Collaborative Clinical, Cross-Discipline Team Leader, and Division Summary Review

Date	See electronic stamp date
From	N Calvin Han, MD, Clinical Reviewer Louis Marzella, MD, PhD, Division Director
Subject	Collaborative Clinical, Cross-Discipline Team Leader, and Division Summary Review
BLA and Supplement Numbers	761173 / S-002
Applicant	Fresenius Kabi USA, LLC
Date of Submission	July 26, 2023
BsUFA Goal Date	September 30, 2023
Proprietary Name (Proper Name)	Stimufend (pegfilgrastim-fpgk)
Product Code Name	MSB11455
Reference Product Proprietary (Proper Name)	Neulasta (pegfilgrastim)
Dosage Form / Strength	Injection: 6 mg/0.6 mL solution in a single-dose pre-filled syringe for manual use
Applicant Proposed Indication/ Population	To increase survival in patients acutely exposed to myelosuppressive doses of radiation.
Applicant Proposed Dosing Regimen	• Two doses, 6 mg each, administered subcutaneously one week apart. Administer the first dose as soon as possible after suspected or confirmed exposure to myelosuppressive doses of radiation, and a second dose one week after. • Use weight based dosing for pediatric patients weighing less than 45 kg
Regulatory Action	Approval

Introduction

On March 27, 2020 Fresenius Kabi USA submitted a BLA for MSB11455 as a proposed biosimilar to Neulasta (pegfilgrastim) (BLA125031) for the same indications as the reference product. The Company did not seek indication of Hematopoietic Syndrome of Acute Radiation Syndrome at that time because of Orphan Drug Exclusivity until 13 November 2022. On September 1, 2022 under authority granted under section 351(k) of the Public Health Service Act, FDA approved STIMUFEND (pegfilgrastim-fpgk) as a biosimilar to U.S.-licensed Neulasta (US-Neulasta) for all indications for which US-Neulasta was then approved, except for treatment of the hematopoietic acute radiation syndrome (H-ARS). For FDA's finding of biosimilarity between STIMUFEND and US-Neulasta in patients with non- myeloid malignancies receiving myelosuppressive anti-cancer drugs – including review of product quality and mechanistic nonclinical studies and clinical pharmacology pharmacokinetic (PK), pharmacodynamic (PD), and antidrug antibody (ADA) bioequivalence (BE) studies in healthy subjects – see complete disciplinary reviews filed internally and/or publicly available at Drugs@FDA for BLA 761173.[i] For additional information on exclusivity, see FDA's "Orphan Drug Designations and Approvals" database.[2]

The sponsor submitted an application on March 31, 2023, Category D supplement for additional indication, increase survival in patients acutely exposed to myelosuppressive doses of radiation. The application was filed on May 31, 2023 and the BsUFA goal date of September 30, 2023.

Information for review was submitted to Supplement 2 of the BLA[ii] with no new scientific information summarizing previously submitted and reviewed safety reporting, as well as justification for extrapolation of prior FDA findings to patients with suspected or confirmed exposure to myelosuppressive doses of radiation. No new study or safety data was collected, needed, or submitted for review, nor was any relied upon for the proposed labeling expansion.

Safety

The Applicant's Position Excerpted from the Application:

Post-Marketing Data

MSB11455 is marketed in the United States as STIMUFEND a 6 mg/0.6 mL solution in a single-dose pre-filled syringe for manual use only. The STIMUFEND BLA 761173 was approved on September 1, 2022. Fresenius Kabi USA gained concurrence from the FDA on the schedule of submission for the Periodic Adverse Experience Report (PAER) and Periodic Benefit Risk Evaluation Report (PBRER).

Safety Conclusions

The safety profile of MSB11455 was inferred from 2 studies (EMR200621-001 and EMR2090621-003) conducted in healthy subjects and is consistent with the safety profile of Neulasta. No new safety signals were identified during the clinical development of MSB11455. The incidence of treatment-emergent adverse events (TEAEs) classified as serious adverse events (SAEs), adverse events (AEs) leading to discontinuation, adverse event of special interest (AESIs), or TEAEs with a severity Grade ≥ 3 were similar between MSB11455 and US-Neulasta.

