (e.g., based on historical studies) will use the term “filgrastim.”

[3] Neupogen’s indication for increased survival in patients acutely exposed to myelosuppressive doses of radiation is protected by orphan drug exclusivity expiring on March 30, 2022. See the Orphan Drug Designations and Approvals database at http://www.accessdata fda.gov/scripts/opdlisting/oopd/index.cfm.

The applicant conducted an analytical comparison between the proposed biosimilar and US-licensed Neupogen (henceforth referred to as US-Neupogen) to support the demonstration that the products are highly similar. The applicant also conducted a head-to-head comparison of the toxicity, immunogenicity, and toxicokinetics (TK) of Theragrastim and US-Neupogen in Sprague-Dawley rats. The Theragrastim clinical development program consisted of two pharmacokinetic (PK) and pharmacodynamic (PD) biosimilarity studies (CL-106 and CL-101) and an immunogenicity study (CL-110). All three studies compared subcutaneous (SC) doses of Theragrastim and US-Neupogen in healthy subjects.

Theragrastim was evaluated and compared to US-Neupogen using multiple orthogonal physicochemical and functional methods. The analytical similarity data submitted in this application indicate that the amino acid sequences of Theragrastim and US-Neupogen are the same. The data indicate that most other attributes assessed in Theragrastim and US-licensed Neupogen support a determination that the products are highly similar. However, a determination that the two products are highly similar is not possible at this point due to a number of deficiencies identified during the manufacturing and analytical assessment of Theragrastim by the Office of Pharmaceutical Quality (OPQ) review teams, including:

1. The Division of Biotechnology Review and Research III (DBRR-III) has identified deficiencies inthe qualification of the in-house reference standard, in the control strategy for purity, potency and protein concentration, in the requalification program for cell banks and in shipping validation, and as to whether Theragrastim and US-Neupogen have a similar impurity profile. Based on the available data and information, OBP cannot determine that the two products are highly similar.

Additional product quality deficiencies were identified:

1. The Division of Microbiology Assessment (DMA), has identified deficiencies in the microbial control of drug substance and drug product and sterility assurance of drug product.

2. The Division of Inspectional Assessment (DIA), noted failure to establish procedures to prevent unauthorized access or changes to data, and to provide adequate controls to prevent manipulation and omission of data; and, failure to control the issuance and use of all GMP documents.

For the foregoing and additional product quality deficiencies, all of which are described in section 3 below, OPQ, CDER, has determined that the data submitted are not sufficient to support a conclusion that the manufacture of Theragrastim is well-controlled and will lead to a product that is safe, pure, and potent for the duration of the shelf-life. Therefore, there is a lack of assurance that the commercial materials will not drift from Theragrastim clinical materials and the materials used in analytical similarity assessment.

The nonclinical pharmacokinetic and toxicity profile of Theragrastim was compared head-to-head with US-Neupogen via subcutaneous administration in Sprague-Dawley rates. Overall, the

animal studies provided in the BLA submission did not identify any safety concerns with Theragrastim or differences in the PK or toxicity profile of Theragrastim compared to US-Neupogen. The Pharmacology and Toxicology discipline has not identified any residual uncertainties.

The pharmacokinetic profiles of Theragrastim and US-Neupogen were evaluated in healthy subjects in study CL-106. The results of this pharmacokinetic similarity study support a demonstration of no clinically meaningful differences between Theragrastim and US-Neupogen. The results of this study also contribute to the totality of the data in support of a demonstration of biosimilarity of Theragrastim to US-Neupogen. Study CL-101, a PK/PD similarity study that did not meet its prespecified PK endpoint, was evaluated for supportive safety data only.

Anti-drug antibodies (ADA) were measured in study CL-110 comparing Theragrastim to US-Neupogen. The data indicate that there is no increase in immunogenicity risk in terms of ADA development for Theragrastim when compared to US-Neupogen, which supports the demonstration of no clinically meaningful differences between Theragrastim and US-Neupogen.

The applicant provided adequate scientific justification for extrapolation of data and information to support licensure of Theragrastim as a biosimilar for the conditions of use for which US-Neupogen has been previously approved.

In considering the totality of the evidence, the data submitted by the applicant support a demonstration that there are no clinically meaningful differences between Theragrastim and US-Neupogen in terms of safety, purity, and potency (safety and efficacy); however, the data did not support a demonstration that Theragrastim is highly similar to US-Neupogen, notwithstanding minor differences in clinically inactive components. Due to the analytical similarity issues and other manufacturing and control deficiencies, described in further detail in section 3 of this review, the application is not recommended for approval.

2. Background

The Biologics Price Competition and Innovation Act of 2009 (BPCI Act) created an abbreviated licensure pathway for biological products shown to be "biosimilar" to or "interchangeable" with an FDA-licensed biological product (the "reference product"). This abbreviated licensure pathway under section 351(k) of the PHS Act permits reliance on certain existing scientific knowledge about the safety, purity, and potency of the reference product, and enables a biosimilar biological product to be licensed based on less than a full complement of product specific nonclinical and clinical data.

