Collaborative Clinical, Clinical Pharmacology, CDTL, and Division Director Summary Review

Date	See electronic stamp date
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Subject	Collaborative Clinical, Cross-Discipline Team Leader, and Division Summary Review
BLA # and Supplement #	761082 S-014 (Category D supplement)
Applicant	Kashiv BioSciences, LLC
Date of Submission	October 29, 2024
BsUFA Goal Date	April 29, 2025
Proprietary Name (Proper Name)	Releuko (filgrastim-ayow)
Product Name (Code)	Theragrastim
Reference Product Proprietary (Proper Name)	Neupogen (filgrastim)
Dosage Form(s) / Strength	No new proposed dosage forms or strengths
Applicant Proposed Indication(s) / Population(s)	Expansion of existing indications to include the following: • 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)
Applicant Proposed Dosing Regimen(S)	Same as reference product dosing regimen
Recommendation on Regulatory Action	Approval

1. Introduction

Kashiv BioSciences, LLC (hereafter referred to as "the Applicant"), submitted a supplemental biologics license application for BLA 761082 (sBLA-014) under section 351(k) of the Public Health Service (PHS) Act to expand the indications for Releuko (proper name: filgrastim-ayow, product name/code: Theragrastim) to include the following additional indications: mobilize autologous hematopoietic progenitor cells (MAHPC) into the peripheral blood for collection by leukapheresis and increase survival in patients acutely exposed to myelosuppressive doses of radiation (Hematopoietic Syndrome of Acute Radiation Syndrome (H-ARS)). The Applicant did not seek licensure for the MAHPC and H-ARS indications in their original BLA submission for Releuko because additional clinical CD34+ cell evaluations were required at that time if they were to seek the MAHPC indication, and the H-ARS indication was protected under orphan drug exclusivity which expired on March 30, 2022.

No new scientific or clinical data were included in this submission. The Applicant cross-referenced the data and information supporting licensure of Releuko under BLA 761082 and provided the supporting scientific justification for extrapolation for the MAHPC and H-ARS indications currently sought for licensure and a pediatric assessment to address PREA requirements. The current submission provided updated labeling to include the MAHPC and H-ARS indications.

2. Background

On February 25, 2022, Releuko (non-proprietary name: filgrastim-ayow, product name: Theragrastim) was approved as biosimilar to US-licensed Neupogen (US-Neupogen) under Section 351(k) of the Public Health Service Act. Releuko (filgrastim-ayow) is a 175 amino acid human granulocyte colony-stimulating factor (G-CSF) manufactured by recombinant DNA technology and approved for the following indications that are the same as US-Neupogen:

- 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

Additionally, US-Neupogen is licensed for the following indications:

- 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)

The original approval of the BLA for Releuko included the following data and information to support approval of Releuko as a biosimilar to US-Neupogen for the above listed indications:

- A comprehensive comparative analytical assessment that compared Theragrastim to US-Neupogen.

- A pharmacokinetic (PK)/pharmacodynamic (PD) similarity study (CL-106) and an immunogenicity study (CL-110) conducted in healthy subjects comparing Theragrastim and US-Neupogen. Study CL-106 evaluated PK (AUC and Cmax) and PD (absolute neutrophil count (ANC)) similarity following a single subcutaneous dose. The incidence of anti-drug antibodies was compared in study CL-110.

- A scientific justification (based on mechanism of action, PK, immunogenicity and toxicity) for extrapolation of data and information submitted in the application to support the licensure of Theragrastim for each of the indications for which the Applicant was seeking licensure and for which US-Neupogen has been previously approved.

In considering the totality of the evidence for the assessment of biosimilarity and the original BLA submission, review of the data submitted by the Applicant showed that filgrastim-ayow is highly similar to US-Neupogen, notwithstanding minor differences in clinically inactive components, and that there are no clinically meaningful differences between filgrastim-ayow and US-Neupogen in terms of the safety, purity, and potency of the product. The Applicant also provided adequate scientific justification for extrapolation of data and information to support licensure of filgrastim-ayow for the non-studied indications sought for approval.