The FDA's Assessment

Clinical review of the Applicant's post-market reporting and the internal review record identified no STIMUFEND safety signals not already addressed in prescribing information, postmarket surveillance, and post-market studies.

Extrapolation

The Applicant's Position Excerpted from the Application:

MSB11455 (STIMUFEND®) [pegfilgrastim-fpgk) a US-Neulasta (pegfilgrastim) biosimilar is licensed in the United States to decrease the incidence of infection, as manifested by febrile neutropenia, in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs. Similarity between MSB11455 and the reference product, US-Neulasta, was established based on data derived from:

- *Primary (i.e., same amino acid sequence and disulfide bonding), secondary and tertiary structures (e.g., α helix, β-sheet, and overall 3-dimensional structure)*
- *Structural and functional characteristics*
- *Nonclinical in vitro pharmacology and in vivo PK*
- *PK, PD, immunogenicity, and safety*

Currently, US-Neulasta is also approved to increase survival in patients acutely exposed to myelosuppressive doses of radiation. The US-Neulasta FDA approval for this indication was based on efficacy studies conducted in animals with support from data on US-Neulasta's effect on severe neutropenia in patients with cancer receiving myelosuppressive chemotherapy. Efficacy studies of US-Neulasta could not be conducted in humans with acute radiation syndrome for ethical and feasibility reasons (refer to Neulasta US Prescribing Information). The H-ARS indication was initially not sought for MSB11455 because of the US-Neulasta exclusivity designation which expired on November 13, 2022.

This section provides the justification for the extrapolation to the H-ARS indication based on applicability of relevant US-Neulasta data to MSB11455, including mechanism of action (MOA) and animal studies demonstrating efficacy, PK, PD, immunogenicity, and safety/toxicity.

Overview of Biopharmaceutics

MSB11455 has the same amino acid sequence and an identical primary structure to Neulasta. The formulation of MSB11455 is the same as that of Neulasta and contains pegfilgrastim (6 mg) formulated in a preservative-free solution at same pH and with the same inactive ingredients.

Mechanism of Action and Animal Study Data on Efficacy

Mechanism of Action

As an FDA-approved biosimilar, MSB11455's MOA has been demonstrated to be similar to its reference product US-Neulasta in in-vitro functional assays through the mechanisms of cytokinesis and accelerated granulopoiesis. Pegfilgrastim-products act on hematopoietic cells by binding to the G-CSF receptor that is present on peripheral neutrophils and precursor cells in the bone marrow. US-Neulasta and MSB11455 produce dose-dependent increases in the number of total circulating neutrophils. The covalent attachment of polyethylene glycol (PEG) to filgrastim in pegfilgrastim-products induces a sustained elevation of absolute neutrophil count (ANC) comparable to the elevation induced by multiple daily doses of a non- PEGylated filgrastim. In H-ARS, radiation exposure > 2 Gy results in the sequelae of neutropenia, thrombocytopenia, and anemia that can result in death from infection and bleeding. Survival following H-ARS is dependent on the recovery of the hematopoietic stem and progenitor cells so that production of mature, functional neutrophils and platelets can occur. Pegfilgrastim products act to enhance neutrophil recovery in patients receiving myelosuppressive chemotherapy. Radiation-induced myelosuppression in animal models of disease is similar to the myelosuppression induced by chemotherapy in patients with cancer. Animal efficacy studies of lethal H-ARS have shown that US-Neulasta enhances neutrophil recovery and increases survival in the animals. Based primarily on these animal efficacy studies US Neulasta is FDA-approved for the treatment of H-ARS. MSB11455 is highly similar to US-Neulasta in its structure and functional attributes. These data support adding the H-ARS indication to MSB11455 by extrapolation.

