CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761173Orig1s000

MULTI-DISCIPLINE REVIEW

Summary Review
Clinical Review
Non-Clinical Review
Statistical Review
Clinical Pharmacology Review

BIOSIMILAR MULTI-DISCIPLINARY EVALUATION AND REVIEW

Application Type	Original 351(k) BLA
Application Number	761173
Submit Date	3/27/2020
Received Date	3/27/2020
BsUFA Goal Date	3/27/2021
Division/Office	Division of Nonmalignant Hematology
Review Completion Date	August 25, 2022
Product Code Name	MSB11455
Proposed Non-Proprietary Name[1]	pegfilgrastim-fpgk
Proposed Proprietary Name[1]	Stimufend
Pharmacologic Class	Leukocyte Growth Factor
Applicant	Fresenius Kabi
Applicant Proposed Indication(s)	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
Recommendation on Regulatory Action	Approval

[1] Section 8 of the Biosimilar Multi-Disciplinary Evaluation and Review discusses the acceptability of the proposed proper and proprietary names, which are conditionally accepted until such time that the application is approved.

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CMC – Immunogenicity (OBP)	Pick-Wei Lau, Yan Wang
CMC – Labeling (OBP)	James Barlow, Pick-Wei Lau
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CMC=Chemistry, Manufacturing, and Controls
OBP=Office of Biotechnology Products
OPMA=Office of Pharmaceutical Manufacturing Assessment
ONDP=Office of New Drug Products

CDRH=Center for Devices and Radiological Health
OPDP=Office of Prescription Drug Promotion
OSI=Office of Scientific Investigations
OSE= Office of Surveillance and Epidemiology
DEPI= Division of Epidemiology
DMEPA=Division of Medication Error and Prevention Analysis
DRISK=Division of Risk Management
DPMH=Division of Pediatric and Maternal Health

Glossary

AC	Advisory Committee
ADA	Anti-drug Antibodies
ADME	Absorption, Distribution, Metabolism, and Excretion
AE	Adverse Event
AESI	Adverse Event of Special Interest
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
ANC	Absolute Neutrophil Count
AST	Aspartate Aminotransferase
BLA	Biologics License Application
BMER	Biosimilar Multi-Disciplinary Evaluation and Review
BMI	Body Mass Index
BPD	Biosimilar Biological Product Development
BsUFA	Biosimilar User Fee Agreements
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CI	Confidence Interval
CMC	Chemistry, Manufacturing, and Controls
CRF	Case Report Form
CRO	Contract Research Organization
CRP	C-reactive Protein
CSC	Computational Science Center
CTD	Common Technical Document
CV	Coefficient of Variation
DEPI	Division of Epidemiology
DMC	Data Monitoring Committee
DMEPA	Division of Medication Error Prevention and Analysis
DPMH	Division of Pediatric and Maternal Health
DRISK	Division of Risk Management
eCTD	Electronic Common Technical Document
ECG	Electrocardiogram
FDA	Food and Drug Administration
FISH	Fluorescence In Situ Hybridization
GCP	Good Clinical Practice
G-CSF	Granulocyte colony-stimulating factor
GMR	Geometric Mean Ratio
ICH	International Conference on Harmonization

IND	Investigational New Drug
ITT	Intention to Treat
LDH	Lactate Dehydrogenase
LLOQ	Lower Limit of Quantitation
MAPP	Manual of Policy and Procedure
mITT	Modified Intention to Treat
MOA	Mechanism of Action
NAb	Neutralizing Antibody
NCI-CTCAE	National Cancer Institute – Common Terminology Criteria for Adverse Events
NCT	National Clinical Trial
OBP	Office of Biotechnology Products
OCP	Office of Clinical Pharmacology
OPDP	Office of Prescription Drug Promotion
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigations
OSIS	Office of Study Integrity and Surveillance
PD	Pharmacodynamics
PEG	Anti-polyethylene glycol
PeRC	Pediatric Review Committee
PK	Pharmacokinetics
PMC	Postmarketing Commitments
PMR	Postmarketing Requirements
PREA	Pediatric Research Equity Act
PHS	Public Health Service
REMS	Risk Evaluation and Mitigation Strategies
ROA	Route of Administration
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SC	Subcutaneous
SGE	Special Government Employee
SOC	System Organ Class
SOP	Standard Operating Procedures
TEAE	Treatment-Emergent Adverse Events
ULOQ	Upper Limit of Quantitation
WBC	White Blood Cell Count

1. Executive Summary

1.1. Product Introduction

Proposed Proprietary Name: Stimufend

Proposed Nonproprietary Name: pegfilgrastim-fpgk

Code Name: MSB11455

Dosage Forms: Injection (6 mg/0.6 mL in a single dose prefilled syringe)

Therapeutic Class: Colony stimulating factor

Pharmacologic Class: Leukocyte growth factor

Chemical Class: Recombinant Protein

Stimufend (pegfilgrastim-fpgk) (MSB11455) is a proposed biosimilar product to U.S.-licensed Neulasta (pegfilgrastim) (hereafter referred to as US-Neulasta).

Mechanism of Action: MSB11455 is a pegylated, human recombinant granulocyte colony-stimulating factor (G-CSF) that acts on hematopoietic cells by binding to specific cell surface receptors, which leads to a dose-dependent increase in neutrophils by increasing proliferation and differentiation of neutrophils from committed progenitor cells, inducing neutrophil maturation, and enhancing survival and function of mature neutrophils.

Proposed Indication: 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.

Dosage/Administration: Single subcutaneous injection of 6 mg administered subcutaneously into the thigh, abdomen, buttocks or upper arm once per chemotherapy cycle in adults.

1.2. Determination under section 351(k)(2)(A)(ii) of the Public Health Service (PHS) Act

During its October 31, 2019 BPD Type 4 meeting, the Applicant and the Agency discussed the proposed data to be included in the 351 (k) BLA and the 120-Day Safety Update Report, and, in a Post Meeting Comment, the Agency agreed with the Applicant's approach to not include animal studies conducted with the (b) (4) (a material from an earlier smaller scale process, manufactured at sites not intended for commercial manufacturing)) in the 351(k) BLA.

The Applicant did not submit animal studies to support its 351(k) application but provided a justification for why such studies are unnecessary (see Section 351(k)(2)(A)(ii)). Specifically, The Applicant stated that animal studies are unnecessary based on the totality of evidence in the evaluation of MSB11455 biosimilarity. The Applicant also referenced the April 10, 2019 BPD Type 2 meeting data package.

As described below, the Applicant's analytical and clinical studies supported a demonstration that MSB11455 is highly similar to US-licensed Neulasta notwithstanding minor differences in clinically inactive components and that there are no clinically meaningful differences between MSB11455 and US-licensed Neulasta in terms of safety, purity, and potency. Additionally, the previously conducted animal studies with (b) (4) (a material from an earlier smaller scale process, manufactured at sites not intended for commercial manufacturing), which were not submitted in the 351(k) application, would not have been informative to the evaluation of the application (see Section 5.1). Accordingly, FDA has determined that animal studies are unnecessary in this 351(k) application.

1.3. Mechanism of Action, Route of Administration, Dosage Form and Strength Assessment

The activity of U.S.-licensed Neulasta (hereafter referred to as US-Neulasta) is mediated by binding to the granulocyte colony stimulating factor (G-CSF) It stimulates the production of neutrophil precursors, and the differentation and release of mature neutrophils from the bone marrow (Crawford 1991). US-Neulasta is a is a conjugate of a 20 kDA polyethylene glycol (PEG) molecule covalently bound to the N-terminal methionyl residue of filgrastim and has a considerably longer half-life than US-licensed Neupogen (15-80 hours compared to 3-4 hours, respectively).

Comparative analytical testing included multiple orthogonal assays relevant to mechanism of action of US-Neulasta which demonstrated that MSB11455 and US-Neulasta have the same mechanism of action, to the extent known.

MSB11455 is proposed for the following indication as previously approved for US-Neulasta:

- *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.*

The Applicant notes that the US-Neulasta indication of *"Increase survival in patients acutely exposed to myelosuppressive doses of radiation (Hematopoietic Subsyndrome of Acute Radiation Syndrome)"* has orphan exclusivity status until 23 Nov 2022 and acknowledges that this indication is protected until the end of the orphan exclusivity period; thus, The Applicant does not seek approval of this indication in this current application.

MSB11455 has the same proposed dosage form, route of administration, and dosing regimen as that of US-Neulasta. The conditions of use for which The Applicant is seeking licensure have been previously approved for US-Neulasta.

The Applicant proposes to develop a preservative-free solution for injection for subcutaneous use (0.6 mL) containing 6 mg of pegfilgrastim-fpgk (6 mg/0.6 mL) in a single-dose prefilled syringe. The strength of MSB11455 in the single-dose prefilled syringe is the same as that of US-Neulasta.

1.4. Inspection of Facilities

The Office of Pharmaceutical Quality (OPQ), CDER, recommends approval of STN 761173 for Stimufend (pegfilgrastim-fpgk) manufactured by Fresenius Kabi USA, LLC. The BsUFA date of March 27, 2021 was missed due to inability to perform an inspection during the review cycle. After the pre-licensed inspections of the G-CSF intermediate manufacturing facility (b) (4) , the MSB11455 DS manufacturing facility (b) (4) and the quality control testing site (b) (4) the OPQ, CDER, recommends approval from facility perspective based on the manufacturing facility assessment. The pre-approval inspection at the major comparative analytical testing site at (b) (4) verified that the tests generated to support a demonstration of highly similar are scientifically sound, fit for their intended use, and provide results that are reproducible and reliable.

1.5. Scientific Justification for Use of a Non-U.S.-Licensed Comparator Product

Not applicable. A non-US-Licensed comparator was not used in the assessment of biosimilarity.

1.6. Biosimilarity Assessment

Table 1: Summary and Assessment of Biosimilarity

Comparative Analytical Studies

Summary of Evidence	• The analytical studies support a demonstration that MSB11455 is highly similar to US-Neulasta notwithstanding minor differences in clinically inactive components. • The strength of MSB11455 in prefilled syringes is the same as that of US-Neulasta. • The dosage form and route of administration are the same as those of US-Neulasta.
Residual Uncertainties and Outcomes	• There are no residual uncertainties based on the comparative analytical studies.
Nonclinical Studies	
Summary of Evidence	• The Applicant did not submit animal studies to support its 351(k) application but provided a justification for why such studies are unnecessary (see Section 351(k)(2)(A)(ii)). FDA concluded that animal studies are unnecessary to support a determination of biosimilarity in this 351(k) application.
Residual Uncertainties and Outcomes	• There are no residual uncertainties from the pharmacology/toxicology assessment.
Clinical Pharmacology Studies	
Summary of Evidence	• PK and PD (absolute neutrophil count) similiarity between MSB11455 and US-Neulasta was demonstrated in healthy subjects (Study EMR200621-001). • Comparable incidence of immunogenicity was observed between MSB11455 and US-Neulasta in healthy subjects (Study EMR200621-003); the upper bound of the 95% CIs for the risk difference of the endpoint of the ADA incidence was within the prespecified bound of <10%. • In summary, the PK, PD and immunogenicity results from Studies EMR200621-001 and EMR200621-003 support a demonstration of no clinically meaningful differences between MSB1145 and US-Neulasta.
Residual Uncertainties and Outcomes	• There are no residual uncertainties based on the clinical pharmacology evaluation.

Clinical Studies	
Summary of Evidence	• In the comparative safety analyses of Studies EMR200621-001 and EMR200621-003, there was no substantial difference in adverse events, laboratory values, vital signs, or ECG changes. • In the comparative analysis of adverse events of special interest in Studies EMR200621-001 and EMR200621-003, there were no substantial differences in acute hypersensitivity, splenomegaly, or increased white blood cell count. • The overall safety profile of MSB11455 was similar to that of US-Neulasta. The analysis of safety results from Studies EMR 200621-001 and EMR200621-003 support demonstration of no clinically meaningful differences between MSB11455 and US-Neulasta.
Residual Uncertainties and Outcomes	• There are no residual uncertainties based on the clinical safety evaluation.
Extrapolation of Data to Support Licensure as a Biosimilar	
Summary of Evidence	• The Applicant has provided adequate scientific justification to support extrapolation of data and information submitted to support licensure of MSB11455 as a biosimilar, under section 351 (k) of the PHS Act, for the following indication for which US-Neulasta has been previously approved: 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.
Residual Uncertainties and Outcomes	• There are no residual uncertainties regarding the extrapolation of data and information to support licensure of MSB11455 as a biosimilar to US-Neulasta for the above indication.

1.7. Conclusions on Licensure

In considering the totality of the evidence submitted, the data submitted by the Applicant show that MSB11455 is highly similar to U.S.-licensed Neulasta, notwithstanding minor differences in clinically inactive components, and that there are no clinically meaningful differences between MSB11455 and U.S.-licensed 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 MSB1145 for the proposed indication, as listed below. The information submitted by The Applicant demonstrates that MSB11455 is biosimilar to U.S.-licensed Neulasta for the following indication for which U.S.-licensed Neulasta is currently licensed and Applicant is seeking licensure of MSB11455:

- *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.*

Author:

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CDTL

2. Introduction and Regulatory Background

2.1. Important Safety Issues with Consideration to Neulasta

The US Prescribing Information for US-Neulasta (pegfilgrastim) include the following adverse reactions and warnings and precautions:

Most Common Adverse Reactions:

- Bone Pain
- Pain in Extremity

Warnings and Precautions:

- Splenic rupture (including with fatal outcome)
- Acute respiratory distress syndrome (ARDS)
- Serious allergic reactions (including anaphylaxis)
- Allergies to acrylics
- Glomerulonephritis
- Severe and fatal sickle cell crises in patients with sickle cell disorders
- Leukocytosis
- Capillary leak syndrome

- Potential for tumor growth stimulatory effects on malignant cells
- Thrombocytopenia
- Myelodysplastic Syndrome (MDS) and Acute Myeloid Leukemia (AML)
- Aortitis

2.2. Summary of Presubmission Regulatory Activity Related to Submission

The clinical development of MSB11455 was conducted outside the US. The relevant regulatory history pertaining to the development of MSB11455 is detailed in the table below.