Releuko (filgrastim-ayow) is approved for the same strengths, dosage form, and routes of administration as those approved for US-Neupogen:

For Subcutaneous (SC) and Intravenous (IV) Use:

- Injection: 300 mcg/mL in a single-dose vial
- Injection: 480 mcg/1.6 mL (300mcg/mL) in a single dose vial

For SC Use:

- Injection: 300 mcg/0.5 mL in a single-dose prefilled syringe
- Injection: 480 mcg/0.8 mL in a single dose prefilled syringe

Additionally, the condition(s) of use for which Releuko is licensed have been previously approved for US-Neupogen.

In this sBLA, the Applicant is seeking licensure for the MAHPC and H-ARS indications. The proposed dosing regimen for MAHPC and H-ARS is same as the reference product, US-Neupogen.

Prior to review of this sBLA, when Applicants sought approval for the MAHPC indication, FDA expected a second PD similarity study, namely a multiple-dose study in healthy subjects to evaluate CD34+ cell counts, in addition to the single dose PD and PK similarity study measuring ANC. The expectation, at that time, for this additional PD data was premised on the concern that ANC is not considered a reliable biomarker to predict CD34+ cell counts prior to leukophoresis in the clinical setting, and therefore a second PD study measuring CD34+ cell counts after multiple doses was recommended to provide additional assurance needed to license a filgrastim biosimilar for MAHPC. In this sBLA, however, the Applicant did not submit data from a multiple dose clinical PD similarity study evaluating CD34+ cell counts following Releuko treatment. Instead, the Applicant cross-referenced the data and information submitted in the original BLA supporting licensure of Releuko and provided a scientific justification for extrapolation in support of licensure of filgrastim-ayow for the MAHPC indication.

During the review of this supplement, the Clinical and Clinical Pharmacology review teams determined that the CD34+ cell count data were not needed to support licensure of Releuko for the MAHPC indication. The rationale for this decision is summarized as follows and is based on FDA's experience with filgrastim products and its review of this supplemental application and publicly available data and studies:

- Filgrastim and biosimilar filgrastim products are small, non-glycosylated, highly purified proteins that are produced in *E. coli* using recombinant DNA technology and can be well-characterized by current analytical technology. The product quality attributes evaluated as part of the comparative analytical assessment used to support a demonstration of biosimilarity include a comprehensive battery of tests that structurally characterize the protein and model in vivo functional effects with a high degree of specificity and sensitivity using in vitro biological and biochemical assays.

- The relationship between quality attributes and clinical efficacy is well understood for filgrastim and these attributes can be evaluated by assays included in the comparative analytical assessment. Filgrastim is an N-methionyl analog of granulocyte colony stimulating factor (G-CSF) which is a hematopoietic growth factor that induces proliferation and differentiation of neutrophil committed progenitor cells into neutrophils. Filgrastim also induces the release of CD34+ hematopoietic progenitor cells from the marrow into the peripheral blood. The mechanism of action of filgrastim in neutropenia and mobilization of hematopoietic stem cells are both directly related to the biological function of G-CSF. Endogenous G-CSF acts on hematopoietic cells by binding to its cognate cell surface receptors and stimulating proliferation, differentiation commitment, and selected end-cell functions. The binding of G-CSF to the G-CSF receptor on myeloid progenitor cells and mature neutrophils initiates transduction signals that lead to the proliferation and differentiation of neutrophil committed progenitor cells, increase of mature neutrophils (ANC as a marker) in the blood and enhanced neutrophil function. These functions are all relevant to the neutropenia indications[1]. The G-CSF receptor also plays critical role in the mobilization of hematopoietic stem cells (HSC). Mobilization of hematopoietic stem cells is initiated by binding of G-CSF to the G-CSF receptor on monocytic cells in the bone marrow. This leads to changes in cells of the osteoblast lineage which results in the disruption of key interactions that regulate HSC.

[1] Panopoulus, A.D. and Watowich, S.S. (2008). Granulocyte colony-stimulating factor: Molecular mechanisms of action during steady state and 'emergency' hematopoiesis. Cytokine 42: 277-288.

The absence of key interactions between cells of the osteoblast lineage and HSC result in mobilization of HSC into the blood stream[2].

- A comparison of clinical PK parameters is relevant to the assessment of whether there are clinically meaningful differences in systemic exposure for filgrastim products. A single-dose, randomized, cross-over study in healthy subjects is generally the preferred design for measuring the PK of filgrastim products. The rapid increase in ANC can be observed following a single-dose and has been recommended as a co-primary endpoint for the study to assess a relevant PD endpoint for proposed filgrastim biosimilars.