Efficacy in Human Studies

In a study of accidental radiation exposure, 8 patients with bone marrow failure after a caesium-137 radiation accident were treated with recombinant human granulocyte- macrophage colony stimulating factor (rHuGM-CSF). The 7 who were evaluable had prompt increases in granulocytes and bone marrow cellularity. Four patients survived, including 2 who were treated early and never became infected.

Efficacy in Animal Studies. Efficacy studies of US-Neulasta for H-ARS could not ethically be conducted in humans. Therefore, FDA approval for H-ARS was based on studies in an irradiated non-human primate (NHP) model of acute radiation injury. Other animal studies support the efficacy/extrapolation of Neulasta to H-ARS, are relevant to MSB11455 and are also listed below.

- *AXG21: A 60-Day good laboratory practice (GLP) efficacy study of subcutaneous pegfilgrastim (US-Neulasta) to treat H-ARS following a lethal dose (LD) 50/60 of total body irradiation (TBI) in NHP. The planned interim analysis showed that US-Neulasta improved survival (91% (21/23) vs. 48% (11/23) in the control arm.*
- *AXG15: The pivotal study for the approval of filgrastim for H-ARS. In this study NHP received TBI of 7.5 Gy, delivered at a rate of 0.8 Gy/min using 6 MV linear accelerator radiation source. Filgrastim (10 mcg/kg daily SC) at 0.023 level of significance increased 60-day overall survival. Survival was 79% (19/24) in the filgrastim group compared to 41% (9/22) in the control group.*
- *ES1152 (ES2014.203): Effects of US-Neulasta on survival endpoints using the partial body irradiation (PBI) bone marrow sparing (BM 2.5%) model in mice (N=60) without antibiotic support. Thirty-day survival rates post 13 Gy PBI were 80%, 50% or 20% in 1mg/kg US-Neulasta, 0.1 mg/kg US-Neulasta, or vehicle control groups, respectively. The rates post 13.5 Gy PBI were 45%, 25% or 5%, respectively.*
- *IU2013.225M [N=44] and IU 2013.239M [N= 110]: Hematopoietic Screening Assay for Radio-mitigating Activity of 2 doses of Subcutaneously Administered Neulasta (1 mg/kg on days 1 and 8) after exposure to the LD50/30 dose of radiation. Pooled data from the two murine studies showed that US-Neulasta, at 1 mg/kg subcutaneously administered at 24±4 hr and on Day 8 post LD50/30 TBI, significantly increased survival compared to vehicle controls (76.9% (40/52) vs. 33.3% (34/102).*

Pharmacokinetics and Immunogenicity

The PK/PD, immunogenicity, and safety of MSB11455 (and its reference product US-Neulasta) in patients with H-ARS have not been assessed but the similarity between MSB11455 and US-Neulasta in healthy adult subjects was demonstrated in a double-blind, randomized PK/PD equivalence study (Study EMR200621-001) and an immunogenicity and safety study (Study EMR200621-003).

As an FDA approved biosimilar to US-Neulasta, the PK/PD of MSB11455 has been demonstrated to be similar to that of US-Neulasta. In both clinical studies, MSB11455 was administered at a dose level of 6 mg/0.6 mL as this is the approved dose for Neulasta when used in sequence with cytotoxic chemotherapy and was used in previous clinical studies (including studies in healthy subjects).

Immunogenicity.

The immunogenicity of MSB11455 and/or US-Neulasta has not been assessed in patients with H-ARS. However, immunogenicity of MSB11455 and US-Neulasta was demonstrated to be similar in healthy subjects. Study EMR200621-003 (a randomized, double-blind, 2 period, parallel-arm study) compared MSB11455 and US-Neulasta. The overall design of randomized, double-blind, parallel Study EMR200621-003 specifically covered the following aspects: study population and stratification factors, number of doses, sample size, primary endpoints and statistical methodology, immunogenicity sampling, and follow-up.