Table 2: Regulatory History

Dates	Milestone
May 9th, 2012	Pre-IND meeting
February 5, 2015	BPD Type 2 meeting • To discuss overall quality of material and clinical development program
December 9, 2015	BPD Type 2 meeting • Advice provided for clinical and analytical assessment for MSB11455 with US-Neulasta
May 31, 2016	Request for clarification • Clarification regarding dose accuracy acceptable criteria relating to protein content provided
January 31, 2017	BPD Type 2 meeting • To discuss proposed comparative immunogenicity study
February 28, 2017	BPD Type 2 meeting • To obtain feedback on proposed comparative PK/PD study (EMR200621-001) • To discuss results of PK-modeling performed in study PG-01-003
December 2018	BPD Type 2 meeting Written Request • Agreement with The Applicant's proposal to submit a summary of clinical safety in Module 2.7.4
January 31, 2017	BPD Type 2 meeting • To discuss proposed comparative immunogenicity study
May 9, 2017	IND amendment proposal

	• Agreement to use group sequential design (GSD) approach for EMR200621-001
June 13, 2018	Proposed human factor study/Usability test plan submission to IND • Determination by DMEPA that Human factors validation study was not required with BLA submission
March 19, 2019	BPD Type 2 written response • Agreement that summary of clinical safety in Module 2.7.4 may be submitted in lieu of an ISS • Agreement that summary of clinical efficacy can serve as ISE
April 10, 2019	BPD Type 2 meeting • Agreement on planned data to be submitted with BLA
October 31, 2019	BPD Type 4 meeting • Discussion of format and content of proposed BLA submission
December 9, 2019	BPD Type 4 meeting follow-up written clarification • Agreement regarding The Applicant's proposed submission timeline for real time shipping study results

2.3. Studies and Publicly Available Information Submitted by The Applicant

Table 3: Submitted MSB11455 Clinical Studies

Study Number	Study Design	Site	Subjects Enrolled	Regimen	Study Endpoints
EMR200621-001	Randomized, two-way crossover, double-blind, single-dose, PK/PD similarity study in healthy adult subjects	2 sites; Australia	292	MSB11455 or US-Neulasta Single SC dose of 6 mg/0.6 mL	Primary PK endpoints: $AUC_{0\text{-last}}$, $AUC_{0\text{-}\infty}$ and C_{max} Primary PD endpoints: $AUEC_{0\text{-t}}$ and E_{max} of baseline ANC Secondary endpoints: safety, tolerability and immunogenicity
EMR200621-003	Randomized, parallel, multiple-dose, immunogenicity study in healthy adult subjects	2 sites; New Zealand	336	MSB11455 or US-Neulasta Two SC doses of 6 mg/0.6 mL	Primary endpoints: Immunogenicity (confirmed anti-drug antibody (ADA) and neutralizing antibodies (NAb) status) Secondary endpoints: safety and tolerability

Source: FDA clinical reviewer

Authors:
Julie Weisman, MD
Clinical Reviewer

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3. Clinical Studies: Ethics and Good Clinical Practice

3.1. Submission Quality and Integrity

The data quality and integrity of the studies were acceptable. The BLA submission was in electronic common technical document (eCTD) format and was adequately organized.

3.2. Statistical Analysis of Clinical Data

The primary analysis dataset were reproduced and randomized treatment assignments were verified in studies EMR200621-001 and EMR200621-003. The quality and integrity of the submitted data and analyses were adequate. The quality control processes were reviewed by The Applicant's own independent quality assurance group or by CRO. The audit was conducted according to applicable standard operating procedures and local regulation.

3.3. Compliance with Good Clinical Practices

All studies were conducted according to Good Clinical Practice (GCP) as described in International Conference on Harmonisation (ICH) Guideline E6 and in accordance with the ethical principles outlined in the Declaration of Helsinki. The studies were conducted in compliance with the protocols. Informed consent, protocol, amendments, and administrative letters for the studies received Institutional Review Board/Independent Ethics Committee approval prior to implementation. Subjects signed informed consent documents. Written informed consent was obtained prior to subjects entering the studies (before initiation of protocol-specified procedures). The investigators explained the nature, purpose, and risks of the study to each subject. Each subject was informed that he/she could withdraw from the study at any time and for any reason. Each subject was given sufficient time to consider the implications of the study before deciding whether to participate. The investigators conducted all aspects of these studies in accordance with applicable national, state, and local laws of the pertinent regulatory authority.

3.4. Financial Disclosures

The Applicant has adequately disclosed financial arrangements with clinical investigators. The application includes the FDA financial disclosure form 3454 and indicated there were no financial arrangements with any of the investigators involved in clinical studies EMR200621-001 and EMR200621-003. The document included a list of all investigators and The Applicant stated that none of the principal investigators reported financial interests or arrangements. The Applicant submitted financial arrangements for the clinical investigators and based on information submitted, there were no reported financial interests or arrangements for the primary investigators.

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4. Summary of Conclusions of Other Review Disciplines

4.1. Chemistry, Manufacturing and Controls (CMC)

The proposed intermediate is a non-glycosylated recombinant methionyl human granulocyte colony-stimulating factor (G-CSF), producted in E. coli. The G-CSF intermediate is composed of 175 amino acids with the same sequence as natural G-CSF, except for the addition of a methionine residue at the N-terminus. To produce the drug substance, MSB11455, a 20kDa mPEG-PAL molecule is covalently linked at the N-terminal methionyl residue of the G-CSF intermediate.

The proposed drug product, MSB11455, is a sterile, clear, colorless, preservative-free solution. Each (b) (4) contains 6mg/0.6mL of MSB11455 at concentration of 10mg/mL with pH of 4.0. Each mL of solution contains 10.0mg MSB11455, 50.0mg (b) (4) sorbitol, (b) (4) , 0.03mg polysorbate 20 and water for injection.

The Office of Pharmaceutical Quality, CDER, has completed review of BLA for MSB11455. From a product quality perspective, the Office of Biotechnology Products (OBP), OPQ, CDER as well as OPMA, OPQ, CDER do not note any product quality differences that would preclude approval of STN 761173 for MSB11455 manufactured by Fresenius Kabo USA, LLC at this time. The comparative analytical data submitted in the application demonstrates that MSB11455 is highly similar to US-licensed Neulasta notwithstanding minor differences in clinically inactive components. The data submitted in this application are sufficient to support a conclusion that the manufacte of MSB11455 (by Fresenius Kabi USA, LLC) is well-controlled and will lead to a product that is safe, pure, and potent for the duration of the shelf-life. MSB11455 (6 mg/0.6 mL in a single-dose prefilled syringe) has the same dosage form, route of administration, and strength as US-Neulasta. Refer to the Executive Summary memo for BLA 761173 dated February 4, 2021 in DARRTS for assessments of comparative analytical assessment, critical quality attributes, risks, lifecycle management, and establishment information.

4.2. Clinical Microbiology

Not applicable.

4.3. Devices

MSB11455 drug product is presented as a ready-to-use, disposable, single-use, fixed dose (6mg/0.6mL) pre-filled syringe (PFS) assembled with a passive Safe'n'Sound® (SnS) needle guard safety system.

4.3.1. Center for Devices and Radiological Health (CDRH)

CDRH recommend the combination product is approvable. The device constituent of the combination product is approvable for the proposed indication. The Sponsor provided a response to the information request to update the design verification package which included the needle safety activation, needle safety override, resistance to pre-activiation after shipping

simulation and resistance to pre-activation after drop testing. The Sponsor has provided full test reports for each test listed above with adequate passing results.

4.3.2. Division of Medication Error Prevention and Analysis (DMEPA)

The DMEPA review of the primary risk assessment review of the labeling included the evaluation of the package insert, container and carton labels, and proposed Instructions for Use, identified unique areas of vulnerability that may lead to medication errors. These were communicated to the Applicant and the Applicant made appropriate revisions.

The DMEPA review of the use-error analysis concluded that there were no new or unique risks when compared to US-Neulasta. We also note that the intended user group, intended uses, and use of environments for Stimufend aligns with the US-Neulasta for the febrile neutropenia indication.

DMEPA determined that the applicant does not need to submit a human factors validation study for the review at this time. Any changes to the use-error analysis would warrant further review.

4.4. Office of Study Integrity and Surveillance (OSIS)

OSIS determined that inspections were not warranted (Memo uploaded in DAARTS on 8/3/2020) for the sites because the past inspections were within the surveillance interval and the final classification for those inspections was no action indicated (NAI).

4.5. Office of Scientific Investigations (OSI)

Two studies (EMR200621-001 [PK/PD] and EMR200621-003 [immunogenicity and safety] were submitted in support of BLA 761173 for MSB11455. Due to the COVID-19 pandemic the ability to conduct on-site GCP investigations was limited and as a result, a remote assessment was conducted for the sponsor using a WebEx platform for meetings, and review of original records that were uploaded to a secure box account licensed to FDA for the investigation. The Fresnenius Kabi SwissBiosim GmbH remote site investigation did not identify regulatory findings with sponsor oversight of these two clinical studies. The Applicant's conduct for clinical studies EMR200621-001 and EMR200621-003 appeared acceptable.

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5. Nonclinical Pharmacology and Toxicology Evaluation and Recommendations

5.1. Nonclinical Executive Summary and Recommendation

No nonclinical data were submitted to the BLA to support the final clinical formulation of MSB11455. FDA agreed with The Applicant in a Biosimilar Biological Product Development Type 2 meeting that nonclinical in vivo pharmacology and toxicology data from studies with (b) (4) an early, non-commercial small-scale batch precursor product to the final MSB11455 product, were not directly relevant to the final proposed clinical formulation.[2] The Applicant provided a justification that those nonclinical data were unnecessary in their application .[3]

In conclusion, the previously conducted animal studies would not be informative to the evaluation of this application

No label changes or updates are recommended from a nonclinical perspective.

5.1.1. Nonclinical Residual Uncertainties Assessment

There are no nonclinical residual uncertainties from the pharmacology/toxicology assessment.

5.2. Product Information

Product Formulation

MSB11455 drug product is formulated as a clear, colorless, ready-to-use, disposable, single-use, fixed dose (6 mg/0.6 mL), pH 4.0 pre-filled syringe (PFS) assembled with a passive "Safe'n'Sound®" needle guard system. The excipients in MSB11455 are identical and quantitatively similar to those in US-Neulasta and included acetate, sorbitol, sodium, and polysorbate 20.

Comments on Novel Excipients

All MSB11455 excipients are compendial, qualitatively and quantitatively similar to the excipients in US-Neulasta, and there are no novel excipients in the formulation.

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[2] IND 113717, Memorandum of Meeting Minutes, 5/9/2019 (Biosimilar Product Development Type 2 Meeting, 4/10/2019)

[3] BLA 761173, Response to Information Request, 5/21/2020

Comments on Impurities/Degradants of Concern

There are no impurities or degradants that pose a safety concern in the proposed drug product. The Applicant conducted a risk assessment of extractable and leachable impurities of potential concern from standard use and accelerated degradation conditions. Maximum Daily Intake (MDI) from each of the potential extractable and leachable compounds were well below the calculated Permissible Daily Exposure (PDE), confirming negligible risk for any extractable or leachable impurity in MSB11455. No elemental impurities were measured in extractable or leachable studies at levels that posed a safety concern. Similarly, drug substance specifications limit elemental impurities to negligible levels and all potential process-related elemental impurities measured during drug substance batch analyses were below PDEs established from ICH impurity guidances.

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6. Clinical Pharmacology Evaluation and Recommendations

6.1 Clinical Pharmacology Executive Summary and Recommendation

Table 4: Clinical Pharmacology Major Review Issues and Recommendations

Review Issue	Recommendations and Comments
Pharmacokinetics Similarity	• In study EMR200621-001, PK similarity was demonstrated between MSB11455 (Stimufend) and US-Neulasta. The 90% CI of the GMR for the primary PK endpoints C_{max} and $AUC_{0\text{-}inf}$ were within the pre-specified margin of 80-125%.
Pharmacodynamics Similarity	• In study EMR200621-001, PD (ANC) similarity was demonstrated between MSB11455 (Stimufend) and US-Neulasta. The 90% CI of the GMR for the primary PD endpoints ANC E_{max} and $AUE_{0\text{-}t}$ were within the pre-specified margin of 80-125%.
Immunogenicity	• In study EMR200621-003, a similar incidence of ADA formation was observed for MSB11455 and US-Neulasta in healthy subjects. The upper bound of the exact 1-sided adjusted 95% CI for risk difference was <10%, and met the prespecified limit.

The Applicant submitted pharmacokinetic (PK), pharmacodynamic (PD), and immunogenicity

data from two clinical studies in healthy subjects to support demonstration of no clinically meaningful differences between MSB11455 and US-Neulasta:

1. Study EMR200621-001 was a double-blind, randomized, 2-sequence, 2-period, 2-treatment crossover, group sequential study, to evaluate the PK and PD (absolute neutrophil count [ANC]) similarity of MSB11455 and US-Neulasta following a single 6 mg/ 0.6 mL subcutaneous (SC) dose in healthy adult subjects (N=240). The results of the study established PK and PD similarity between MSB-11455 and US-Neulasta based on the primary PK (C_{max}, $AUC_{0-\infty}$, and AUC_{0-last}) and PD (observed ANC E_{max} and AUE_{0-t}) endpoints.

2. Study EMR200621-003 was a randomized, 2-treatment, parallel study to evaluate the immunogenicity of MSB11455 and US-Neulasta following multiple doses of 6 mg/0.6 mL administered subcutaneously (2 doses, 4-5 weeks apart) in healthy subjects (N=336). The observed antidrug antibodies (ADA) formation were similar between MSB11455 and US-Neulasta. The study results demonstrated non-inferiority of MSB11455 over US-Neulasta for the confirmed treatment induced ADA positive status.

Overall, the results from study EMR200621-001 and study EMR200621-003 support the demonstration of no clinical meaningful differences between MSB11455 and US-Neulasta and add to the totality of the evidence to support a demonstration of biosimilarity between MSB11455 and US-Neulasta (Tables 4,5 and 6).

6.1.1. Clinical Pharmacology Residual Uncertainties Assessment

The clinical studies adequately demonstrated PK and PD similarity of MSB11455 with US-Neulasta and showed similar incidence of ADA formation between MSB11455 and US-Neulasta. There are no residual uncertainties from the clinical pharmacology assessment.

6.2. Clinical Pharmacology Studies to Support the Use of a Non-U.S.-Licensed Comparator Product

Not applicable. The Applicant used US-licensed Neulasta to demonstrate biosimilarity in their studies.

6.3. Human Pharmacokinetics and Pharmacodynamics

Clinical Pharmacology Study Design Features

The Applicant conducted one clinical pharmacology PK/ PD similarity study (EMR200621-001) comparing MSB11455 to US-Neulasta in healthy subjects. The study design of study EMR200621-001 is considered adequate to demonstrate PK/PD similarity for the following reasons:

- A study in healthy subjects is considered safe and an appropriately sensitive study population.
- A single SC dose of 6 mg is the approved dose for US-Neulasta.
- A cross-over study design was used to assess the PK/PD similarity of MSB11455 and US-Neulasta. Refer to Section 7.2 for more detailed description on study design.
- A target washout period of 42 days between each treatment was used. As per the US-Neulasta labeling, the half-life of pegfilgrastim ranged from 15 to 80 hours (0.63 to 3.33 days) after subcutaneous injection. Based on observation, ANC returned to baseline by around Day 15 after each treatment.
- Absolute neutrophil count (ANC), the PD marker of drug efficacy, has been well characterized in patients with chemotherapy-induced myelosuppression in clinical studies.

