Collaborative Clinical, Cross-Discipline Team Leader, and Division Summary Memo of BLA 761084/S-007

Date	See Electronic Stamp Date
From	Juwaria Waheed, MD, Clinical Reviewer (OTBB) Michelle Luo, MD, Ph.D, CTL/CDTL (OTBB) Libero (Louis) Marzella, MD, PhD, Division Director (DIRM)
Subject	Collaborative Clinical, Cross-Discipline Team Leader, and Division Summary Review
BLA # and Supplement#	761084/S-007 (351 (k) Category D supplement)
Applicant	Kashiv Biosciences, LLC
Date of Submission	October 29, 2024
BSUFA Goal Date	April 29, 2025
Product Code Name	TPI-120
Nonproprietary name	pegfilgrastim-pbbk
Proprietary Name	Fylnetra
Reference Product	Neulasta (pegfilgrastim)
Applicant Proposed Indication(s)/Population(s)	To increase survival in patients acutely exposed to myelosuppressive doses of radiation (Hematopoietic Subsyndrome of Acute Radiation Syndrome)
Applicant Proposed Dosing Regimen(s)	Same as Neulasta for the respective indication
Recommendation on Regulatory Action	Approval

1. Introduction

Kashiv Biosciences (hereafter referred to as “the Applicant”) submitted this supplement 007 for BLA 761084 to expand the indication of Fylnetra (pegfilgrastim-pbbk) to increase survival in patients acutely exposed to myelosuppressive doses of radiation (Hematopoietic Subsyndrome of Acute Radiation ((H-ARS)). The H-ARS indication was previously protected under orphan drug exclusivity. US-Neulasta’s H-ARS orphan drug exclusivity expired on November 13, 2022.

No new clinical information is included nor required for the Applicant’s submission. The Applicant revised the Agreed initial Pediatric Study Plan (iPSP) with this supplement including the pediatric assessment to address PREA requirement for the new indication. The Applicant has provided a scientific justification for extrapolation to H-ARS indication and updated labeling to include the additional indication sought for licensure.

2. Background

Fylnetra is a leukocyte growth factor. On August 11, 2020, Kashiv submitted BLA 761084 under section 351(k) of the Public Health Service Act for TPI-120 as a proposed biosimilar product to US-licensed Neulasta (Amgen Inc). A complete response letter (CRL) for

product quality, microbiology, and device deficiencies was issued on August 11, 2021. The Applicant resubmitted the application on November 29, 2021, addressing the deficiencies noted in the CRL.

- Fylnetra was approved as a biosimilar to US-Neulasta on May 26, 2022, under section 351(k) of the Public Health Service Act. Fylnetra is currently 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 febrile neutropenia.

Additionally, US-Neulasta is licensed for the following:

- to increase survival in patients acutely exposed to myelosuppressive doses of radiation (Hematopoietic Subsyndrome of Acute Radiation Syndrome)

In considering the totality of the evidence for the original BLA submission, review of the data submitted by the Applicant showed that Fylnetra is highly similar to US-Neulasta, notwithstanding minor differences in clinically inactive components, and that there are no clinically meaningful differences between Fylnetra and US-Neulasta 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 Fylnetra for the non-studied indications sought for approval.

In this Cat D BLA supplement, the Applicant has submitted justification for extrapolation of the data and information in support of licensure of Fylnetra for H-ARS indication. The proposed dosing regimen for H-ARS is same as the reference product, US-Neulasta.

Fylnetra is approved for the same strength, dosage form, and route of administration as those approved for US-Neulasta:

- Injection: 6 mg/0.6 mL in a single-dose prefilled syringe for manual use only

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

3. CMC/Product Quality

No new product quality information was submitted nor required for this BLA supplement (sBLA). There are no CMC or product quality issues that would preclude approval of the indications sought for licensure.

4. Nonclinical Pharmacology/Toxicology

No new nonclinical pharmacology/toxicology information was submitted nor

required for this sBLA. There are no nonclinical pharmacology/toxicology issues that would preclude approval of the indications sought for licensure.

5. Clinical Pharmacology

No new clinical pharmacology information was submitted nor required for this sBLA. There are no clinical pharmacology issues that would preclude approval of the indications sought for licensure.

6. Clinical/Statistical-Efficacy

Fylnetra was previously evaluated in a single-dose PK/PD similarity study (TPI-CL-109-A) in healthy subjects and a repeat-dose comparative immunogenicity and safety study (ADL-CL-112) in healthy subjects. The data were previously reviewed and summarized in the clinical and statistical reviews in the Biosimilar Multidisciplinary Evaluation and Review (BMER) for the original BLA, dated April 25, 2022 in DARRTS. No new clinical/statistical efficacy information was submitted nor required for the current sBLA. There are no clinical/statistical efficacy issues that would preclude approval of the indication sought for licensure.

7. Safety

The safety of Fylnetra was evaluated in two studies conducted in healthy subjects, Studies TPI-CL-109-A and ADL-CL-112. The overall safety profile of TPI-120 was similar to US-Neulasta. The data were previously reviewed and summarized in the BMER for the original BLA review dated April 25, 2022 in DARRTS. No new safety data were submitted nor required for this sBLA. There are no clinical safety issues that would preclude approval of the indication sought for licensure.