Section 351(k) of the PHS Act defines the terms "biosimilar" or "biosimilarity" to mean that "the biological product is highly similar to the reference product notwithstanding minor differences in clinically inactive components" and that "there are no clinically meaningful differences between the biological product and the reference product in terms of the safety, purity, and potency of the product."

Development of a biosimilar product differs from development of a biological product intended for submission under section 351(a) of the PHS Act (i.e., a "stand-alone" marketing application). The goal of a "stand-alone" development program is to demonstrate the safety, purity, and potency of the proposed product in each indication based on data derived from a full complement of clinical and nonclinical studies. The goal of a biosimilar development program is to demonstrate that the proposed product is biosimilar to the reference product. While both standalone and biosimilar product development programs generate analytical, nonclinical, and clinical data, the number and types of studies conducted will differ based on differing goals and the different statutory standards for licensure.

The "totality of the evidence" submitted by the applicant should be considered when evaluating whether an applicant has adequately demonstrated that a proposed product meets the statutory standard for biosimilarity to the reference product. Such evidence generally includes comparative structural and functional characterization, animal study data, human PK and, if applicable, pharmacodynamics (PD) data, clinical immunogenicity data, and other clinical safety and effectiveness data.

In general, an applicant needs to provide information to demonstrate biosimilarity based on data directly comparing the proposed biosimilar product with the US-licensed reference product.

Regulatory History

May 2, 2012	Therapeutic Proteins International, LLC, (TPI) requested a meeting to discuss their development plan for Theragrastim, IND 115333. FDA provided preliminary comments to the meeting questions; however, FDA cancelled the meeting because the meeting package contained insufficient analytical data to determine whether the proposed product could be developed as a biosimilar biological product under section 351(k) of the PHS Act. The FDA encouraged TPI to submit a new meeting request that contains a more complete CMC assessment, including analytical similarity data from at least one lot representative of the material to be used in the initial clinical study comparing Theragrastim to US-licensed Neupogen.
Oct 28, 2013 Biological Product Development (BPD) Type 2 meeting	TPI presented their biosimilar development plan. FDA recommended: • A single dose, crossover study design to evaluate PK similarity and PD similarity with respect to ANC. • Subcutaneous product administration, as this is more sensitive to differences between products than the intravenous route. • The selected dose(s) should be in the linear ascending part of the dose-response curve. Doses less than 10 µg/kg are preferred in healthy subjects to minimize adverse events, such as bone pain, observed at higher doses. While both the 2.5 and 5 µg/kg doses of US-licensed Neupogen are in the linear ascending part of the dose-response curve, for development of a proposed biosimilar product, a PK and PD evaluation of only the 5 µg/kg SC dose is necessary.

Nov 4, 2014 BPD Type 2 meeting	TPI presented results of CL-101, a double-blinded, two-way, two dose-cohort (2.5 and 5 µg/kg) crossover study in healthy subjects (N = 116). CL-101 was designed to show PK similarity; however, the PK parameters did not meet pre-defined acceptance criteria. (b) (4) [redacted] As a result, CL-101 could not support PK similarity. FDA concurred with TPI's proposal to conduct CL-106.
June 9, 2016 BPD Type 3 meeting	TPI requested the Agency's feedback on the adequacy of their analytical similarity data between Theragrastim and US-Neupogen to support a 351(k) BLA. FDA stated: • FDA provided extensive advice regarding the analytical similarity assessment. • Comparative clinical immunogenicity studies, either in patients with cancer or in healthy subjects, were required to demonstrate no clinically meaningful differences between Theragrastim and US-licensed Neupogen. • A parallel-arm study design is needed so that ADA may be attributed to a specific product. To reflect real-world exposure, FDA recommended a two-cycle parallel-arm study in which the subjects are given 5 daily doses of drug during Cycle 1 and a single dose during Cycle 2. Cycles should be at least 4 weeks apart. • Samples for ADA should be collected prior to administration of the first dose; 7 to 14 days after the first of 5 daily doses to evaluate IgM responses; 21 to 28 after initiation of the Cycle 1 but prior to initiation of the Cycle 2 to evaluate IgG responses; and 21 to 28 days after the administration of the second cycle single dose. ADA-positive subjects should be followed until ADA levels return to baseline. Confirmed ADA positive samples should be assayed for titer, persistence, and neutralizing capability. • Safety testing should include an evaluation for clinically meaningful differences in class adverse reactions using grouped terms, such as Musculoskeletal and connective tissue disorders (MedDRA SOC) for musculoskeletal pain, Injection site reactions (MedDRA HLT) for injection site reactions, and Hypersensitivity (MedDRA SMQN) as well as Anaphylactic reaction (MedDRA SMQN) for hypersensitivity reactions.
Feb 7, 2017 BPD Type 3 meeting	FDA stated that the clinical program consisting of two PK/PD trials (CL-101 and CL-106) and an immunogenicity and safety trial (CL-110) may be sufficient to support the filing of a BLA.