Clinical Pharmacology Study Endpoints

In Study EMR200621-001, the prespecified PK endpoints were C_{max} and $AUC_{0\text{-}inf}$, and the prespecified PD endpoints were observed ANC E_{max} and $AUE_{0\text{-}t}$. PK and PD similarities were established if the 90% CI of GMR of each parameter between MSB11455 with US-Neulasta were within the prespecified limits of 80-125%.

Blood sample measurements were as follows:

- PK – blood samples for PK measurement were collected at pre-dose, and 1, 6, 12, 14, 16, 18, 20, 24, 30, 36, 48, 72, 96, 120, 168, 216, 264, 312, 360 hours post-dose
- PD – blood samples for ANC measurements were collected at pre-dose, and 1, 6, 12, 14, 16, 18, 20, 24, 30, 36, 48, 72, 96, 120, 168, 216, 264, 312, 360 hours post-dose
- ADA – blood samples for anti-pegfilgrastim antibodies were collected at day 1 pre-dose (baseline), day 16, 42 (this sample also serves as a pre-dose sample for Period 2), 84 after first study drug administration (period 1) and day 16 (period 2) after the second study drug administration.

Bioanalytical PK Method and Performance

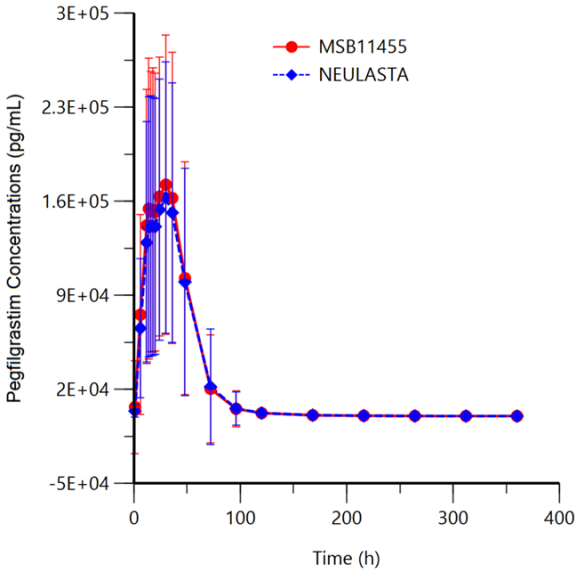
See section 16.3.1.1. for details

PK Similarity Assessment

PK similarity between MSB11455 and US-Neulasta was demonstrated in the single-dose crossover study EMR200621-001. The 90% CI of the GMR for PK (C_{max} and $AUC_{0\text{-}inf}$) endpoints were within 80-125%. (Table 2). The geometric mean concentration-time profiles and a summary of the calculated PK parameters are shown in table 5 and figure 1.

Figure 1: Mean concentrations (pg/mL) versus time (hours) from study EMR200621-001

A. Linear Scale (Error bars – Standard deviation)



B. Semi-logarithmic scale

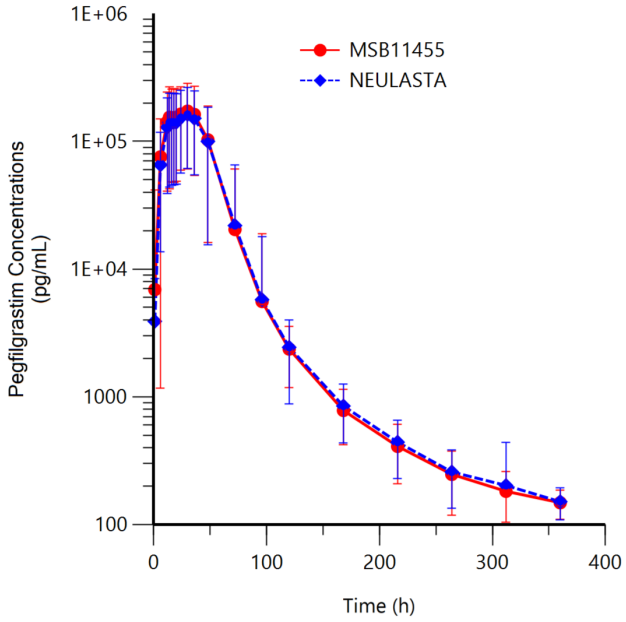


Table 5. Summary of statistical analyses for assessment of PK similarity (Study EMR200621-001)

Parameter	Statistic	MSB11455	U.S. – Neulasta	Geometric Mean Ratio* (90% CI)
				MSB11455 vs US-Neulasta

$AUC_{0\text{-}inf}$ (pg*h/mL) (n=242)	Geometric Mean (CV%)	6518666 (54.3)	6215139 (54.3)	104 (97.2, 112.9)
C_{max} (pg/mL) (n=242)	Geometric Mean (CV%)	157348 (58.7)	149017 (58.7)	105 (97.5, 114.3)

*Presented as percent. Source: Reviewer's analysis

PD Similarity Assessment

PD (ANC) similarity between MSB11455 and US-Neulasta was demonstrated in the single-dose crossover study EMR200621-001 (Figure 2). The 90% CIs of the GMR for PD (ANC E_{max} and $AUE_{0\text{-}t}$) endpoint were within 80-125% (Table 6)

Figure 2: Mean ANC concentration (x 10^9/L) vs. time (hr) from Study EMR200621-001 (Error bars – Standard deviation)

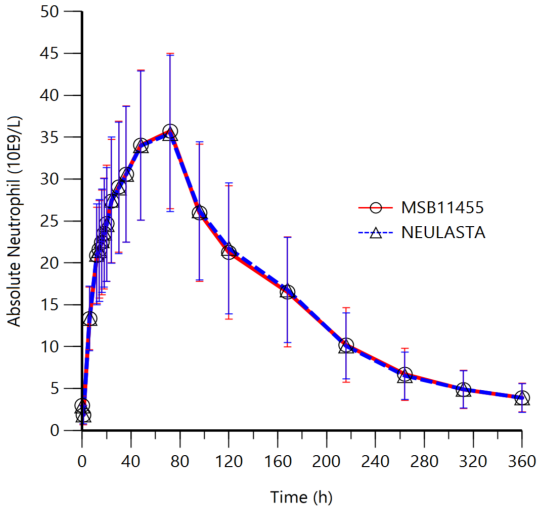


Table 6. Summary of statistical analyses for assessment of PD (biomarker) similarity (Study EMR200621-001)

Parameter	Statistic	MSB11455	U.S. – Neulasta	Geometric Mean Ratio* (90% CI)
				MSB11455 vs US-Neulasta
$AUE_{0\text{-}t}$ (10^9*h/L) (n=233)	Geometric LS Mean (CV%)	5560 (24.5)	5620 (24)	98.75 (97.3, 100.23)
ANC Emax (10^9/L) (n=240)	Geometric LS Mean (CV%)	36.77 (24.5)	36.56 (25.1)	100.55 (98.74, 102.39)

Source: EMR200621-001 CSR sponsor analysis
*Presented as percent

6.4. Clinical Immunogenicity Studies

- Immunogenicity Assessment in study EMR200621-003

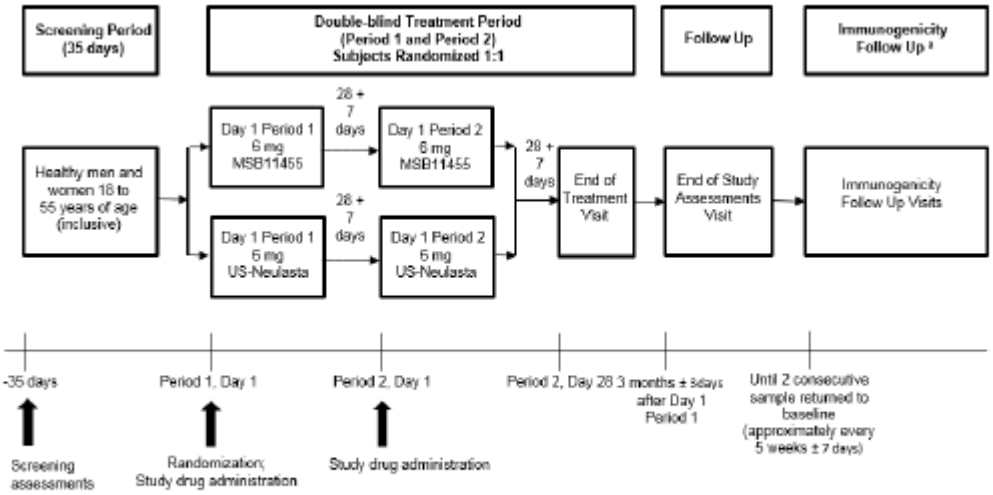
Design features of the clinical immunogenicity assessment

The Applicant conducted an immunogenicity study (EMR200621-003) in healthy subjects, as described in table 4 in section 6.4. This was a randomized, double-blind, parallel group, controlled study to compare the immunogenicity and safety of MSB11455 and US-Neulasta in healthy adult subjects. Overall, 336 healthy adult subjects were randomized in either of the treatment arms, MSB11455 or US-Neulasta (n=168/ treatment arm).

The primary objective of this study was to demonstrate similarity of MSB11455 to US-licensed Neulasta with respect to immunogenicity in healthy subjects. The primary endpoint was confirmed treatment-induced positive anti-drug antibodies (ADA) and neutralizing anti-body (NAb) status to pegfilgrastim from pre-dose on Day 1 of Period 1 up to the EOS Assessment Visit i.e. 84 ± 3 days after Day 1 of Period 1. The secondary objective of the study was to compare the safety and tolerability of MSB11455 and US-Neulasta. The secondary endpoints were assessed based on treatment emergent adverse events (TEAEs) and serious adverse events (SAEs) according in subjects receiving MSB11455 and US-Neulasta from the first dose received until end of study (EOS) assessment visit. Based on the study design described above, study EMR200621-003 is considered adequate to assess immunogenicity risk.

The study design consisted of two treatment periods (MSB11455 and US-Neulasta). Each randomized subject received a single subcutaneous injection of either MSB11455 or US-Neulasta on the morning of Day 1 in each of the 2 periods, for a total of 2 injections, separated by a washout period of 28 to 35 days. The randomization was stratified, based on the site and the anti-PEG antibody status (qualitative assessment) at screening. The study design schematic is represented in Figure 3.

Figure 3: Study Schematic EMR200621-003 (Source – Clinical study report EMR200621-003)



a Only subjects with a confirmed positive for treatment-induced antidrug antibodies by the End of Study Assessments Visit will be followed until 2 consecutive samples returned to Baseline (every 5 weeks ± 7 days)

Blood samples for immunogenicity assessments were collected at day 1 pre-dose (baseline), day 13 (period 1), day 28 (period 1) after the first dose (this sample also serves as a pre-dose sample for period 2), day 13 (Period 2) after the second dose, day 28 (Period 2) after the second dose, day 84 after the first dose. In addition, subjects with confirmed positive treatment-induced ADA by the EOS Assessments Visit (84 days after day 1 of period 1) were followed until 2 consecutive samples returned to baseline (every 5 weeks ± 7 days). WBCs would also be measured. Moreover, samples with confirmed ADA to pegfilgrastim were further evaluated for antibodies against PEG and granulocyte colony-stimulating factor (G-CSF).

General safety assessments such vital signs were conducted at days 1, ,2, 3, 4, 5, 6, 7, 8, 13 of periods 1 and 2, and during EOS and EOT as well.

Immunogenicity endpoints

The primary endpoint is confirmed treatment-induced positive ADA status to MSB11455 or US-Neulasta from predose on Day 1 of Period 1 up to the End of Study Assessment Visit (3 months [84 days] ± 3 days after Day 1 of Period 1). The primary analysis consisted of the estimation (along with the corresponding exact 95% 1-sided adjusted confidence interval [CI]) of the difference in treatment-induced ADA-confirmed positive rates between MSB11455 and US-Neulasta, along with testing the null hypothesis H0 that the confirmed treatment-induced ADA positive rate of MSB11455 is at least 10% higher than the confirmed treatment-induced ADA positive rate in the US-Neulasta arm.

Immunogenicity assay's capability of detecting the antidrug antibodies (ADA) in the presence of proposed product, reference product, and any other comparator product (as applicable) in the study samples

The immunogenicity assays were capable of detecting the ADA in the presence of MSB11455 and US-Neulasta in the study samples. The sensitivity of the ADA assay was 10 ng/mL for anti-study drug antibodies and 19 ng/mL for anti-PEG antibodies (specificity assay). Drug tolerance was also evaluatedfor both MSB11455 and US-Neulasta. For MSB11455, drug tolerance at low positive control (LPC) level was 0.250 ng/mL, at high positive control (HPC) it was 10.000 ng/mL. For US-Neulasta, drug tolerance at LPC level was 0.125 ng/mL, at HPC it was 10.000 ng/mL. The sensitivity of the Nab assay was 337 ng/mL for pegylated study drug and 328 ng/mL for the non-pegylated component of the study drug. Refer to the Immunogenicity Review by the Office of Biotechnology Products for details regarding the ADA assay methods.

Adequacy of the sampling plan to capture baseline, early onset, and dynamic profile (transient or persistent) of ADA formation

Sampling plan in study EMR200621-003 was adequate to capture baseline, early onset, and the dynamic profile (transient or persistent) ADA formation. Samples for ADA assessment were collected as follows:

- Period 1: Day 1 (predose), day 13 and day 84 (± 3 days)
- Period 2: Day 1 (equivalent to day 28 post first dose), day 13, D28 (+7 End of treatment) /Early Withdrawal

Additionally, subjects with confirmed positive treatment-induced ADA by the EOS Assessments Visit were followed until 2 consecutive samples returned to baseline (every 5 weeks ± 7 days).

Incidence of ADA (Provide the incidence of pre-existing antibodies at baseline and the incidence of ADA throughout the study)

Table 7. Statistical Analysis of the Difference in Treatment-induced ADA Positive Status Between Treatments - Intent-to-treat Analysis Set

		Anti-drug antibody (ADA)			G-CSF-specific Nab
	N	Baseline	Treatment-Induced	Risk Difference	
MSB11455	168	3/168 (1.8%)	15/168 (8.9%)	-0.6% (Upper Limit of Adjusted 95.0% CI: 6.25%)	0
US-Neulasta	168	5/168 (3%)	16/168 (9.5%)		0

Source: Sponsor analysis

As per the intent-to-treat (ITT) analysis (table 7), the risk difference of MSB11455 – US-Neulasta is -0.6% with an upper limit of the exact 1-sided adjusted 95.0% confidence interval (6.25%) for the treatment difference in confirmed treatment-induced ADA positive status. This risk difference was below the predefined non-inferiority margin of 10%.