8. Considerations for Extrapolation of Biosimilarity in Other Conditions of Use

Fylnetra is a leukocyte growth factor licensed 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 febrile neutropenia. In this supplement, the applicant referenced the original BLA application and submitted a scientific justification for extrapolation of the data and information to support licensure of Fylnetra for the non-studied indication of H-ARS (Increase survival in patients acutely exposed to myelosuppressive doses of radiation). (Also, see Section 9 Pediatrics).

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

- Biosimilarity has previously been established between Fylnetra and US-Neulasta. The data supporting its approval included comparative analytical characterization data, and comparative PK, safety, and immunogenicity data demonstrating that Fylnetra is biosimilar to the reference product, US-Neulasta.

- In Supplement 7, in their response to an Information Request (BLA 761084, SDN 127 *Clinical Overview* dated December 20, 2024), the Applicant has provided adequate scientific justification supporting extrapolation of data and information from the original BLA submission that addresses the mechanism of action, PK, immunogenicity, and safety for each non-studied indication for which the applicant is seeking licensure and for which the reference product has been approved.

- The mechanism of action - the binding to specific cell surface receptors resulting in stimulating proliferation, differentiation, and commitment of end cell functional activation is the same in Fylnetra and US-Neulasta for all indications currently approved for US-Neulasta to the extent that the mechanisms of action are known or can reasonably be determined.

- PK similarity was demonstrated between Fylnetra and US-Neulasta. There were no product-related attributes that would increase uncertainty that the PK/biodistribution may differ between Fylnetra and US-Neulasta in the H-ARS indication. A similar PK profile would be expected between Fylnetra and US-Neulasta in patients being treated for H-ARS.

- Immunogenicity and safety profiles were shown to be similar in Fylnetra and US-Neulasta. Similar immunogenicity and safety profiles would be expected between Fylnetra and US-Neulasta in patients being treated for the H-ARS indication.

In conclusion, the totality of evidence and scientific justification discussed above are adequate to justify extrapolating data and information submitted to this sBLA to support licensure of Fylnetra for the H-ARS indication to increase survival in patients acutely exposed to myelosuppressive doses of radiation.

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.

An Agreed Initial Pediatric Study Plan (iPSP) was issued on September 1, 2017.

During the review cycle for this supplement (S-007), an Information Request (IR) was issued asking the Applicant to revise the iPSP to address the PREA requirements for the H-ARS indication. The Applicant responded with a revised iPSP on December 20, 2024. To fulfill the PREA requirement for the pediatric patients for the H-ARS indication, the Applicant provided an adequate scientific justification to support extrapolation of the pediatric data and information from the reference product US-Neulasta to the biosimilar product Fylnetra based on the demonstration of biosimilarity between US-Neulasta and Fylnetra.

Since the issuance of the Agreed iPSP for Fylnetra, the reference product, US-Neulasta received a PREA Postmarketing Requirement (PMR) to develop a pediatric formulation for pediatric patients who weigh less than 45 kg and require doses that are less than 0.6 mL (6 mg).Because a PREA PMR is required for the biosimilar product to US-Neulasta, a PREA PMR was issued on May 26, 2022 for Fylnetra, to develop a pediatric formulation as noted below:

4277-1: Develop an appropriate formulation (presentation) that can be used to directly and accurately administer Fylnetra (pegfilgrastim-pbbk) to pediatric patients who weigh less than 45 kg and require doses that are less than 0.6 mL (6 mg) and conduct any necessary human factors studies to evaluate the ability of healthcare providers and/or caregivers to measure the appropriate doses.

The Applicant requested a deferral extension of the required pediatric assessment for developing a pediatric formulation to accurately administer Fylnetra to pediatric patients who weigh less than 45 kg and require doses that are less than 0.6 mL (6 mg) until the required study for US-Neulasta is completed. On September 18, 2024, the Agency agreed to a deferral extension for this PMR until 04/2028 because the completion date for the pediatric presentation development for the reference product US-Neulasta has been extended to April 30, 2025.

On March 18, 2025, the Pediatric Review Committee (PeRC) reviewed the Applicant’s proposal for PREA assessment for the H-ARS indication and the timeline of the PREA PMR for the pediatric dosing and agreed with the Division’s recommendations.

The Applicant addressed PREA for the currently approved indications during the original review of the BLA. See the BMER dated April 25, 2022.

10. Other Relevant Regulatory Issues

None

11. Labeling

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. The proposed Fylnetra prescribing information incorporated relevant data and information from the US-Neulasta prescribing information, with appropriate modifications.

12. Postmarketing Recommendations

There are no new safety or efficacy issues identified in this review that warrant further assessment with a postmarketing requirement or commitment.

13. Risk Evaluation and Mitigation Strategies

The review team did not identify a need for Risk Evaluation and Mitigation Strategies (REMS) to ensure the safe use of Fylnetra.

14. Recommended Regulatory Action

Approval

15. Division Director Comments

I concur with the team's assessment of the data and information submitted in this supplemental BLA.

No additional data, new PMRs, PMCs, or REMS are required for this supplement.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

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