The Agency has gained significant experience in evaluating analytical differences between proposed biosimilars products and their reference products and understanding their impact on clinical performance, since the first biosimilar was approved by FDA ten years ago in 2015 (Zarxio; filgrastim-sdnz). [3,4,5,6] There is now growing recognition that clinical efficacy endpoint(s) are not sensitive to the types and small degree of differences observed in comparative analytical assessments (CAA), due to insensitivity of endpoints and dosing regimens in the therapeutic plateau.[7,8] Similarly, and for the reasons discussed herein, additional clinical CD34+ similarity data from a multiple-dose study are also considered to lack the sensitivity to detect differences that would otherwise be observed in the comparative analytical assessment, and potentially from the comparative PK/ PD study measuring ANC. Therefore, we have determined an additional PD similarity study evaluating CD34+ cell counts is unnecessary to support a decision to approve Releuko for the MAHPC indication.

3. CMC/Product Quality

For sBLA-014, no new product quality information was submitted nor required. There are no CMC or product quality issues that would preclude approval of the indication sought for licensure.

4. Nonclinical Pharmacology/Toxicology

No new nonclinical pharmacology/toxicology information was submitted nor required for this supplemental BLA.

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[2] Greenbaum AM and Link DC (2011). Mechanisms of G-CSF-mediated hematopoietic stem and progenitor mobilization. Leukemia, 25: 211-217.

[3] FDA Biosimilar Action Plan (July 2018; updated April 2024) https://www.fda.gov/drugs/biosimilars/biosimilars-action-plan

[4] FDA Revised BsUFA III Research Roadmap (January 2024) https://www.fda.gov/drugs/biosimilars/biosimilars-science-and-research

[5] FDA and International Pharmaceutical Regulators Program Biosimilar Working Group workshop "Increasing the Efficiency of Biosimilar Development Programs - Reevaluating the Need for Comparative Clinical Efficacy Studies" (September 2023) https://www.fda.gov/drugs/news-events-human-drugs/increasing-efficiency-biosimilar-development-programs-reevaluating-need-comparative-clinical

[6] EMA Concept paper for the development of a reflection paper on a tailored clinical approach in biosimilar development (January 2024) https://www.ema.europa.eu/en/human-regulatory-overview/research-and-development/scientific-guidelines/multidisciplinary-guidelines/multidisciplinary-biosimilar/concept-paper-development-reflection-paper-tailored-clinical-approach-biosimilar-development

[7] Patrizia Cavazzoni & Sarah Yim, *The Science of Biosimilars – Updating Interchangeability,* JAMA (2024). https://jamanetwork.com/journals/jama/fullarticle/2823807

[8] Nadine Kirsch-Stefan et al. Do the Outcomes of Clinical Efficacy Trials Matter in Regulatory Decision-Making for Biosimilars? (2023). https://pubmed.ncbi.nlm.nih.gov/37831324/

5. Clinical Pharmacology

No new clinical pharmacology data were submitted, and FDA determined that no new clinical pharmacology data are required for this sBLA. Although an additional clinical PD study for CD34+ cell evaluations was expected to support licensure for the MAHPC indication in the past, the Office of Clinical Pharmacology (OCP), in consultation with the Division of Nonmalignant Hematology (DNH) and OTBB, have determined that additional CD34+ cell data are not necessary to support licensure of the MAPHC indication for Releuko. See the rationale described in Section 2 of this CDTL memo. There are no clinical pharmacology issues that would preclude approval of the H-ARS and MAPHC indications sought for licensure.

6. Clinical/Statistical-Efficacy

No new clinical/statistical efficacy information was submitted, and FDA determined that no new clinical/statistical efficacy information are required for this sBLA. Although an additional clinical PD study for CD34+ cell evaluations was expected to support licensure for the MAHPC indication in the past, the DNH, in consultation with OCP and OTBB, have determined that additional CD34+ cell data are not necessary to support licensure for the MAPHC indication for Releuko. See the rationale described in Section 2 of this CDTL memo. There are no clinical/statistical efficacy issues that would preclude approval of the H-ARS and MAPHC the indications sought for licensure.

7. Safety

There are no clinical safety issues that would preclude approval of the indications sought for licensure.