There is no significant difference in immunogenicity between the biosimilar product and the reference product.

Neutralizing antibodies

No NAb specific antibodies against the non-pegylated component of the study drug were detected in either treatment arm.

Anti-PEG antibodies

Anti-PEG antibodies evaluation was conducted at screening. At screening, 8 subjects tested positive (4.8%) for anti-PEG antibodies in every treatment arm (MSB11455 and US-Neulasta).

Immunogenicity assessments for study EMR200621-003

The treatment-induced ADA positivity over time is comparable across treatments. The highest positivity rate is observed at Day 13 of Period 1 and decreased until the End of Study. There were no relevant differences between the median ADA titers over time across the treatment arms.

The overall post-dose ADA positive status, not constrained to treatment-induced, was comparable between treatments, with an overall of 15 subjects (8.9%) in the MSB11455 treatment arm and 18 subjects (10.7%) in the US-Neulasta treatment arm with an ADA positive status at any time.

Table 8: Treatment-induced ADA Positive Status

	MSB11455 (N=168)		US-Neulasta (N=168)	
Visit	n/ N(%)	95% CI	n/ N(%)	95% CI
Period 1, day 1 predose	3/168 (1.8)	0.4, 5.1	5/168 (3)	1, 6.8
Period 1, day 13	14/ 167 (8.4)	4.7, 13.7	13/ 168 (7.7)	4.2, 12.9
Period 2, day 1	8/ 166 (4.8)	2.1, 9.3	5/ 165 (3.0)	1, 6.9
Period 2, day 13	5/ 166 (3.0)	1, 6.9	1/ 166 (0.6)	0, 3.3
Period 2, day 28	4/ 162 (2.5)	0.7, 6.2	2/ 164 (1.2)	0.1, 4.3
Early termination	0/3 (0)	-	0/2 (0)	-
End of study	4/ 163 (2.5)	0.7, 6.2	1/ 163 (0.6)	0, 3.4
Follow-up 1	2/3 (66.7)	9.4, 99.2	0/ 2 (0)	-
Follow-up 2	1/1 (100.0)	-	NA	NA

The ADAs of subjects with ADA post-dose status were mostly directed against the PEG portion of MSB11455 or US-Neulasta and no relevant differences in specificity are observed across the treatments:

- 22 subjects had ADAs that were positive only in the PEG specificity assay during the study: 10 in the MSB11455 treatment arm and 12 in the US-Neulasta treatment arm

- 5 subjects had ADAs that were positive both in the PEG and in the G-CSF specificity assays in at least 1 of their visits: 4 subjects in the MSB11455 and 1 subject in the US-Neulasta treatment arm
- 1 subject in the US-Neulasta treatment arm had ADAs that were positive only in the G-CSF specificity assay
- 5 subjects had ADAs that were negative both in the PEG and in the G-CSF specificity assays during the study: 1 in the MSB11455 treatment arm and 4 in the US-Neulasta treatment arm

Table 9: Immunogenicity analysis from study EMR200621-003

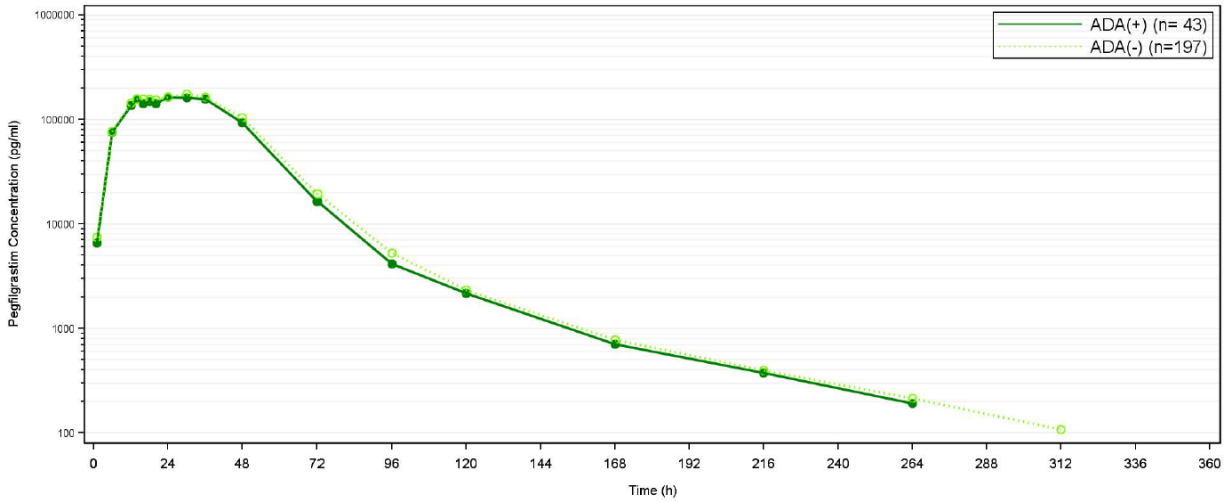
Immunogenicity analysis	Post-dose ADAs	MSB11455 (n=168)		US-Neulasta (n=168)	
		n	% of total	n	% of total
Overall post-dose ADA positive status (not constrained to treatment induced)	+	15	8.9	18	10.7
ADAs positive only for PEG specificity assay	+	10	5.9	12	7.1
ADAs positive only for G-CSF specificity assay	+	0	-	1	0.59
ADAs positive for both PEG & G-CSF specificity assay	+	4	2.3	1	0.59
ADAs negative for both PEG & G-CSF specificity assay	-	1	0.59	4	2.3
Detectable neutralizing activity	+	3	1.7	1	0.59

Out of the 33 subjects with at least 1 confirmed post-dose ADA positive samples, 4 subjects had at least 1 post-dose sample with detectable neutralizing activity to MSB11455 or US-Neulasta: 3 subjects in the MSB11455 and 1 subject in the US-Neulasta treatment arm. As per the Applicant, none of the tested samples showed neutralizing activity for the unrelated macrophage colony-stimulating factor (MCSF). Most importantly, no NAb specific against the non-pegylated component of the study drug was detected in either treatment arm.

Impact of ADA on the PK, PD, safety, and clinical outcomes of the proposed biosimilar product

Arithmetic mean serum concentration-time profiles of pegfilgrastim according to the treatment-induced ADA status are displayed in Figure 4 for MSB11455. The serum concentration-time profiles of both ADA status groups were superimposable throughout the entire observation period. Thus, it can be concluded that the ADA status did not impact PK parameters for MSB11455.

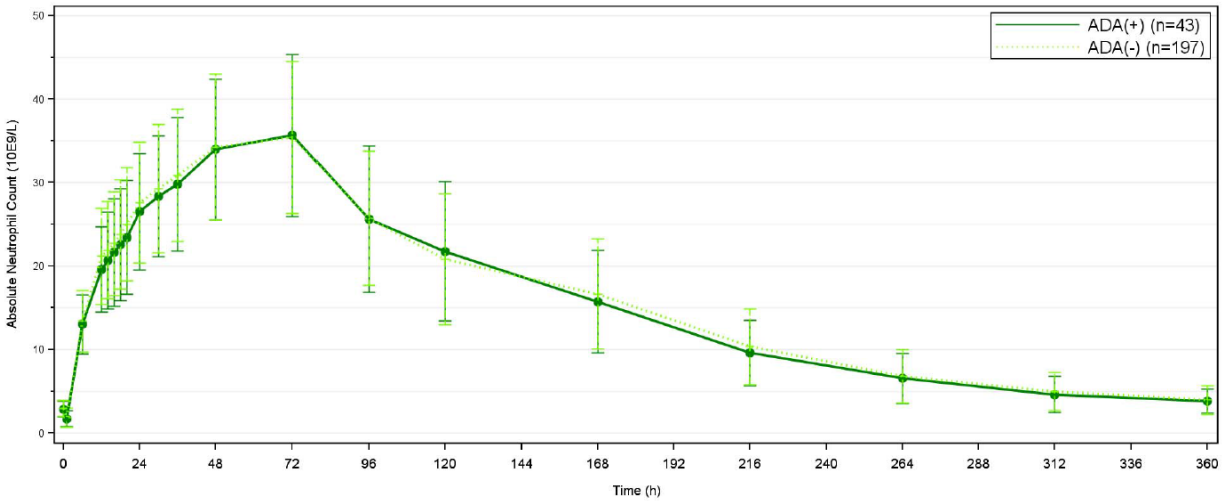
Figure 4: Arithmetic Mean study drug Serum Concentration-time Profile (Semilog Scale) by Treatment-induced Confirmed ADA Status after Treatment with MSB11455 (EMR200621-001)



Source: Appendix II Figure 2.9.

The mean ANC-time profiles according to the treatment-induced ADA status are displayed in Figure 5 for MSB11455. The ANC-time profiles of both ADA status groups were superimposable throughout the entire observation period. The ADA status did not impact PD parameters for MSB11455.

Figure 5: Mean (± SD) Absolute Neutrophil Count-time Profiles (Observed Values) by Treatment-induced Confirmed ADA Status after Treatment with MSB11455 (EMR200621-001)



Source: Appendix II Figure 2.11.

Authors:

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Primary Clinical Pharmacology reviewer

Anusha Ande
Secondary Clinical Pharmacology Reviewer

7. Statistical and Clinical Evaluation and Recommendations

7.1. Statistical and Clinical Executive Summary and Recommendation

This BLA submission contained a clinical PK/PD crossover study (EMR200621-001) and a randomized, parallel, immunogenicity study (EMR200621-003) to support licensure of MSB11455 as a biosimilar product to US-Neulasta.

The comparative safety evaluation of MSB11455 compared to US-Neulasta was assessed in two clinical studies in healthy adult subjects; EMR200621-001 and EMR200621-003. Most treatment emergent events (TEAEs) were mild to moderate in severity. There were no deaths related to study treatment in either of the clinical studies. Increased spleen size was noted for subjects receiving MSB11455, with six events classified as adverse events of special interest (AESIs) (2 subjects in study EMR200621-001 and 2 subjects in EMR200621-003). All events of increased spleen size resolved without intervention and were considered to be within the known safety profile of US-Neulasta. There were no events of adult respiratory distress syndrome, glomerulonephritis, capillary leak syndrome, leukocytosis with a white blood cell count ≥ 100 $x10^9$/L, or severe allergic reactions, which are rare but serious events known to be

associated with pegfilgrastim product treatment. The overall safety profile of MSB11455 is similar to US-Neulasta with bone pain and headache as the most frequently reported TEAEs. There were no apparent impact of immunogenicity on safety in both studies.

In summary, the safety results from the comparative clinical studies support demonstration of no clinically meaningful differences between MSB11455 and US-Neulasta.

7.1.1. Statistical and Clinical Residual Uncertainties Assessment

There are no residual uncertainties based on clinical safety evaluation.

7.2. Review of Comparative Clinical Studies with Statistical Endpoints

Study EMR200621-001

Title
"A randomized, double-blind, crossover study to compare the pharmacokinetic and pharmacodynamic bioequivalence of a single injection of MSB11455 and Neulasta in healthy adult subjects"

Study Initiation Date: August 2017

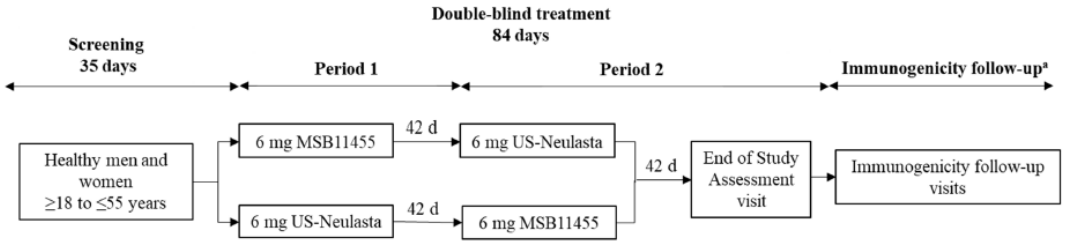
Study Completion Date: May 2018

Study Site: The study was conducted at 2 sites in Australia.

Study Design and Endpoints

This study was a randomized, double-blind, crossover, comparative, PK and PD study of subcutaneous injection of 6mg/0.6 mL; MSB11455 and US-Neulasta in healthy adult subjects. This study included a screening period of 35 days prior to the first study drug administration. Subjects were assigned using a 1:1 randomization to one of the 2 sequences: MSB11455/US-Neulasta or US-Neulasta/MSB11455. There were no stratification factors. Subjects received either MSB11455 or US-Neulasta on Day 1 of Period 1. After a washout period of 42 days, subjects who received MSB11455 in Period 1, received US-Neulasta on Day 1 of Period 2 and subjects who received US-Neulasta in Period 1, received MSB11455 on Day 1 of Period 2. In each study period, samples for PK and PD were collected. An overview of the study design is provided in the figure below.

Figure 1: Study EMR200621-001 Study Design



Source: MSB11455 Clinical overview

Objectives:

The primary objective of the study was to show equivalence between the PK/PD profile of MSB11455 and US-Neulasta.

Secondary objectives were to compare the PK/PD profile on other PK/PD parameters of MSB11455 compared with US-Neulasta and to assess and compare the safety, tolerability, and immunogenicity of MSB11455 and US-Neulasta.

Key Inclusion criteria

- Subjects had to voluntarily give written informed consent before any study-related activities were carried out.
- Healthy men and women 18 to 55 years of age (both inclusive).
- Body mass index (BMI) of 18 to 29.9 kg/m^2 (both inclusive) and body weight 50 to 100 kg.
- In generally, good health as determined by the Investigator.
- At Screening:
    - White blood cell (WBC) count within normal local laboratory reference and the ANC had to be in the range of 1.5 x 10^9/L to 8 x 10^9/L.
    - Renal function:
        - Creatinine clearance ≥ 80 mL/min (as measured by Cockcroft-Gault formula)
        - Serum/plasma creatinine ≤ 1.5 x upper limit of normal (ULN)
    - Hepatic function:
        - Total bilirubin, aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 1.5 x ULN, alkaline phosphatase (ALP) < 2 x ULN
    - All other laboratory parameters within the normal range of normal.
- Smokers who smoked < 10 cigarettes per day were allowed.
- Women must not have been pregnant. Women of childbearing potential had to have a negative serum pregnancy test at screening and negative urine pregnancy test at Day-1 before randomization. Women of childbearing potential had to agree to use a highly effective contraception.
- Women must not be lactating or breastfeeding.

- Mend had to be surgically sterile or had to agree to use a condom and to have their female partners use a highly effective form of contraception.