July 8, 2017: BLA 761091 submitted to FDA.

3. CMC/Device

Source: CMC/Quality/Micro/Facilities Reviews; CMC Executive Summary dated February 8, 2018; OPQ Drug Product Microbiology Review dated April 2, 2018

Discipline	Reviewer	Branch/Division
Drug Substance	Joao Pedras-Vasconcelos, Fabiola Gomez, Tracy Denison	DBRR III/OBP/OPQ
Drug Product	Fabiola Gomez	DBRR III/OBP/OPQ
Analytical similarity	Tracy Denison	DBRR III/OBP/OPQ
Immunogenicity	Joao Pedras-Vasconcelos	DBRR IIIOBP/OPQ
Labeling	Vicky Borders-Hemphill	OBP/OPQ
Facility	Laura Fontan/Peter Qiu (TL)	DIA/OPF/OPQ
Microbiology	Kathleen Jones, Monica Commerford, Reyes Candau-Chacon	DMA/OPF/OPQ
RBPM	Kelly Ballard	OPRO/OPQ
Application Technical Lead	Maria Cecilia Tami	DBRR III/OBP/OPQ
Tertiary Reviewer	Maria Teresa Gutierrez-Lugo	DBRR III/OBP/OPQ

Final Product Quality Team Recommendation: Complete Response

General product quality considerations

Endogenous G-CSF is a glycoprotein produced by monocytes, fibroblasts, and endothelial cells, and regulates the maturation, proliferation and differentiation of the precursor cells of neutrophilic granulocytes within the bone marrow. G-CSF activates the G-CSF receptor (CD114) on the surface of leukocytes. The cross-linking of this receptor initiates the cascade of signaling events that lead to proliferation and differentiation of precursor cells into mature granulocytes.

The therapeutic protein Theragrastim (rHu-met-G-CSF) is a 175 amino acid protein produced in *E. coli.* The primary sequence of Theragrastim is identical to natural G-CSF, except for an additional methionine residue at the N-terminus as a consequence of production in bacterial culture; for the same reason, the therapeutic protein product is non-glycosylated. It was developed to have the same formulation and presentations as described in the product labeling for US-Neupogen, namely a prefilled syringe with strengths of 300 mcg/0.5ml and 480 mcg/0.8 ml, and vials with solution for injection at strengths of 300 mcg/1.0 ml and 480 mcg/1.6 ml.

Theragrastim is used to treat clinical neutropenia and to induce the mobilization of hematopoietic stem cells. The therapeutic protein is administered to oncology patients to accelerate recovery from neutropenia after chemotherapy, and in other settings characterized by neutropenia, including severe congenital neutropenia.

Theragrastim drug substance is manufactured at Adello Biologics, LLC, Chicago, IL, USA, [redacted] (b) (4)

(b) (4)

The Office of Biotechnology Products, OPQ, CDER, has completed review of this application and determined that the data submitted are not sufficient to support a conclusion that the manufacture of Theragrastim is well-controlled and will lead to a product that is safe, pure, and potent for the duration of the shelf-life. There are deficiencies in the qualification of the in-house reference standard, in the control strategy for purity, potency and protein concentration, in the requalification program for cell banks and in shipping validation. Therefore, there is a lack of assurance that the commercial materials will not drift from Theragrastim clinical materials and the materials used in analytical similarity.

Thus, overall, the data submitted in this application are not sufficient to support a conclusion that the manufacture of Theragrastim DS and DP is well-controlled and will lead to a product that is pure and potent for the duration of the shelf-life. Therefore, OBP is recommending a Complete Response. Additional deficiencies were identified. Refer to the Complete Response letter for a complete list of deficiencies.

Microbiology reviews

The Division of Microbiology Assessment, Office of Process and Facilities (OPF), OPQ has identified deficiencies in the microbial control of drug substance and drug product and sterility assurance of drug product. (b) (4)

Refer to the Complete Response letter for a complete list of deficiencies and additional comments.

Facilities review/inspection

The Division of Inspectional Assessment (DIA), OPF, OPQ recommendation for the BLA 761082 from the outcome of the pre-licensed inspection was "withhold." This recommendation is based on the pre-licensing inspection of the drug substance manufacturer, Adello Biologics, LLC. in Chicago, IL. This inspection was conducted in support of BLA 761082/0 for Theragrastim. A six-item Form FDA 483 was issued to management including observations concerning inadequate quality oversight, inadequate laboratory procedures, inadequate deviation investigation, inadequate control of critical materials, inadequate written procedures, and written

procedures are not always followed. DIA evaluated the responses supplied by the firm to the FDA-483 observations and found them inadequate.

In addition, a for-cause inspection was conducted January 22 to 26, 2018, to perform a data integrity audit of the submission data associated with BLA 761082, Theragrastim. Adello currently has no FDA-approved drug products being marketed in the United States. The for-cause inspection was conducted by the Office of Regulatory Affairs (ORA)in support of BLA 761082. A 4-item FDA 483 was issued including observations for: failure to ensure that all test procedures are scientifically sound and appropriate; procedures for review of analytical data were not established and followed; failure to prevent unauthorized access or changes to data, and to provide adequate controls to prevent manipulation and omission of data; and, failure to control the issuance and use of all GMP documents.