8. Extrapolation

In this supplement, the Applicant referenced the original BLA application and provided a scientific justification to support extrapolation of the data and information to support licensure of Releuko to mobilize autologous hematopoietic progenitor cells into the peripheral blood for collection by leukapheresis (MAHPC) and increase survival in patients acutely exposed to myelosuppressive doses of radiation (Hematopoietic Syndrome of Acute Radiation Syndrome (H-ARS).

Scientific considerations for the extrapolation of data and information to support licensure for the MAHPC and H-ARS indications are outlined below:

- Releuko has previously been established as biosimilar to US-Neupogen. The data and information supporting its approval included comparative analytical characterization and clinical studies comparing PK, PD (ANC), and immunogenicity between Releuko and US-Neupogen.
- In Supplement 014, the Applicant cross-referenced the data and information supporting licensure of Releuko provided in the original application. The Applicant also provided an additional scientific justification in this sBLA submission supporting the extrapolation of data and information to address the mechanism of action, PK, immunogenicity, and safety for the proposed MAPHC and H-ARS indications for which the applicant is seeking licensure and for which US-Neupogen has been approved.

- The mechanism of action, relevant to decreasing 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 (the studied population) is also relevant to MAHPC and H-ARS.
- PK similarity was demonstrated between Releuko and US-Neupogen. There were no product-related attributes that would increase uncertainty that the PK/biodistribution may differ between Releuko and US-Neupogen in the MAPHC and H-ARS indications. A similar PK profile would be expected between Releuko and US-Neupogen in patients being treated for MAPHC and H-ARS.
- Immunogenicity and safety profiles were shown to be similar in Releuko and US-Neupogen. Similar immunogenicity and safety profiles would be expected between Releuko and US-Neupogen in patients being treated for MAPHC and H-ARS indications.

In conclusion, the totality of evidence and scientific justification discussed above are adequate to justify extrapolating data and information submitted to support licensure of Releuko for the following two indications: to mobilize autologous hematopoietic progenitor cells into the peripheral blood for collection by leukapheresis (MAHPC), and to increase survival in patients acutely exposed to myelosuppressive doses of radiation (Hematopoietic Syndrome of Acute Radiation Syndrome (H-ARS)).

9. Pediatrics

Under the Pediatric Research Equity Act (PREA) (section 505B of the FD&C Act), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain a pediatric assessment to support dosing, safety, and effectiveness of the product for the claimed indication unless this requirement is waived, deferred, or inapplicable. Section 505B(l) of the FD&C Act provides that a biosimilar product that has not been determined to be interchangeable with the reference product is considered to have a “new active ingredient” for purposes of PREA, and a pediatric assessment is generally required unless waived or deferred or inapplicable.

To address the PREA requirement for the indications of MAHPC and H-ARS, the Applicant submitted an amended agreed pediatric study plan (PSP) with a scientific justification for extrapolation that included pediatric patients for the MAHPC and H-ARS indications. The Applicant proposed to fulfil the PREA requirements for pediatric patients for the MAHPC and H-ARS indications by satisfying the statutory requirements for demonstrating biosimilarity and providing an adequate scientific justification for extrapolating the pediatric information from US-Neupogen to Releuko. On March 18, 2025, The Pediatric Review Committee (PeRC) agreed with the Applicant’s approach for the MAHPC and H-ARS indications.

The Applicant addressed PREA for the currently approved indications during the original review of the BLA. See the CDTL memo dated May 9, 2018. The Applicant has fully addressed PREA for the MAHPC and H-ARS indications, and there are no additional PREA requirements for this supplemental BLA.

10. Other Relevant Regulatory Issues

None

11. Labeling

Prescribing Information

It was determined that the proposed labeling is compliant with Physician Labeling Rule (PLR) and pregnancy and Lactation Labeling Rule (PLLR) and is consistent with the labeling guidance recommendation, and conveys the essential scientific information needed for safe and effective use of the product.

In this application the proposed Releuko prescribing information incorporated relevant data and information from the US-Neupogen prescribing information, with updates to include indications of MAHPC and H-ARS.

Labeling consultants, including Office of Therapeutic Biologics and Biosimilar (OTBB)-labeling, Office of Biotechnology Products (OBP)-labeling, and the Office of Prescription Drug Promotion (OPDP) reviewed the proposed labeling. The final label will be included in the approval letter.

12. Post-Marketing Recommendation

None.

13. Risk Evaluation and Mitigation Strategies

None.

14. Regulatory Action

Approval.

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/s/

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