Key Exclusion criteria

- Prior exposure to any colony stimulating or growth factor.
- Prior exposure to therapeutic monoclonal antibodies, if administered in a study targeting the bone marrow or blood cells. Exposure to monoclonal antibodies not affecting the bone marrow or blood cells was allowed if discontinued > 3 months or 5 half-lives prior to Screening.
- Positive result for drugs of abuse at Screening.
- Smoking >10 cigarettes per day.
- Prior history of, or current alcohol abuse or excessive intake of alcohol.
- Donation of blood or plasma within 3 months prior to Screening.
- Stem cell or bone marrow donation within the previous 12 months prior to Screening.
- Clinical diagnosis of hypertension, significant hypercholesterolemia, or thyroid function test abnormalities.
- History of unexplained syncopal episode, vascular, sickle cell disorders, significant musculoskeletal or malignant diseases, hematologic disorder, or leukemia.
- Significant infection or known inflammatory process at Screening.
- A clinically significant history of atopic allergy, hypersensitivity, or allergic reactions.
- Positive test for hepatitis B surface antigen, hepatitis B core antibody, hepatitis C antibody, or HIV types 1 or 2.
- Subjects who had splenomegaly (spleen size > 13 cm in the craniocaudal dimension by ultrasound) at Screening.
- History of pulmonary infiltrate or pneumonia within 6 months prior to Screening.
- Subject had acute gastrointestinal symptoms at the time of screening.
- Any abnormality in 12-lead ECG that was clinically significant and/or suggestive of underlying cardia abnormality.
- Use of any prescribed or over-the-counter medication.
- A WBC count outside the local laboratory reference range and ANC < 1.5 x 10^9/L or > 8 x 10^9/L on Day -1 of Period 1.
- Legal incapacity or limited legal capacity.

Dosing: Each subject received a single subcutaneous (SC) injection of 6 mg/0.6 mL of the study drug (MSB11455 or US-Neulasta) on the morning of Day 1 in Period 1 and Period 2. In Period 1, MSB11455 or US-Neulasta was preferably injected into the back of the upper arm and the other treatment was injection into the back of the opposite arm in Period 2. The injection site was recorded in the CRF. The study drug was administered by an unblinded study site staff member.

Schedule of Events: The duration of the clinical part of the study was about 84 days. The study included a screening period of 35 days prior to dosing in Period 1. Physical examination, including vital signs, routine laboratory testing, 12-lead electrocardiograms (ECGs), adverse events (AEs), and concomitant medication data were assessed from the time of giving informed consent and throughout the study. An abdominal ultrasound was performed during Screening on Day -1 and the End of Study Assessment visit.

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Figure 2: Study EMR200621-001 Schedule of Assessments

Activity/ Assessment	Screening	Period 1 and Period 2														Early Termination[a]	EOS Assessment	Immunogenicity Follow-up[b]
		Resident				Nonresident												
Day	-35 to -2	-1	1	2	3	4	5	6	8	10	12	14	16	28 (±2)	42 (±2)[c]		3 months (84 days) after Period 1 Day 1 (±3 days)	Every 5 weeks (±7 days)
Informed consent	X																	
Eligibility	X	X													X[d]			
Demographics	X																	
Medical history	X																	
Serology[e, m]	X																	
Alcohol breath test, urine screen for and drugs of abuse[f]	X	X													X[d]			
Thyroid function test[m]	X																	
Pregnancy test[g]	X	X													X[d]	X	X	
Anti-PEG antibodies	X																	
Admission		X													X[d]			
Discharge					X[h]													
Randomization			X[i]															
Study drug administration			X															
Physical examination, height, weight, and BMI	X[j]	X[j]				X[j]									X[d,j]	X[j]	X[j]	X[j]
Spleen ultrasound		X[k]													X[d]	X[k]	X[k]	
Hematology[m]	X	X			X	X	X	X							X[d]	X	X[l]	X[l]

Activity/ Assessment	Screening	Period 1 and Period 2														Early Termination[a]	EOS Assessment	Immunogenicity Follow-up[b]
		Resident				Nonresident												
Day	-35 to -2	-1	1	2	3	4	5	6	8	10	12	14	16	28 (±2)	42 (±2)[c]		3 months (84 days) after Period 1 Day 1 (±3 days)	Every 5 weeks (±7 days)
Biochemistry[m]	X	X						X							X[d]	X	X	
FSH testing[n]	X																	
Urinalysis[m]	X	X													X[d]	X	X	
Coagulation[m]	X																	
Iron tests[m]	X																	
Vital signs[o]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[d]	X	X	X
12-lead ECG[p]	X	X			X										X[d]	X	X	
Injection site assessment by Investigator			X[q]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
PK and PD sampling[r]			X	X	X	X	X	X	X	X	X	X	X			X		
Immunogenicity blood sampling[s,b]	X[t]		X[u]										X			X	X	X
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Source: EMR 200621-001 Clinical Protocol

Statistical Methodologies

Subject Disposition

Two-hundred and ninety-four subjects were randomized to Study EMR200621-001 and 292 were dosed with either MSB11455 or US-Neulasta. Two-hundred and forty-four subjects completed both treatments. Forty-eight patients discontinued treatment and a total of twenty-

two patients discontinued the study. Reasons for study withdrawal included adverse events, withdrawal of consent, protocol non-compliance, and lost to follow-up of the subject.

Demographics and Baseline Characteristics

See Table 8 in Section 7.3.

Analysis of Primary Clinical Endpoint(s)

For analysis of primary endpoint, see sections 6 and 7.

Potential Effects of Missing Data

There was no concern for potential effects of missing data for this study.

Analysis of Secondary Clinical Endpoint(s)

For analysis of secondary endpoint, see sections 6 and 7.

Other Clinical Endpoints

Analysis of this study consisted of primary and secondary clinical endpoint analysis. There were no other clinical endpoints analyzed for this BLA submission.

Additional Analyses

There were no additional analyses for this BLA submission.

Study EMR200621-003

Title

"A randomized, double-blind, parallel group, controlled study to compare the immunogenicity and safety of MSb11455 and Neulasta in healthy adult subjects"

Study Initiation Date: August 2017

Study Completion Date: May 2018

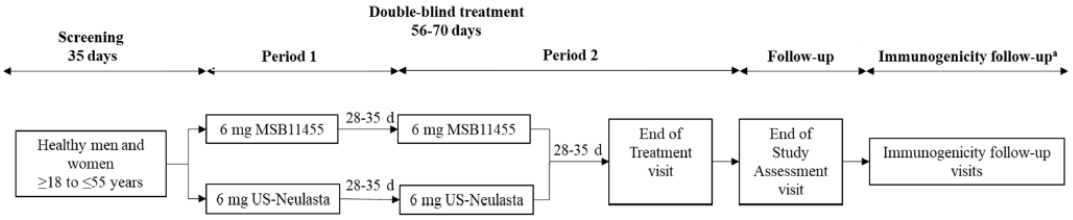
Study Site: The study was conducted at 2 sites in New Zealand.

Study Design and Endpoints

This study was a randomized, double-blind, parallel group, controlled study to compare the immunogenicity and safety of MSB11455 and US-Neulasta in healthy adult subjects.

This study included a screening period of 35 days prior to the first study drug administration. Subjects were randomized to one of 2 treatment arms, which was stratified based on site and anti-polyethylene glycol (PEG) antibody status at screening. Each subject received 2 study drug administrations of either MSB11455 or US-Neulasta. Subjects received either MSB11455 or US-Neulasta on Day 1 of Period 1. After a washout period of 28 to 35 days, subjects received the same study drug on Day 1 of Period 2. An overview of the study design is provided in the figure below.

Figure 3: Study EMR200621-003 Study Design



Source: MSB11455 Clinical overview

Objectives:

The primary objective of the study was to compare immunogenicity of MSB11455 and US-Neulasta.

Secondary objectives were to compare the safety and tolerability of MSB11455 and US-Neulasta and secondary immunogenicity objectives including anti-drug antibody (ADA) status.

Key Inclusion criteria

- Subjects had to voluntarily give written informed consent before any study-related activities were carried out.
- Healthy men and women 18 to 55 years of age (both inclusive).
- Body mass index (BMI) of 18 to 29.9 kg/m^2 (both inclusive) and body weight 50 to 100 kg.
- In generally, good health as determined by the Investigator.
- At Screening:
    - White blood cell (WBC) count within normal local laboratory reference and the ANC had to be in the range of 1.5 x 10^9/L to 8 x 10^9/L.
    - Renal function:
        - Creatinine clearance ≥ 80 mL/min (as measured by Cockcroft-Gault formula)
        - Serum/plasma creatinine ≤ 1.5 x upper limit of normal (ULN)
    - Hepatic function:
        - Total bilirubin, aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 1.5 x ULN, alkaline phosphatase (ALP) < 2 x ULN

    - All other laboratory parameters within the normal range of normal.
- Smokers who smoked < 10 cigarettes per day were allowed.
- Women must not have been pregnant. Women of childbearing potential had to have a negative serum pregnancy test at screening and negative urine pregnancy test at Day-1 before randomization. Women of childbearing potential had to agree to use a highly effective contraception.
- Women must not be lactating or breastfeeding.
- Mend had to be surgically sterile or had to agree to use a condom and to have their female partners use a highly effective form of contraception.

Key Exclusion criteria

- Prior exposure to any colony stimulating or growth factor.
- Prior exposure to therapeutic monoclonal antibodies, if administered in a study targeting the bone marrow or blood cells. Exposure to monoclonal antibodies not affecting the bone marrow or blood cells was allowed if discontinued > 3 months or 5 half-lives prior to Screening.
- Positive result for drugs of abuse at Screening.
- Smoking >10 cigarettes per day.
- Prior history of, or current alcohol abuse or excessive intake of alcohol.
- Donation of blood or plasma within 3 months prior to Screening.
- Stem cell or bone marrow donation within the previous 12 months prior to Screening.
- Clinical diagnosis of hypertension, significant hypercholesterolemia, or thyroid function test abnormalities.
- History of unexplained syncopal episode, vascular, sickle cell disorders, significant musculoskeletal or malignant diseases, hematologic disorder, or leukemia.
- Significant infection or known inflammatory process at Screening.
- A clinically significant history of atopic allergy, hypersensitivity, or allergic reactions.
- Positive test for hepatitis B surface antigen, hepatitis B core antibody, hepatitis C antibody, or HIV types 1 or 2.
- Subjects who had splenomegaly (spleen size > 13 cm in the craniocaudal dimension by ultrasound) at Screening.
- History of pulmonary infiltrate or pneumonia within 6 months prior to Screening.
- Subject had acute gastrointestinal symptoms at the time of screening.
- Any abnormality in 12-lead ECG that was clinically significant and/or suggestive of underlying cardia abnormality.
- Use of any prescribed or over-the-counter medication.
- A WBC count outside the local laboratory reference range and ANC < 1.5 x 10^9/L or > 8 x 10^9/L on Day -1 of Period 1.
- Legal incapacity or limited legal capacity.

Dosing: Each subject received a single subcutaneous (SC) injection of 6 mg/0.6 mL of the study drug (MSB11455 or US-Neulasta) on the morning of Day 1 in each of the 2 periods. In Period 1, MSB11455 or US-Neulasta were preferably injected into the back of the upper arm and the other treatment was injection into the back of the opposite arm in Period 2. The injection site was recorded in the CRF. The study drug was administered by an unblinded study site staff member.

Schedule of Events: The duration of the clinical part of the study was about 84 days. The study included a screening period of 35 days prior to dosing in Period 1. Physical examination, including vital signs, routine laboratory testing, 12-lead electrocardiograms (ECGs), adverse events (AEs), and concomitant medication data were assessed from the time of giving informed consent and throughout the study. An abdominal ultrasound was performed during Screening on Day -1 and the End of Study Assessment visit. Subjects with confirmed positive for treatment-induced antidrug antibodies (ADA) by the End of Study Assessments Visit were followed until 2 consecutive samples returned to baseline. Follow-up subjects were scheduled for assessments every 5 weeks.

Figure 4: Study EMR200621-003 Schedule of Assessments

Activity/ Assessment	Screening	Period 1 and Period 2										Period 1	Period 2	Early Termination [e]	EOS Assessments	Immunogenicity Follow-up [a]
		Resident				Nonresident									3 months (84 days) after Day 1 Period 1 (± 3 days)	Every 5 weeks (± 7 days)
Day	-35 to -2	-1 [b]	1	2	3	4	5	7	8	10 [c]	13	28 [b] (+7)[d]	EOT 28 (+7)			
Urinalysis [m, p]	X	X											X	X	X	
Coagulation [m]	X														X	
Iron tests [m]	X															
Vital signs [q]	X	X	X	X	X	X	X	X	X		X		X	X	X	X
12-lead ECG [r]	X	X			X						X		X	X	X	
Injection site assessment by the Investigator			X [s]	X	X	X	X	X	X		X	X	X	X		
PK and PD blood sampling [t]			X	X	X	X		X			X					
Immunogenicity blood sampling [a, u]			X [v]								X		X	X	X	X
AEs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Source: EMR 200621-003 Clinical Protocol

Statistical Methodologies

The primary endpoint of this immunogenicy study is confirmed treatment-induced positive ADA status to pegfilgrastim from predose on Day 1 of Period 1 up to the End of Study Assessment Visit (3 months [84 days] ± 3 days after Day 1 of Period 1). The primary analysis consisted of the estimation (along with the corresponding exact 95% 1-sided adjusted confidence interval [CI]) of the difference in treatment-induced ADA-confirmed positive rates between MSB11455 and US-Neulasta, along with testing the null hypothesis H0 that the confirmed treatment-induced

ADA positive rate of MSB11455 is at least 10% higher than the confirmed treatment-induced ADA positive rate in the Neulasta arm.

Sample Size

The study was planned to enroll a maximum of 404 subjects but the study was stopped at interim with 336 subjects (168 per arm) completed the study, which constitutes 83% information fraction.

Design Paramerters

Study EMR200621-003 used a non-inferiority design with the following parameters:

• 90% power to declare MSB11455 is no worse than US-Neulasta (either at interim or final) with respect to a non-inferiority margin.

• One-sided type I error was pre-set at 5%.

• The background ADA rate for Neulasta was assumed to be 12% (π_0 = 0.12). The justification for the background rate of 0.12 was based on the upper bound of the 95% confidence interval of Neulasta's ADA rate as estimated in Study PG-01-003, among subjects receiving at least 1 dose of the study drug.

• Not being worse was defined by $\pi_1 - \pi_0$ not exceeding a non-inferiority margin of 10%.

The null and alternative hypotheses are H_0: $\pi_1 - \pi_0 \geq 0.10$ and H_1: $\pi_1 - \pi_0 = 0 < 0.10$

Statistical Methods

Statistical analyses of immunogenicity and safety data allowed a comparison of the immunogenicity and safety profile of MSB11455 relative to US-Neulasta.