Responses to the deficiencies were evaluated and are inadequate to give assurance that the data submitted for BLA 761082 was not impacted. The responses do not address whether the lack of these controls impacted data submitted for Theragrastim. There is no confidence that the data submittedis accurate and complete. In addition, responses did not include any description of training performed or commitment to future training to ensure that new procedural updates were understood by employees and would be followed.

OPF/DIA concurs with the initial withhold recommendation made for the pre-license inspection for BLA 761082.

Analytical similarity assessment

The analytical similarity assessment was performed to demonstrate that Theragrastim and US-Neupogen are highly similar, notwithstanding minor differences in clinically inactive components.

Up to 28 lots of US-licensed Neupogen and 27 lots of Theragrastim DP and 3 lots of Theragrastim DS were evaluated, including lots used in the PK/PD similarity and safety clinical studies and lots manufactured by the proposed commercial manufacturing process. The assessment of analytical similarity was supported by comparative statistical analysis. To determine the comparative analyses to be used to support a demonstration of highly similar through analytical testing, quality attributes were ranked into categories of high, medium, and low criticality based on information on the impact of each attribute to product safety, potency, PK, and immunogenicity. The sponsor selected the high criticality attribute most important for the mechanism of action of the product which could be analyzed using a quantitative analytical method. Analytical similarity of this attribute was evaluated using statistical equivalence testing. Results from other attributes were assessed using “quality ranges” and comparison of graphical data, referred as Tier 2 and Tier 3 statistical methods, respectively. Orthogonal methods were used for some quality attributes. Overall, the results from analytical similarity indicate that most quality attributes assessed in Theragrastim and US-licensed Neupogen support that the products are highly similar including potency, receptor binding, primary sequence, identity, primary structure, higher-order structure, protein concentration, and purity by SE-HPLC. However, data

regarding the impurity profile of Theragrastim compared to US-licensed Neupogen with regards to type and amount of impurities is insufficient to support a demonstration that the two products are highly similar. Therefore, based on the available data and information, FDA cannot determine that the two products are highly similar.

Reviewer Comment: I concur with the OBP/OPQ review team's conclusion that the analytical similarity data do not support a determination that Theragrastim is highly similar to US-Neupogen. Thus, because of this conclusion, as well as outstanding manufacturing and control issues, this application is not recommended for approval. Refer to the Complete Response Letter for the deficiencies.

Immunogenicity

The information submitted in the immunogenicity assay reports indicate that the screening and confirmatory assays are suitable for detecting anti-drug antibodies (ADA) in clinical samples. The applicant utilized one assay based on the proposed biosimilar product to detect anti-drug antibodies to either US-Neupogen or Theragrastim. The applicant performed study CL-110, a randomized two-cycle parallel group study in healthy subjects (n=67 per group) to assess potential differences in the risk of immunogenicity of US-Neupogen and Theragrastim. The design of the study was appropriate to assess immunogenicity. The biosimilar candidate drug product batch 300-16022 used in the study was manufactured using process 3a and is representative of the proposed commercial manufacturing process. A total of 26 of 257 tested samples screened positive (~4.9% false positive rate), which support adequate performance of the screening assay. Only one subject in the Theragrastim treatment group confirmed positive at d-1 and d-7, but the ADA responses were not treatment emergent because the subject tested positive for the presence of ADA at baseline (before treatment) and ADA responses did not increase during the study. Immunogenicity rates were 1/67 (1.49%) in the Theragrastim group and 0/67 (0%) in the US-Neupogen group, with no statistically significant difference between the groups. The results from the immunogenicity assessment from study CL-110 support a conclusion of no clinically meaningful differences between Theragrastim and US-licensed Neupogen.

Reviewer Comment: I concur with the immunogenicity reviewer's conclusion that the submitted study adequately demonstrated similar immunogenicity between Theragrastim and US-Neupogen. The immunogenicity data indicate that there is no increase in immunogenicity risk for Theragrastim when compared to US-Neupogen, which supports a demonstration of no clinically meaningful differences between Theragrastim and US-Neupogen.

CMC Statistical Review

Source: CMC Statistical Review dated March 30, 2018 (Tianhua Wang and Meiyu Shen)

The CMC statistical reviewer in the Office of Biostatistics analyzed the comparative results of one critical quality attribute: relative potency by bioassay, which was recommended for equivalence testing analysis by the Office of Biotechnology. The biological activity of Theragrastim and US-Neupogen were tested using the M-NFS-60 cell proliferation assay (STM-

0118). Tier 1 statistical equivalence testing was conducted using equivalence margins of ± 1.5σ_R, where σ_R represents US-Neupogen variability. Fifteen lots of Theragrastim drug products and 16 lots of US-Neupogen were used for equivalence testing for relative potency by bioassay. The results are summarized in Table 1. The results from the statistical equivalence testing of relative potency by bioassay support a demonstration that the proposed biosimilar Theragrastim is highly similar to US-licensed Neupogen.