Safety study

The safety profile of MSB11455 as inferred from 2 studies (EMR200621-001 and EMR2090621-003) conducted in healthy subjects is consistent with the safety profile of US-Neulasta. No new safety signals were identified during the clinical development of MSB11455. The incidence of treatment-emergent adverse events (TEAEs) classified as serious adverse events (SAEs), adverse events (AEs) leading to discontinuation, adverse event of special interest (AESIs), or TEAEs with a severity Grade ≥ 3 were similar between MSB11455 and US-Neulasta.

Expected Toxicities
Safety of MSB11455 and/or US-Neulasta has not been assessed in patients with H-ARS. Clinical safety information to support the use of US-Neulasta in patients with H-ARS was primarily drawn from existing clinical safety data from human studies conducted to support approval of pegfilgrastim in patients exposed to myelosuppressive chemotherapy.

As an FDA approved biosimilar to US-Neulasta, clinical studies were required to demonstrate equivalent safety of CHS-1701. Studies comparing the safety of CHS-1701 to US-Neulasta included CHS-1701-01, CHS-1701-03, CHS 1701 04, CHS-1701-05, and CHS-1701-07. Results demonstrated that there were no clinically meaningful differences in the incidence, frequency, severity, or duration of treatment emergent adverse events (TEAEs) between CHS-1701 and US-Neulasta. The most common TEAEs included back pain, headache, pain in extremity, and arthralgia. The majority of TEAEs were generally mild to moderate in severity.

The presence of ADA did not impact the safety profile of CHS-1701 with musculoskeletal pain and headache, the most common TEAEs in ADA-positive and ADA-negative subjects across the CHS-1701 clinical studies. Immune responses, including hypersensitivity reactions and moderate or severe injection site reactions, were uncommon. These data support the safety extrapolation of CHS-1701 to H-ARS. No new safety concerns or toxicity are expected in patients with H-ARS.

Two non-clinical studies were performed to assess toxicity and to provide additional support for the demonstration of similarity. These studies were performed with DRL_PG.

Pediatrics

The approval of MSB11455's reference (US-Neulasta) to increase survival in pediatric patients acutely exposed to myelosuppressive doses of radiation was based on efficacy studies conducted in animals and clinical data supporting the use of US-Neulasta in patients receiving myelosuppressive chemotherapy. Efficacy studies of US-Neulasta could not be conducted in humans with acute radiation syndrome for ethical and feasibility reasons.

The FDA's Assessment

We agree with the Applicant's proposed scientific justification for extrapolation of data and information to support approval of STIMUFEND for the treatment of H-ARS. Based on investigational data previously submitted and reviewed from 292 subjects and 244 subjects exposed to MSB11455 and US-Neulasta, respectively, FDA has previously agreed with the extrapolation of data obtained in healthy adult subjects to the patient population of intended use. In particular, compared to extrapolation across the gap between healthy adults and patients with malignancies receiving myelosuppressive anti-cancer drugs, the Applicant and review team agree that the scientific gap is relatively smaller between healthy subjects and patients acutely exposed to myelosuppressive doses of radiation for the following reasons. Specifically, the mechanism of action for each indication is no different and most patients who develop H-ARS may be healthy or have no or less serious pre-existing disease prior to radiation exposure compared to patients with cancer.

We conclude that the Applicant has provided sufficient scientific justification (including assessment of mechanism of action, pharmacokinetics, immunogenicity, and toxicity profile) for extrapolation of the data and information submitted in the application to support licensure to increase survival in patients acutely exposed to myelosuppressive doses of radiation.

Recommended Regulatory Action
Approval

[1]https://darrts.fda.gov/darrts/faces/ViewDocument?documentId=090140af806819b7
[2] \\CDSESUB1\evsprod\BLA761173\0001\m2\25-clin-over

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/

NYUN C HAN
09/25/2023 07:48:58 AM

LIBERO L MARZELLA
09/25/2023 09:27:22 AM