A group sequential design with an unblinded interim analysis was implemented. The unblinded interim analysis was for futility (nonbinding) and the non-inferiority was taken place when exactly 336 subjects were randomized (corresponding to 83% of planned 404 subjects) and had completed the End of Study Assessments Visit/Early Termination Visit.The last subject last visit for the unblinded interim cut-off was 03 May 2018.

The primary analysis of the primary endpoint, treatment-induced ADA positive status up to the End of Study Assessments Visit/Early Termination Visit, was performed on the Intent-to-treat (ITT) Analysis Set and was repeated based on the Per Protocol (PP) Analysis Set. It consisted of the estimation (along with the corresponding exact 95% 1-sided adjusted confidence interval [CI]) of the difference in treatment-induced ADA-confirmed positive rates between MSB11455 and US-Neulasta, along with testing the null hypothesis *H_0* that the confirmed treatment-induced ADA positive rate of MSB11455 is at least 10% higher than the confirmed treatment-induced ADA positive rate in the US-Neulasta arm. The Blackwelder statistic was used to test the hypotheses and was compared to the predefined stopping boundaries. The Blackwelder statistics:

$$Z=[(\hat{\pi}_{MSB11455}- \hat{\pi}_{Neulasta})- 0.1]/\text{standard error } (\hat{\pi}_{MSB11455}- \hat{\pi}_{Neulasta})$$

Where $\hat{\pi}_{MSB11455}$ and $\hat{\pi}_{Neulasta}$ denote respectively the estimates of π_{MSB11455} and π_{Neulasta} based on n_{MSB11455} and n_{Neulasta} and standard error of $(\hat{\pi}_{MSB11455}-\hat{\pi}_{Neulasta}) =$

$$\sqrt{\{(\hat{\pi}_{MSB11455}(1-\hat{\pi}_{MSB11455})/n_{\text{MSB}})+(\hat{\pi}_{Neulasta}(1-\hat{\pi}_{Neulasta})/n_{\text{Neulasta}})\}}$$

As the interim analysis was performed with exactly 168 subjects per treatment arm, the boundary for claiming non-inferiority was -2.2 and for futility was − 1.1.

Applicant's Immunogenicity Results:

The Applicant demonstrated non-inferiority of MSB11455 over US-Neulasta for the confirmed treatment-induced ADA positive status based on the Intent to treat (ITT) Analysis Set. They had Blackwalder Z statistic − 3.356 which was less than − 2.2, and the upper limit of the exact 1-sided adjusted 95% CI for the treatment difference in confirmed treatment-induced ADA positive status 6.25%, which was below the predefined non-inferiority margin of 10%. The primary analysis results were confirmed with the sensitivity analysis performed on the Per Protocol (PP) Analysis Set (Z = − 3.296; upper limit of exact 1-sided adjusted 95% CI = 6.12%). The Applicant's results supported non-inferior immunogenicity of MSB11455 to US-Neulasta.

FDA Statistical Reviewer's Analysis Results:

The Applicant used the upper limit of one-sided 95% CI of the difference for Treatment-induced ADA-confirmed positive rate between MSB11455 and US-Neulasta arm to compare with the 10% NI margin. Concerning that the study was terminated earlier than the planned study enrollment, the statistical review team asked the Applicant to clarify the alpha they used in the ASA analysis. The Applicant's response was received on 8/26/2020. Since the study had been stopped at the 83% information fraction of the planned study completion, the one-sided 95% CI used in The Applicant's analysis, which did not adjust the alpha spending at the interim analysis, was determined not to be appropriate. Using the O'Brien-Fleming alpha spending function with 83% information fraction, the FDA reviewer determined that the non-inferiority should be assessed by the one-sided upper limit of 96.8% CI.

Using the same calculations as described in Jennison and Turnbull (Jennison, 2000) and The Applicant's R code, the FDA reviewer confirmed that The Applicant's upper limit of the one-sided 95% CI, was 0.0625. It was also noted that The Applicant calculated this upper limit of one-sided 95% CI (0.0625) by assuming the true rate of 3% in US-Neulasta arm. By assuming a true rate of 0% in Neulata arm and using the exact test in SAS, the FDA statistical reviewer obtained the one-sided upper limit of 96.8% CI 0.0978. Because 0.0978 is still less than the pre-specified NI margin of 10%, the non-inferiority of MSB11455 to Neulasta still holds.

Subject Disposition

Three-hundred and thirty-six subjects were randomized to Study EMR 200621-003 and 56 were dosed with either MSB11455 or US-Neulasta. Two-hundred and eighty subjects completed both treatments. Fifty-six patients discontinued treatment and a total of ten patients discontinued the study. Reasons for study withdrawal included withdrawal of consent and lost to follow-up of the subject.

Demographics and Baseline Characteristics

See Table 9 in Section 7.3.

Analysis of Primary Clinical Endpoint(s)

For analysis of primary endpoint, see Section 6

Potential Effects of Missing Data

There was no concern for potential effects of missing data for this study.

Analysis of Secondary Clinical Endpoint(s)

For analysis of secondary endpoint, see section 6 and 7.

Other Clinical Endpoints

Analysis of this study consisted of primary and secondary clinical endpoint analysis. There were no other clinical endpoints analyzed for this BLA submission.

Additional Analyses

There were no additional analyses for this BLA submission.

7.3. Review of Safety Data

7.3.1. Methods

The clinical review of safety for this BLA was based on the safety data from 2 healthy subject studies comparing MSB11455 to US-Neulasta. The results are described in the sections below.

The key materials used for the review of MSB11455 include:

- BLA datasets (raw and derived)
- Clinical study reports
- Relevant published literature on US-Neulasta
- Relevant prior regulatory history for MSB11455
- Relevant applicant submissions in response to information request from review team
- Major safety analyses were reproduced
- Existing labels

Analysis by the clinical reviewer were performed using JMP 14 (SAS, Inc. Cary. N.C. USA). MedDRA Adverse Events Diagnostic (MAED) (Clinical Trials & Surveys Corporation, Owings Mills, MD, USA) was used to assess for safety signals.

Clinical Studies Used to Evaluate Safety

Safety data was available from studies EMR200621-001 and Study EMR200621-003. This included an adult healthy volunteer population. All patients who received a dose of MSB11455 or US-Neulasta were included. There were no major concerns regarding data integrity. The overall quality was acceptable for safety evaluation.

Population Demographics

Study EMR200621-001

A total of 294 healthy subjects were randomized to 1 of 2 treatment sequences. All 292 subjects received at least one dose of study medications (MSB11455 or US-Neulasta) and were included in the safety analysis set. The study population was 41.1 % male and 58.9% female. The median age was 27 years (range, 18-56 years). Two-hundred and forty (82.2%) of subjects were White. The baseline demographic information for subjects enrolled in this study is provided in the table below.

Table 5: EMR200621-001 Demographics

	Statistics	Study EMR200621-001 (N=292)
Age (Years)	Median	27
	Range	18-56
Gender	Male, n (%)	120 (41.1)
	Female, n (%)	172 (58.9)
Race	White, n (%)	240 (82.2)
	Black or African American, n (%)	4 (1.4)
	Asian	34 (11.6)
	Native Hawaiian or Other Pacific Islander	4 (1.4)
	American Indian or Alaska Native	2 (0.7)
	Other	8 (2.7)
Ethnicity	Hispanic	34 (11.6)
	Not Hispanic	258 (88.4)
Height	Mean ± SD (cm)	171 ± 8.6
Weight	Mean ± SD (kg)	70.2 ± 10.8
BMI	Mean ± SD (kg/m^2)	23.9 ± 3

Source: FDA Analysis

Study EMR200621-003

A total of 336 healthy subjects were randomized to either MSB11455 or US-Neulasta. All 336 subjects received at least one dose of study medications (MSB11455 or US-Neulasta) and were included in the safety analysis set. The study population was 56.8 % male and 43.2% female. The median age was 25 years (range, 18-55 years). Two-hundred and fifty-one (74.7%) of subjects were White. An overview of the demographic information for subjects enrolled in this study is provided in the table below.

Table 6: EMR200621-003 Demographics

	Statistics	Study EMR200621-003 (N=336)
Age (Years)	Median	25
	Range	18-55
Gender	Male, n (%)	191 (56.8)
	Female, n (%)	145 (43.2)
Race	White, n (%)	251 (74.7)
	Black or African American, n (%)	5 (1.5)
	Asian	29 (8.6)
	Native Hawaiian or Other Pacific Islander	7 (2.1)
	American Indian or Alaska Native	1 (0.3)
	Other	43 (12.8)
Ethnicity	Hispanic	24 (7.1)
	Not Hispanic	312 (92.9)
Height	Mean ± SD (cm)	173 ± 8.7
Weight	Mean ± SD (kg)	72.4 ± 11.1
BMI	Mean ± SD (kg/m^2)	24.2 ± 2.8

Source: FDA Analysis

Clinical Reviewer Comment: There were no clinically significant differences in the baseline demographic characteristics.

Categorization of Adverse Events

The ADAE data files for each of the 2 studies were used for the safety review. All adverse events were coded and classified according to the Medical Dictionary for Regulatory Activities (MedDRA) version 21.0 and higher. Only AEs occurring after start of treatment were included in the ADAE data files.

Adverse event grading system used by The Applicant was according to the National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE).

Safety Analyses

Safety analysis was completed for each individual study (EMR200621-001 and EMR200621-003). Studies were not combined for analysis.

Summary tables of TEAEs were presented per preferred term based on the MedDRA version 21.1 terminology list for study EMR200621-001 and the MedDRA version 21.0 terminology list for Study EMR200621-003.

Summary statistics of clinical laboratory data and vital signs were generated by treatment group.

Adverse events of special interest (AESI)

Adverse events of special interest were chosen based on serious events known to be associated with pegfilgrastim product use. The AESIs chosen were based on the "Warning and Precautions" in the USPI of US-Neulasta and considered by The Applicant to be relevant for the study population. The below events were defined as AESIs.

- Acute hypersensitivity defined as signs of symptoms of hypersensitivity in the opinion of the Investigator occurring within 48 hours after administration of the Investigational Product.
- Absolute neutrophil count (ANC) ≥ 75 x 10^9/L (or white blood cell count (WBC) ≥ 90 x 10^9/L), or signs and symptoms of hyperviscosity syndrome.
- Clinically significant increase in spleen size.

Exposure

Study EMR200621-001:

- In study EMR200621-001, 146 subjects in each treatment sequence were exposed to atleast one 6 mg SC injection of US-Neulasta or MSB11455. One hundred and twenty subjects in the MSB11455/US-Neulasta treatment sequence and 124 subjects in the US-Neulasta/MSB11455 treatment sequence received both injections. The remaining subjects discontinued treatment after the first injection of the assigned treatment sequence.

Table 7: EMR200621-001 Summary of exposure to study drug

	Cumulative Dose	MSB11455	US-Neulasta
Nuber of subjects (Period 1)	6 mg	146	146
Number of subjects (Period 2)	6 mg	124	120

Source: FDA Analysis

Study EMR200621-003:

- In study EMR200621-003, 168 healthy subjects received at least one dose of US-Neulasta or MSB11455. 140 subjects in each treatment group were exposed to 2 doses (full or partial). One subject received a partial injection in the MSB11455 treatment arm of Period 1 and one subject received a partial injection in the US-Neulasta treatment arm of Period 2.

Table 8: EMR200621-003 Summary of exposure to study drug

	Cumulative Dose	MSB11455	US-Neulasta
Number of subjects (1 dose)	6 mg	168	168
Number of subjects (2 doses)	12 mg	140	140

Source: FDA Analysis Relevant Characteristics of the Population Evaluated for Safety

Relevant Characteristics of the Population Evaluated for Safety

Studies for MSB11455 included only healthy adult volunteer subjects. All subjects who received any study treatment were included in the safety analysis.

Deaths

There were no deaths reported in study EMR200621-001 or in study EMR200621-003.

Treatment Emergent Adverse Events

Study EMR200621-001

In study EMR200621-001, approximately 93% of treated subjects who received MSB11455 and 97% of subjects who received US-Neulasta experienced at least one TEAE. The majority of TEAEs were categorized as mild or moderate in severity. Nine subjects in the MSB11455 group and 8 subjects in the US-Neulasta group experienced a Grade 4 TEAE of neutropenia. One subject in the MSB11455 goup experienced a Grade 4 TEAE of thrombocytopenia. One subject experienced an SAE, an allergy to arthropod sting after receiving MSB11455. Two subjects experienced an SAE who received US-Neulasta. The first SAE was pericarditis, requiring hospitalization and resolved within 5 days. The second SAE was a stress fracture in the setting of excessive exercise, osteopenia and possible osteoporosis seen on bone scans. The AEs were similar between MSB11455 and US-Neulasta.

Table 9: Study EMR200621-001 TEAEs by preferred term in decreased order of incidence

Preferred Term	MSB11455	US-Neulasta

	N= 270 n (%)	N=266 n (%)
Headache	151 (55.9)	150 (56.4)
Musculoskeletal Pain	133 (49.3)	114 (42.9)
Bone Pain	67 (24.8)	70 (26.3)
Back Pain	45 (16.7)	55 (20.7)
Upper Respiratory Tract Infection	32 (11.9)	20 (7.5)
Nausea	30 (11.1)	31 (11.7)
Injection Site Pain	28 (10.4)	25 (9.4)
Myalgia	27 (10)	23 (8.6)
Neutropenia	24 (8.9)	22 (8.3)
Abdominal Pain	23 (8.5)	21 (7.9)
Palpitations	23 (8.5)	14 (5.3)
Abdominal Pain Upper	13 (4.8)	19 (7.1)
Injection Site Bruising	17 (6.3)	18 (6.8)
Leukocytosis	13 (4.8)	14 (5.3)
Chest Pain	13 (4.8)	6 (2.3)
Fatigue	9 (3.3)	13 (4.9)
Arthralgia	8 (3)	13 (4.9)
Malaise	12 (4.4)	2 (0.08)

Source: FDA Analysis

Clinical Reviewer Comment: In study EMR200621-001, headache and musculoskeletal pain were the most common TEAEs in both treatment groups. The incidence of bone pain was slightly lower after subjects received MSB11455 compared to US-Neulasta. One subject had an SAE after receiving MSB11455, which is unlikely related to study drug. Two subjects experienced an SAE after receiving US-Neulasta including pericarditis and stress fracture. The pericarditis event is most likely attributable to US-Neulasta in the setting of a previously healthy, young subject. Overall, the AEs were similar between MSB11455 and US-Neulasta, and the minor differences in AEs and SAEs noted do not preclude a demonstration of no clinically meaningful differences between MSB11455 and US-Neulasta.