Comparison	# of lots	Mean Difference %	90% CI for Mean Difference	Equivalence Margin, %	Pass Equivalence Testing?
Theragrastim vs. US-Licensed Neupogen	(15, 16)	3.42	(-0.22, +7.07)	(-7.95, 7.95)	Yes

Reviewer Comment: I concur with the CMC statistical reviewers' conclusion that the submitted data adequately demonstrated similarity between the biological activity of Theragrastim when compared to that of US-Neupogen as the 90% CI of the mean difference falls within the prespecified statistical equivalence margin, which supports a demonstration that Theragrastim and US-Neupogen are highly similar, notwithstanding minor differences in clinically inactive components.

4. Nonclinical Pharmacology/Toxicology

Source: Pharmacology and Toxicology primary Review dated April 12, 2018, 2018 (Emily Place and Christopher Sheth)

Final Pharmacology/Toxicology Team Recommendations: Approval.

General toxicology studies of Theragrastim include a GLP-compliant repeat-dose study in rats with subcutaneous administration of Theragrastim or US-Neupogen once weekly for a total of 5 doses with a 2-week recovery period. Sprague-Dawley rats were administered vehicle, or 1.5, 11.5, 115, or 1150 μg/kg Theragrastim or US-Neupogen by subcutaneous injection. One death occurred in the high dose Theragrastim group prior the end of the study. Drug related toxicities shared between Theragrastim and US-Neupogen included increased white blood cell (WBC) count, increased % neutrophils correlating with decreased % lymphocytes, increased alkaline phosphatase values, and hematopoietic proliferation in the bone marrow and spleen. The variability observed in the toxicokinetic parameters from the rat study was not reflected in the pharmacodynamic response. The nonclinical data submitted in support of this BLA support a determination that Theragrastim is similar to US-Neupogen.

Reviewer Comment: I concur with nonclinical team's conclusion that the submitted pharmacology and toxicology data were adequate to demonstrate similarity in the toxicity and TK profiles of Theragrastim and US-Neupogen in rats.

5. Clinical Pharmacology

Source: Clinical Pharmacology Review dated April 4, 2018 (Xianhua (Walt) Cao, Sarah J. Schrieber and Nam Atiqur Rahman)

Final Clinical Pharmacology Team Recommendations: Approval

The application included pharmacokinetic (PK), pharmacodynamics (PD), and immunogenicity data to support a demonstration of no clinical meaningful differences between Theragrastim and US-Neupogen in terms of safety, purity, and potency. The PK/PD similarity study CL-106 and the immunogenicity study CL-110 were conducted in healthy subjects comparing Theragrastim and US-licensed Neupogen. Study CL-106 was a randomized, double-blind, 2-period crossover study in 58 healthy subjects designed to determine the PK and PD (absolute neutrophil count (ANC)) similarity of Theragrastim and US-Neupogen following a single 5 μg/kg subcutaneous dose. PK and PD similarity was established if the prespecified 90% CI of the geometric mean ratios between Theragrastim and US-licensed Neupogen were within the limits of 80% to 125%. The results of the study established the PK and PD similarity between Theragrastim and US-Neupogen based on the primary PK endpoints of C_{max} and $AUC_{0\text{-}inf}$ and PD endpoints of ANC_{max} and ANC $AUEC_{last}$.

The incidence of anti-drug antibodies (ADAs) was compared in study CL-110, a randomized, multiple-dose, parallel study in 134 healthy subjects. The results indicate no treatment emergent ADA for either Theragrastim or US-Neupogen. The assessment of the impact of ADA on PK, PD, and safety are limited due to no subjects with treatment emergent ADA, and no PK sampling. The data indicate that there is no increase in immunogenicity risk for Theragrastim as compared to US-Neupogen. In conclusion, the PK, PD, and immunogenicity results support a demonstration of no clinically meaningful differences between Theragrastim and US-Neupogen and add to the totality of the evidence to support a demonstration of biosimilarity of Theragrastim and US-Neupogen.

Reviewer Comment: I concur with clinical pharmacology team's conclusion that the submitted PK/PD data are adequate to demonstrate similarity in the PK/PD profiles of Theragrastim and US-Neupogen in healthy subjects. The PD endpoint of this study, absolute neutrophil count, is the efficacy endpoint for this proposed biosimilar application. The submitted data are sufficient to support a demonstration of no clinically meaningful differences between Theragrastim and US-Neupogen.

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical- Efficacy

Source: Clinical Review (Michael Brave and Sanjeeve Balasubramaniam) and Clinical Pharmacology Review (Xianhua (Walt) Cao, Sarah Schrieber, and Nam Atiqur Rahman)

Final Clinical/Statistical Team Recommendations: Approval

The primary study supporting PK/PD similarity between Theragrastim and US-Neupogen is CL-106.