Study EMR200621-003

In study EMR200621-003, approximately 94% of treated subjects experienced at least one TEAE. The majority of TEAEs were categorized as mild or moderate in severity. The highest toxicity grade reported was Grade 3. One subject in the MSB11455 experienced a grade 3 TEAE of presyncope. In the US-Neulasta arm, one subjects had diarrhea (Grade 3), increased liver function tests (Grade 3), abdominal pain (Grade 3), and vomiting (Grade 3) and 1 subject had lower abdominal pain (Grade 3). One subject experienced an SAE, acute febrile neutrophilic dermatosis (Sweet Syndrome) after receiving MSB11455, which resolved after receiving a steroid taper course as an outpatient. Two subjects experienced an SAE who received US-Neulasta. The first SAE was spontaneous abortion of the subject's pregnant partner. The second

SAE was abdominal pain in the setting of chronic abdominal pain requiring evaluation in the emergency department. The AEs were similar between MSB11455 and US-Neulasta.

Table 10: Study EMR200621-003 TEAEs by preferred term in decreased order of incidence

Preferred Term	MSB11455 N= 168 n (%)	US-Neulasta N=168 n (%)
Bone Pain	116 (69.q)	107 (63.7)
Headache	105 (62.5)	120 (71.4)
Spinal Pain	67 (39.9)	68 (40.5)
Nausea	32 (19)	19 (11.3)
Upper Respiratory Tract Infection	32 (19)	20 (11.9)
White Blood Cell Count Increased	23 (13.7)	27 (16.1)
Myalgia	19 (11.3)	17 (10.1)
Vomiting	18 (10.7)	9 (5.4)
Injection Site Bruising	12 (7.1)	10 (6)
Musculoskeletal Chest Pain	12 (7.1)	17 (10.1)
Abdominal Pain	9 (5.4)	15 (8.9)
Diarrhea	8 (4.8)	15 (8.9)
Oropharyngeal Pain	12 (7.1)	14 (8.3)
Injection Site Bruising	12 (7.1)	10 (6)
Dizziness	11 (6.5)	11 (6.5)
Fatigue	7 (4.2)	11 (6.5)
Back Pain	8 (4.8)	9 (5.4)

Source: FDA Analysis

Clinical Reviewer Comment: In study EMR200621-003, bone pain, headache, and spinal pain were the most common TEAEs in both treatment groups. The incidence of headache was slightly lower after subjects received MSB11455 compared to US-Neulasta. One subject had an SAE of Sweet Syndrome after receiving MSB11455, which is a known adverse reaction of pegfilgrastim, as noted in (b) (4) *USPI. Two subjects experienced an SAE after receiving US-Neulasta, including spontaneous abortion of the subject's pregnant partner and abdominal pain. The spontaneous abortion event with partner reporting non-compliance with contraception restriction is most likely attributable to US-Neulasta. The SAE of abdominal pain occurred in a patient with known history of chronic abdominal pain with normal radiographic films. Us-Neulasta cannot be excluded as a possible etiology for the cause of abdominal pain. Overall, the AEs were similar between the two groups. There were no notable differences in the type or incidence of TEAEs between the two treatments in any of the studies. TEAE severities were mostly mild to moderate with MSB11455 and US-Neulasta and without*

meaningful differences. The SAEs noted do not preclude a demonstration of no clinically meaningful differences between MSB11455 and US-Neulasta.

Dropouts and/or Discontinuations

Study EMR200621-001

In study EMR200621-001, after exposure to MSB11455, 3% of subjects experienced a TEAE leading to study withdrawal. After exposure to US-Neulasta, 2.3% of subjects experienced a TEAE leading to study withdrawal.

Table 11: Study EMR200621-001 Adverse events resulting in treatment discontinuation by preferred term

Preferred Term	MSB11455 N= 270 n (%)	US-Neulasta N= 266 n (%)
Splenomegaly	3 (1.1)	0 (0)
Transaminases Increased	1 (0.3)	2 (0.8)
Decreased Platelet Count	1 (0.3)	0 (0)
Leukocytosis	0 (0)	1 (0.4)
Lower Back Soft Tissue Swelling	1 (0.3)	0 (0)
Abdominal Pain	1 (0.3)	0 (0)
Worsening Eczema	0 (0)	1 (0.4)
Shortness of Breath	0 (0)	1 (0.4)
Lower Respiratory Tract Infection	1 (0.3)	0 (0)
Angioedema Due to Dust Allergy	1 (0.3)	0 (0)
Benign Positional Vertigo	0 (0)	1 (0.4)

Source: FDA Analysis

Three subjects in the MSB11455 arm developed increased spleen size, which was a predefined study withdrawal criteria. Two patients experienced an increase in transaminitis in the US-Neulasta arm and one patient in the MSB11455 arm. All events were mild to moderate in severity, two subjects experienced Grade 3 elevated transaminitis and one subject experienced Grade 3 benign positional vertigo.

Study EMR200621-003

In study EMR200621-003, after exposure to MSB11455, 14.9% of subjects experienced a TEAE leading to study withdrawal. After exposure to US-Neulasta, 14.9% of subjects experienced a TEAE leading to study withdrawal.

Table 12: Study EMR200621-003 Adverse events resulting in treatment discontinuation by preferred term

Preferred Term	MSB11455 N= 168 n (%)	US-Neulasta N= 168 n (%)
Acute Febrile Neutrophilic Dermatosis	1 (0.6)	0 (0)
White Blood Cell Count Increased	16 (9.5)	20 (11.9)
Increased Alanine Aminotransferase	1 (0.6)	0 (0)
Generalized Rash	1 (0.6)	0 (0)
Gout Left Metatarsophalangeal Joint	1 (0.6)	0 (0)
Acute Hypersensitivity Reaction	0 (0)	2 (1.2)
Rash, Maculopapular	1 (0.6)	0 (0)
Injection Site Pruritus	1 (0.6)	0 (0)
Injection Site Erythema	2 (1.2)	0 (0)
Injection Site Swelling	1 (0.6)	0 (0)
Drug-Related Rash	0 (0)	1 (0.6)
Rash	0 (0)	1 (0.6)
Blepharitis	0 (0)	1 (0.6)

Source: FDA Analysis

The most common TEAE leading to treatment discontinuation was white blood cell count (WBC) increased after receiving both MSB11455 and US-Neulasta. The number of subjects who discontinued treatment due to WBC increased were similar between treatment groups. Hypersensitivity accounted for the second most common TEAE leading to treatment discontinuation for both treatment groups including Acute Febrile Neutrophilic Dermatosis or rash. All events were mild to moderate in severity. No subjects experienced a Grade 4 TEAE.

Clinical Reviewer Comment: There were no notable differences in AEs resulting in discontinuation of treatment with MSB11455 and US-Neulasta. Moreover, the small differences in adverse events resulting in treatment discontinuation and inconsistent trends are likely due to chance alone and do not indicate meaningful differences between MSB11455 and US-Neulasta. The increased spleen size, White Blood Cell Count increase, and hypersensitivity reactions noted are within the known safety profile of pegfilgrastim as noted in the USPI. See the Product Specific Safety Concerns section for further discussion regarding Adverse Events of Special Interest (AESI) including splenomegaly, hypersensitivity reactions, and White Blood Cell Count increased.

Product Specific Safety Concerns

Adverse events of special interest were assessed as described in the safety analysis.

Adverse events of special interest were chosen based on serious events known to be associated with pegfilgrastim product use. In both studies, there were no events of splenic rupture, ARDS,

glomerulonephritis, leukocytosis (WBC > 100 x 10^9/L), sickle cell crisis, aortitis, capillary leak syndrome, or severe allergic reaction.

Table 13: Adverse events of special interest

	Study EMR200621-001		Study EMR200621-003	
	MSB11455	US-Neulasta	MSB11455	US-Neulasta
AESI	N= 270 n (%)	N= 266 n (%)	N= 168 n (%)	N= 168 n (%)
Acute Hypersensitivity	0 (0)	0 (0)	0 (0)	3 (1.8)
ANC ≥ 75 x 10^9/L or WBC ≥ 90 x 10^9/L	0 (0)	0 (0)	0 (0)	0 (0)
Increase in Spleen Size	2 (0.7)	0 (0)	2 (1.2)	0 (0)

Acute Hypersensitivity

Acute hypersensitivity was defined by The Applicant as signs or symptoms of hypersensitivity in the opinion of the Investigator occurring within 48 hours after administration of investigational product.

Study EMR200621-001

In study EMR 200621-001, there were no subjects with acute hypersensitivity.

Study EMR200621-003

In study EMR 200621-003, there were no subjects in the MSB11455 group with acute hypersensitivity. There were three subjects in the US-Neulasta group with AESIs of acute hypersensitivity. Two subjects (1.2%) had an event of drug hypersensitivity and 1 subject (0.6%) had an event of drug eruption. All AEs were mild to moderate.

ANC ≥ 75 x 10^9/L (or WBC ≥ 90 x 10^9/L) or signs or symptoms of hyperviscosity syndrome

In the initial clinical study protocol for both studies, the threshold for this AESI was defined as WBC ≥ 50 x 10^9/L. The clinical study protocols were amended in Protocol Amendment 1 to an ANC ≥ 75 x 10^9/L (or WBC ≥ 90 x 10^9/L) after a similar proportion of subjects in both treatment group of study EMR200621-003 reported this AESI resulting in study withdrawal. The justification provided for the protocol amendment was that the initial value was chosen based on the Neulasta Summary of Product Characteristics. The Applicant stated that an increase in WBC count is an expected pharmacological effect of pegfilgrastim and this effect may be even more pronounced in healthy subjects compared with patients who receive myelosuppressive cancer drugs or radiation therapies. Therefore, the value initially selected for withdrawal was relevant for immunocompromised patients treated with cytotoxic chemotherapy; however, was too low for healthy subjects with intact hematopoiesis potency stimulated by granulocyte

colony-stimulating factor (G-CSF). Per The Applicant, the value was amended to better reflect the hematopoietic potency of healthy subjects.

Study EMR200621-001

In study EMR200621-001, there were no AESI's of ANC ≥ 75 x 10^9/L (or WBC ≥ 90 x 10^9/L) or signs or symptoms of hyperviscosity syndrome. Of note, this study was initiated after Study EMR200621-003, which The Applicant uses as justification to support why there were fewer subjects with events of WBC Count Increased compared with study EMR200621-003. After Protocol Amendment 1 increased the ANC and WBC count threshold for withdrawal criterion and for definition of AEIs, no additional AESIs were reported.

Study EMR200621-003

Prior to study amendment in study EMR200621-003, 23 subjects (13.7%) receiving MSB11455 and 27 subjects (16.1%) receiving US-Neulasta reported this AESI. Of those subjects with a WBC Count Increased event, 9.5% of subjects receiving MSB11455 and 11.9% of subjects receiving US-Neulasta were withdrawn from the study due to this AESI. After Protocol Amendment 1 increased the ANC and WBC count threshold for withdrawal criterion and for definition of AEIs, no additional AESIs were reported. All events were self-limiting and returned spontaneously to normal levels within 10 days. All events were graded as mild.

Increase in spleen size

In both studies, an enlarged spleen was defined as a spleen >13 cm in the craniocaudal dimension by ultrasound. Spleen ultrasounds were performed per protocol on Day 1, at End of Treatment visits, and as needed for clinical concern for enlarged spleen on physical examination.

Study EMR200621-001

In study EMR 200621-001, there were two cases of splenomegaly on physical examination reported as AESIs, both in patients who received MSB11455 and subsequently confirmed on spleen ultrasound. One subject was noted to have a palpable spleen on examination (Grade 2) 3 days after MSB11455 administration, with confirmed spleen size of 14.7 cm on ultrasound compared to baseline spleen size of 12.3 cm. Splenomegaly improved on ultrasound 6 weeks after administration and resolved without intervention on ultrasound 3 months after drug administration. The subject withdrew from study prior to second dose of study drug. The second AESI was reported 4 days after administration of MSB11455, in setting of symptoms of abdominal pain and nausea. Spleen ultrasound revealed a spleen size of 13.1 cm (Grade 1), with a normal spleen size on ultrasound 7 days after drug administration. For reference, the subject's baseline spleen size on ultrasound was 10.3 cm. The subject withdrew from the study. There were no AESIs of increased spleen size in subjects who received US-Neulasta.

Study EMR200621-003

In study EMR200621-003, there were two cases of splenomegaly on physical examination considered AESIs in subjects who received MSB11455. The first subject's baseline spleen size was 10.7 cm on ultrasound. Spleen size was confirmed to be 14.6 cm on ultrasound (Grade 2), 9 days after second dose of MSB11455 in the setting of left flank pain and tonsillitis, which was treated with amoxicillin. Splenomegaly resolved 32 days after drug administration. The second subject developed left upper quadrant abdominal pain with nausea and vomiting 4 days after the second dose of MSB11455 with splenomegaly on physical exam (Grade 1). Ultrasound of the spleen was 12.9 cm, which did not meet the study's definition of increased spleen size. This subject's spleen size decreased to 11.5 cm on ultrasound 28 days after the second dose administration of MSB11455. There were no AESIs of increased spleen size in subjects who received US-Neulasta.

Clinical Reviewer Comment: The hypersensitivity reaction events were only in subjects who received US-Neulasta. Hypersensitivity/allergic reaction is a known adverse reaction of pegfilgrastim highlighted in Section 6 Post Marketing Experience of the USPI. No hypersensitivity AESIs occurred in subjects who received MSB11455 in either trial.

There were no AESIs of White Blood Cell Count Increased reported in study EMR200621-001. In Study EMR200621-003, the proportion of subjects with AESIs of White Blood Cell Count Increased (≥ 50 x 10^9/L*) was similar (13.7% in MSB11455 arm and 16.1% in US-Neulasta arm), prior to the protocol amendment to the WBC Count Increased threshold definition. There were no AESIs of WBC Count Increased reported for either study after the threshold was modified to ANC ≥ 75 x 10^9/L (or WBC ≥ 90 x 10^9/L). Per the Warnings and Precautions Section of the US-Neulasta USPI, a WBC Count of 100 x 10^9/L or greater has been observed in patients receiving pegfilgrastim. Therefore, the WBC count increased observed are an expected reaction to pegfilgrastim use.*

There were 4 AESIs of increased spleen size reported; 2 subjects in study EMR200621-001 and 2 subjects in EMR200621-003. All 4 AESIs were in subjects who received MSB1455. All events resolved without intervention. Despite all events occurring in subjects who received MSB11455, per the USPI for US-Neulasta, splenic enlargement is a known adverse reaction and importantly, no subjects experienced splenic rupture. Additionally, there is the potential that the spleen ultrasounds routinely performed in both trials were able to detect evidence of splenic enlargement with greater accuracy than on physical exam alone. Therefore, these events appear to be within the known safety profile of pegfilgrastim.

7.3.2. Additional Safety Evaluations

Laboratory Findings

Study EMR200621-001

Hematology:

In study EMR200621-001, no meaningful difference in hematology parameters were observed across the two arms. The median values of neutrophils and leukocytes increased after administration of each study drug with a peak at Day 3, and returning to baseline by the End of Study Assessment Visit. No subjects had an elevated leukocyte count of ≥ 100 $x10^9$/L during the study. White Blood Cell Count Increased was an AESI discussed in the Product Specific Safety Concerns section.