Refer to Section 5 of this document, Clinical Pharmacology, for a brief discussion of the results of study CL-106, which established the PK and PD similarity of Theragrastim and US-Neupogen.

None of the studies submitted were designed to prospectively compare Theragrastim and US-Neupogen for a clinical efficacy or safety endpoint in an intended population. Because the mechanism of action of filgrastim in healthy subjects is the same as the mechanism of action for filgrastim in the conditions of use for which the applicant is seeking licensure, and because the PD endpoint in CL-106 (ANC) is sufficiently sensitive and well-correlated with the intended clinical outcome, the demonstration of PK and PD similarity of Theragrastim and US-Neupogen in healthy volunteers is sufficient to support a demonstration that there are no clinically meaningful differences between Theragrastim and US-Neupogen.

8. Safety

Source: Clinical Review (Michael Brave and Sanjeeve Balasubramaniam) and Statistical Review dated April 2, 2018 (Haiyan Chen, Lei Nie, and Thomas Gwise)

Final Clinical/Statistical Team Recommendations: Approval

The studies evaluated for safety include CL-106 and CL-110, with data from CL-101 as supportive data, all conducted in healthy subjects. An integrated safety analysis was performed by pooling the demographic and safety data from CL-101, CL-106 and CL-110. Safety endpoints in all three studies included adverse events (AEs), physical examinations, vital signs, 12-lead ECGs, local tolerability assessments, hematology, serum chemistry, and urinalysis. In addition, CL-110 assessed immunogenicity.

AEs overall occurred more frequently at the higher dose and with multiple doses. Leukocytosis (the most common AE reported) occurred only in multiple-dose cohorts and was of similar frequency in the Theragrastim and US-Neupogen arms. The clinical safety profile of

Theragrastim across all three studies was similar to that of US-Neupogen when administered SC at a single dose of 2.5 μg/kg and of 5 μg/kg. Overall, both Theragrastim and US-Neupogen were well tolerated in healthy adult subjects exposed to single SC doses (2.5 or 5 μg/kg) or multiple SC doses (5 μg/kg), with no differences in safety events observed. The results support the demonstration of no clinically meaningful differences between Theragrastim and US-Neupogen.

The primary endpoints in study CL-110 was difference of anti-drug antibodies (ADA) (i.e., anti-rhG-CSF) positive rates between the two groups. There was no neutralizing antibody detected. The number of patients with ADA confirmed positive is 1/67 in the Theragrastim arm and 0/67 in US-Neupogen arm. The difference in ADA rates is 1.5% between the arms and 1-sided 95% upper bound is 6.9%, which is less than the pre-specified non-inferiority margin of 10%. This study supports a conclusion of no clinically meaningful differences between Theragrastim and US-Neupogen.

Reviewer Comment: The comparative safety results obtained by pooling data from studies CL-101, CL-106, and CL-110 support a demonstration of no clinically meaningful differences between Theragrastim and US-Neupogen. Immunogenicity was similar between the two products, as evaluated in CL-110. I concur with clinical and statistical teams' conclusion that the submitted clinical studies adequately support a demonstration that there are no clinically meaningful differences in terms of safety between Theragrastim and US-Neupogen. Due to outstanding analytical similarity, manufacturing, and controls issues, however, this BLA cannot be approved.

9. Considerations for Extrapolation of Biosimilarity

Source: Clinical Review (Michael Brave)

The applicant seeks licensure for all indications for which US-Neupogen is licensed, except for the indications for mobilizing autologous hematopoietic progenitor cells into the peripheral blood for collection by leukapheresis and increasing survival in patients acutely exposed to myelosuppressive doses of radiation.

The healthy subject population in studies CL-101, CL-106, and CL-110 is an acceptable, homogenous, and sensitive population to evaluate for no clinically meaningful differences between Theragrastim and US-Neupogen. The mechanism of action of filgrastim in healthy subjects is the same as the mechanism of action for filgrastim in the conditions of use (e.g., indications) for which the applicant is seeking licensure. Furthermore, the PD endpoint in CL-106 (ANC) is sufficiently sensitive and well-correlated with the intended clinical outcome. For these reasons, the study population and primary pharmacodynamic endpoint of absolute neutrophil count used in studies CL-106 and CL-110 is acceptable to support approval of Theragrastim for the indications for which US-Neupogen has been previously approved.

The applicant has submitted the following scientific justifications for extrapolation of data and information to support licensure of Theragrastim as a biosimilar for the conditions of use for which US-Neupogen has been previously approved:

- The mechanism of action of filgrastim is the same across all indications sought as the target receptor involved is the same across indications

- Theragrastim and US-Neupogen share comparable receptor binding

- The available safety data of the reference product does not indicate that there are any significant differences in expected toxicities for each condition of use and patient population

- The dose and route of administration of Theragrastim and US-Neupogen are similar across all indications

- PK and PD results support a demonstration of no clinically meaningful differences between Theragrastim and US-Neupogen

- Immunogenicity was low and similar between Theragrastim and US-Neupogen

However, these assertions are contingent upon the demonstration that Theragrastim and US-Neupogen are highly similar to the reference product notwithstanding minor differences in clinically inactive components; as discussed elsewhere in this document, this demonstration has not been made for this application.

As described in the Guidance for Industry: "Biosimilars: Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009," a biological product must meet the statutory requirements for licensure as a biosimilar product under section 351(k) of the PHS Act based on, among other things, data derived from a clinical study or studies sufficient to demonstrate safety, purity, and potency in an appropriate condition of use, in order for that product to be licensed for one or more additional conditions of use for which the reference product is licensed. Despite the finding that there are no clinically meaningful differences, the applicant has not demonstrated that Theragrastim is highly similar to US-Neupogen with respect to analytical attributes; thus, due to analytical similarity issues and manufacturing and control deficiencies, extrapolation of indications cannot be determined at this time.

Reviewer Comment: I concur with clinical team's conclusion that the justification provided supports the extrapolation of data and information to supports licensure of Theragrastim as a biosimilar, for the conditions of use for which US-Neupogen has previously been approved and for which the applicant is seeking licensure is scientifically justified.

10. Advisory Committee Meeting

An advisory committee meeting was not held for this application.

11. Pediatrics

US-Neupogen was approved for use in pediatric patients in 1991. This approval was supported by a multi-center, randomized trial that demonstrated the efficacy and safety of filgrastim in reducing infection-related events in pediatric patients with severe idiopathic neutropenia, cyclic neutropenia, or congenital neutropenia.

On February 17, 2016, the applicant submitted an initial pediatric study plan (iPSP). On April 27,2016, the FDA Pediatric Review Committee discussed BLA 761082 and agreed with the iPSP. On May 17, 2016, the FDA provided an iPSP Written Response. On June 2, 2016, the applicant submitted an Agreed Initial Pediatric Study Plan (Agreed iPSP) for Theragrastim under PREA (IND #115333/SN0028). This Agreed iPSP argued that additional pediatric studies for Theragrastim are not needed, as the following considerations justify extrapolation of pediatric data from US-Neupogen to Theragrastim :

- Comparison of weight-normalized doses shows the PK/PD of filgrastim in pediatric patients to be indistinguishable to that observed in adult cancer patients.
- Physiochemical, analytical, and toxicokinetic data, as well as PK/PD studies in healthy adult volunteers show Theragrastim and Neupogen to be similar.
- The Applicant plans to package Theragrastim in vial and syringe presentations similar to Neupogen, allowing weight-appropriate dosing to pediatric patients.
- Acceptable efficacy and safety was demonstrated in pediatric clinical trials conducted by Amgen in Neupogen.

On June 27, 2016, DHP issued an Agreed iPSP Agreement Letter. The Applicant justified, as part of their iPSP, that adequate pediatric assessments for the conditions of use for which the Applicant is seeking are available in reference product labeling to support biosimilar extrapolation. The applicant may satisfy PREA requirements for the proposed indications by satisfying the statutory requirements for showing biosimilarity and providing an adequate scientific justification under the BPCIA Act for extrapolating the pediatric information from the reference product to the proposed biosimilar product. Thus, no new pediatric clinical studies would be necessary.

12. Other Relevant Regulatory Issues

Application Integrity Policy (AIP)
The application contained statements from Adello Biologics that they certified that they did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.

Exclusivity or patent Issues

Not applicable.

Financial disclosures

The applicant certifies that:

- It did not enter into any financial arrangement with clinical investigators whereby the value of compensation to the investigator could be affected by the outcome of the study, as defined in 21CFR 54.2(a).

- Each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21CFR 54.2(b) did not disclose any such interests.

- No listed investigator was the recipient of significant payments or other sorts as defined in 21 CFR 54.2(f).

Bioequivalence Inspections

The Office of Study Integrity and Surveillance (OSIS) conducted an inspection of the analytical portion of in Studies CL-106 and CL-110 conducted at (b) (4) from (b) (4). Some objectionable conditions were observed during the inspection, and Form FDA 483 was issued. The final inspection classification is Voluntary Action Indicated (VAI). After reviewing the inspectional findings and the firm's response to Form FDA 483, the objectionable conditions did not impact the reliability of the data from the audited studies. Therefore, OSIS recommend that the data from CL-106 and CL-110 be accepted for further Agency review.

OSIS conducted an inspection of Study CL-106 conducted at (b) (4) from (b) (4) Form FDA 483 was issued at the inspection close-out. The final inspection classification is VAI. After reviewing the inspectional findings and the firm's response to Form FDA 483, there was evidence that the objectionable conditions impacted the reliability of the anti-GCSF antibody confirmatory assay data for CL-106. The impact on the PK data for CL-106 is pending the firm's report amendment. However, the objectionable conditions did not impact the reliability of all the inspected studies conducted at the site and the overall performance of the site. OSIS recommended that the anti-GCSF antibody data from the confirmatory assays in study CL-106 not be accepted for Agency review, and that acceptance of PK data from study CL-106 be dependent on the firm's validation report amendment, expected Feb. 28, 2018. However, the ADA data from study CL-106, a single-dose cross-over study, were not meaningful and therefore not incorporated into the review of this product, and did not affect the evaluation of immunogenicity; study CL-110 was designed to evaluate immunogenicity and the data from that study were considered adequate and reliable.

Clinical Inspections

On July 7, 2017, the Division of Hematology Products, OHOP/CDER, submitted to CDER's Office of Study Integrity and Surveillance (OSIS) a request for inspection of the clinical and

bioanalytical sites for studies CL-106 and CL-110. On October 11, 2017, OSIS recommended accepting data without an on-site inspection. The rationale for this recommendation was that OSIS recently inspected both these sites, and the outcome from the inspections was classified as No Action Indicated (NAI).

Other Discipline Consultations

Nicole Garrison and Hina Mehta, from the Office of Medication Error Prevention and Risk Management (OMEPRM) completed a review dated September 19, 2018, that concluded that the proposed proprietary name, Releuko, is conditionally accepted until such time that the application is approved.

Tingting Gao and Lubna Merchant from OMEPRM completed a review dated January 30, 2018 that determined that the 4-letter suffix "-ayow" for the proper name, filgrastim-ayow, is conditionally accepted until such time that the application is approved.

On August 3, 2017, The CDER Exclusivity Board determined that there is no unexpired reference product exclusivity under section 351(k)(7) of the Public Health Service (PHS) Act for US-Neupogen (filgrastim) (BLA 103353; Amgen) that would prohibit the submission, or approval, of any 351(k) application under this statutory provision for a proposed biosimilar (or interchangeable) product to US-Neupogen (filgrastim).

Pediatric and Maternal Health

Theragrastim labeling incorporates information regarding use in pregnancy and lactation. No additional studies have been performed in these populations and submitted to this BLA. Labeling also contains information regarding pediatric use for dosage as well as safety and effectiveness. No additional pediatric studies have been performed for this BLA.

13. Labeling

Proposed labeling submitted by the applicant was generally consistent with recommendations contained within FDA's draft Guidance for Industry "Labeling for Biosimilar Products" which recommends that the biosimilar product labeling incorporate relevant data and information from the reference product labeling, with appropriate product specific modifications. Some information in the labeling was revised to reflect Theragrastim-specific information as well as to comply with current labeling practices. The review teams reserve final comment on the proposed labeling, container labels, and carton labeling until the application is otherwise adequate.

14. Recommendations/Risk Benefit Assessment

Recommended Regulatory Action

The applicant is seeking licensure for indications that are the same as those licensed for US-Neupogen pertaining to stimulation of proliferation of peripheral blood neutrophils, but not those for hematopoietic progenitor cell mobilization or increasing survival after radiation exposure. The data submitted to the BLA from the clinical development program of Theragrastim support a demonstration of no clinically meaningful differences between Theragrastim and US-Neupogen in terms of safety, purity, and potency. However, the applicant has not adequately demonstrated that Theragrastim is highly similar to US-Neupogen based on evaluation of the submitted analytical data. Thus, we cannot conclude that the totality of the evidence supports a demonstration of biosimilarity of Theragrastim to US-Neupogen.

Because of the drug substance manufacturing facility inspection classification (i.e., withhold) as well as the product quality and analytical similarity deficiencies identified by OPQ, as summarized in section 3 of this review, the 351(k) BLA 761082 for Theragrastim is not recommended for approval. Specifically, the data submitted in this application were not found to be sufficient to support a conclusion that the manufacture of Theragrastim is well controlled and will lead to a product that is safe, pure, and potent for the duration of the shelf-life, and that the products are highly similar.

Risk Benefit Assessment

Section 351(i) of the PHS Act defines the terms "biosimilar" or "biosimilarity" to mean that "the biological product is highly similar to the reference product notwithstanding minor differences in clinically inactive components" and that "there are no clinically meaningful differences between the biological product and the reference product in terms of the safety, purity, and potency of the product." Both parts of the statutory definition must be met to establish biosimilarity, but the foundation of the data demonstrating biosimilarity is extensive structural and functional characterization to support a demonstration that the products are highly similar.

As explained above, the data submitted to the 351(k) BLA do not support licensure of Theragrastim as biosimilar to US-Neupogen under section 351(k) of the PHS Act. Accordingly, Theragrastim cannot be considered to have a favorable risk-benefit profile for all requested conditions of use. Additionally, because of the inspectional outstanding issues and product quality deficiencies identified by OPQ, as summarized in section 3 of this review, this application is not recommended for approval.

Recommendation for Postmarketing Risk Evaluation and Management Strategies

None.

Recommendation for other Postmarketing Requirements and Commitments

None.

Recommended Comments to Applicant

See Complete Response letter.

Recommended Regulatory Action

Complete Response.

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

/s/

SANJEEVE BALASUBRAMANIAM
05/09/2018