Table 14: Study EMR200621-001 Summary of Hematology Laboratory Tests

		MSB11455 N= 270	US-Neulasta N= 266
Neutrophils ($x10^9$/L)	Baseline	3.7	3.6
	Day 3	33.7	33.4
	Day 42	3.6	3.7
	End of Assessment Visit	2.9	3.1
	Follow-Up Visit 1	2.7	3.1
Leukocytes ($x10^9$/L)	Baseline	6.4	6.4
	Day 3	38.9	28.5
	Day 42	6.1	6.2
	End of Assessment Visit	5.1	5.5
	Follow-Up Visit 1	5.3	5.5
Hemoglobin (g/L)	Baseline	136	136
	Day 3	135	135
	Day 42	133	136
	End of Assessment Visit	137	135
	Follow-Up Visit 1	133	141
Platelets ($x10^9$/L)	Baseline	243	242
	Day 3	226	228
	Day 42	239	236
	End of Assessment Visit	244	241
	Follow-Up Visit 1	249	235

*The median values are listed in the table
[Source: Adapted from CSR]

Biochemistry:

No meaningful difference in biochemistry parameters was observed across the two arms. A mean increase in alkaline phosphatase (ALP) from baseline to post dose on Day 6 for both treatments was noted. The mean returned to baseline values by Day 42. Most of the abnormalities were Grade 1 or 2. The only Grade 3 or 4 biochemistry laboratory abnormalities that occurred was transaminase increase and alanine aminotransferase (ALT) increased. However, the incidence of Grade 3/4 transaminase increase was balanced across the two arms.

Study EMR200621-003

Hematology:

In study EMR200621-003, the changes in hematology and biochemistry laboratory values from baseline were similar with no meaningful differences in hematology parameters were observed between MSB11455 and US-Neulasta. The median values of neutrophils and leukocytes increased after administration of each study drug with a peak at Day 3, and returning to baseline by the End of Study Assessment Visit of each period. No subjects had an elevated leukocyte count of ≥ 100 $x10^9$/L during the study.

Table 15: Study EMR200621-003 Summary of Hematology Laboratory Tests

		MSB11455 N= 168	US-Neulasta N= 168
Neutrophils ($x10^9$/L)	Baseline	2.66	2.8
	Period 1, Day 3	32	31.9
	Period 1, Day 13	4.3	4.8
	Period 2, Day 1	2.3	2.3
	Period 2, Day 3	2.7	3.1
	Period 2, Day 28	2.5	2.5
	End of Assessment Visit	2.6	2.6
Leukocytes ($x10^9$/L)	Baseline	5.3	5.5
	Period 1, Day 3	37.3	37.7
	Period 1, Day 13	6.9	7.4
	Period 2, Day 1	4.8	4.8
	Period 2, Day 3	39.6	40.2
	Period 2, Day 28	5.2	4.8
	End of Assessment Visit	5.2	5
Hemoglobin (g/L)	Baseline	142	140
	Period 1, Day 3	142	138
	Period 1, Day 13	136	133
	Period 2, Day 1	134	133
	Period 2, Day 3	136	133

	Period 2, Day 28	133	131
	End of Assessment Visit	138	138
Platelets ($x10^9$/L)	Baseline	249	242
	Period 1, Day 3	232	228
	Period 1, Day 13	176	175
	Period 2, Day 1	273	269
	Period 2, Day 3	254	255
	Period 2, Day 28	279	274
	End of Assessment Visit	252	239

*The median values are listed in the table
[Source: Adapted from CSR]

Biochemistry:

No meaningful difference in biochemistry parameters was observed between MSB11455 and US-Neulasta. A mean increase in ALP, ALT, lactate dehydrogenase (LDH), and uric acid were noted for both treatment arms from Baseline to post dose Day 7 of both Period 1 and Period 2. Values returned to baseline by the End of Assessment Visit. All of the abnormalities were Grade 1 or 2 and balanced across arms.

Vitals

Study EMR200621-001

In study EMR200621-001, 133 subjects (49.4%) treated with MSB11455 and 121 subjects (45.7%) treated with US-Neulasta had an increase in heart rate > 20 beats per minute, and 9 subjects (3.3%) treated with MSB11455 and 12 subjects (4.5%) treated with US-Neulasta >40 beats per minute. The increase in both arms started after Day 2 and returned to baseline by Day 6 post dose.

An increase of >20 mmHg in systolic blood pressure was reported in 44 subjects (16.5%) treated with MSB11455 and in 40 subjects (15.1%) treated with US-Neulasta, and >40 mm/Hg for 1 subject treated with MSB11455. An increase in diastolic blood pressure was reported for 35 subjects (13%) treated with MSB11455 and in 26 subjects (9.8%) treated with US-Neulasta, and >40 mmHg for 1 subject treated with MSB11455. An increase in respiratory rate >10 breaths per minute was reported for 1 subject (0.4%) treated with US-Neulasta.

Study EMR200621-003

In study EMR200621-003, the mean changes in vital signs from baseline were comparable between treatments.

Six subjects (3.6%) in the MSB11455 treatment arm and 7 subjects (4.2%) in the US-Neulasta arm had a decreased heart rate >20 beats per minute. One subject (0.6%) in the US-Neulasta arm experienced a decrease in respiratory rate of >10 breaths per minute, and 1 subject (0.6%) in each of the treatment arms experienced an increase in respiration rate of >10 breaths per minute. No other clinically significant abnormal vital sign measurements were reported.

Electrocardiogram

Study EMR200621-001

In study EMR200621-001, per The Applicant, there were several abnormal ECG results reported with only one result considered to be of clinical significance. One subject had an abnormal ECG result considered clinically significant after an unscheduled visit after treatment with US-Neulasta. At the following visit, the ECG was normal.

Study EMR200621-003

In study EMR200621-003, The Applicant reported several ECG results as abnormal, but none were considered of clinical significance.

Clinical Reviewer Comment: Overall, the incidence of laboratory, vital sign, and ECG abnormalities were similar between MSB11455 and US-Neulasta.

7.4. Clinical Conclusions on Immunogenicity

Study EMR200621-001

In study EMR200621-001, 31 subjects (21.2%) in the MSB11455/US-Neulasta treatment sequence and 24 subjects (16.4%) in the US-Neulasta/MSB11455 treatment sequence had post dose ADA positive status. In total, 15 subjects (5.1%) entered the Follow-up Visit for ADA positivity monitored after the End of Study Assessment Visit, 10 subjects (6.8%) in the MSB11455/US-Neulasta and 5 subjects (3.4%) in the US-Neulasta/MSB11455 treatment sequence.

The Applicant states that the TEAE profiles of treatment-induced ADA positive subjects, including AESIs were similar to those reported in the ADA negative subjects. The highest positivity rate was observed at Day 16 of Period 1 and decreased until the end of study. The Applicant reports that there were no relevant differences between the median ADA titers over time across treatment sequences. There were no apparent differences in TEAEs reported for ADA positive subjects in the MSB11455 and US-Neulasta treatment groups. Additionally, there was no notable pattern in the occurrence of injection site reactions with regard to treatment-induced ADA status.

Study EMR200621-003

In study EMR200621-003, 15 subjects (8.9 %) treated with MSB11455 and 16 subjects (9.5%) treated with US-Neulasta were found to be treatment-induced ADA positive. Overall, the proportion of ADA positive subjects was comparable between treatment groups. Seven subjects (2.1%) entered the Follow-up for ADA positivity monitoring after the End of Study Assessment Visit.

The Applicant states that no clinically relevant differences in TEAEs, including AESIs were observed between treatment groups with regard to ADA status and in TEAE profile in subjects who were anti-PEG positive at screening and those who were negative at screening. Additionally, there was no notable pattern in the occurrence of injection site reactions with regard to treatment-induced ADA status.

7.5. Extrapolation to Support Licensure of Non-Studied Indications

The Applicant is seeking licensure of MSB11455 as a biosimilar product to US-Neulasta for the following indication, which has been previously approved for US-Neulasta and for which MSB11455 has not been directly studied: 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.

The Applicant has provided adequate scientific justification to support extrapolation to support licensure of non-studied indications. The comparative analytical data support a demonstration that MSB11455 is highly similar to US-Neulasta notwithstanding minor differences in clinically inactive components. In addition, the data support a demonstration there are no clinically meaningful differencesbetween MSB11455 and US-Neulasta in terms of safety, purity and potency.

Division of Non-Malignant Hematology (DNH)

Overall, the collective results from the comparative clinical studies support the demonstration of no clinically meaningful difference between MSB11455 and US-Neulasta in terms of safety, purity, and potency based on similar PK, PD, safety, and immunogenicity to support licensure of MSB11455 for the proposed indication.

- The Applicant provided data to support that MSB11455 has the same mechanism of action as US-Neulasta to the extent known, which supports extrapolation for the sought indication. MSB11455 is highly similar to US-Neulasta notwithstanding minor differences in clinically inactive components.

- Similar PK and bio-distribution of MSB11455 was demonstrated with US-Neulasta in the comparative PK/PD Study (EMR200621-001) as concluded in section 6. The comparative PK data indicate MSB11455 will have a PK profile similar to US-Neulasta for the sough indication for licensure.
- The immunogenicity profile of MSB11455 was comparable to US-Neulasta in the healthy volunteer studies as assessed by the incidences of anti-drug antibodies and the impact on PK, PD, and safety. These results support a demonstration of no clinically meaningful differences between MSB11455 and US-licensed Neulasta. Further, the incidence of immunogenicity for MSB11455 is expected to be similar to that of US-licensed Neulasta for the sought indication for licensure.
- The Applicant demonstrated that the overall safety profile of MSB11455 was similar to that of US-Neulasta. The safety results from the comparative clinical studies supports demonstration of no clinically meaningful differences between MSB11455 and US-Neulasta. The safety profile of MSB11455 is expected to be similar to that of US-licensed Neulasta for the sought indication for licensure.

DNH concludes that The Applicant has provided sufficient scientific justification based on the mechanism of action, PK, immunogenicity, and toxicity profile, to support extrapolation of data and information in the application, to support licensure of MSB11455 for the sought indication.

Authors:

Julie Weisman, MD
Clinical Reviewer

Tanya Wroblewski, MD
Clinical Team Leader

Jiaxi Zhou, MS
Statistical Reviewer

Yeh-Fong Chen, PhD
Statistical Team Leader

8. Labeling Recommendations

8.1. Nonproprietary Name

The Applicant's proposed nonproprietary name, pegfilgrastim-fpgk, was found conditionally acceptable by the Division of Medication Error Prevention and Analysis (DMEPA). Refer to DMEPA's memorandum dated February 1, 2021.

8.2. Proprietary Name

The proposed proprietary name, Stimufend, was found conditionally acceptable. Refer to letter issued by DMEPA on June 19, 2020.

8.3. Other Labeling Recommendations

MSB11455 is a proposed biosimilar to US-Neulasta. The Applicant is proposing the following dosage forms and strengths:

- Injection: 6 mg/0.6 mL in a single-dose prefilled syringe

The proposed prescribing information for MSB11455 incorporated relevant data and information from the US-Neulasta prescribing information, with appropriate modifications.

The Applicant is seeking licensure for the following indication, for which US-Neulasta has been previously approved: 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.

The Applicant is not seeking licensure for the following indication, for which US-Neulasta has been previously approved: Increase survival in patients acutely exposed to myelosuppressive doses of radiation.

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 labeling guidance recommendations and CDER/OND best labeling practices and policies, is clinically meaningful and scientifically accurate, and conveys the essential scientific information needed for safe and effective use of the product. The Applicant agreed to changes requested by the Division to improve readability, clarity, and accuracy of the prescribing information.

Authors:
Virginia E. Kwitkowski DNH, Assoc. Director for Labeling

9. Advisory Committee Meeting and Other External Consultations

This application was not discussed at an Advisory Committee Meeting.

Author:
Julie Weisman, MD

Clinical Reviewer

10. Pediatrics

MSB11455 is a proposed biosimilar to US-Neulasta. Like US-Neulasta, MSB11455 is packaged in a 6 mg/0.6 mL ungraduated prefilled syringe, which is not designed to allow for direct administration to pediatric patients weighing less than 45kg. MSB11455 also has the same strength, dosage form, and route of administration as US-licensed Neulasta; and the proposed labeling for MSB11455, is in relevant part, substantially the same as the product labeling for US-Neulasta, including pediatric use information.

DMEPA conducted analyses of medication error reports associated with doses of pegfilgrastim products less than 0.6 mL (6 mg), and identified 13 "wrong dose" error reports and six "potential wrong dose" error reports from 2002 until August 2019. Although these error reports did not describe serious clinical consequences, medication errors and adverse events generally are underreported, and "wrong dose" errors associated with pegfilgrastim products could result in infection manifesting as neutropenic fever (if underdosed); leukocytosis, bone pain, edema, dyspnea, pleural effusion, and potential for delay of chemotherapy (if overdosed).

On October 10, 2019, FDA issued an order letter pursuant to section 505B(b) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) to the sponsor of US-Neulasta, requiring it to submit pediatric assessments as described in section 505B(a)(2)(A) of the FD&C Act. As provided in that letter, the sponsor of US-Neulasta is subject to a postmarketing requirement (with a Final Report due October 2022) referred to as submission of pediatric assessments of Neulasta (pegfilgrastim) as described in section 505B(a)(2)(A) of the FD&C Act, including development of an "appropriate formulation" (presentation) that can be used to directly and accurately administer Neulasta (pegfilgrastim) to pediatric patients who weigh less than 45 kg and require doses that are less than 0.6 mL (6 mg), and conducting any necessary human factors studies to evaluate the ability of healthcare providers and/or caregivers to measure the appropriate doses. In the letter, FDA stated it believed that a pediatric presentation – such as a vial or a pediatric sized pre-filled syringe containing an appropriate concentration of product – that can be used to directly and accurately deliver doses of less than 0.6 mL (6 mg) of pegfilgrastim to pediatric patients could be an "appropriate formulation" as described in section 505B(a)(2)(A) of the FD&C Act.

Given the foregoing, the DMEPA review concluded that if the requirements for biosimilarity were met, MSB11455 would be expected to be associated with the same type of dosing errors and potential correlated consequences as US-Neulasta. The DMEPA review further concluded that MSB11455 does not pose any new or different risks from US-Neulasta in terms of use errors and any potential correlated consequences.

To address the reuqirements of the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), the Applicant proposed to defer the following postmarket requirement that can be referred to as:

Submit pediatric assessments for MSB11455 (pegfilgrastim-fpgk) as described in section 505B(a)(2)(A) of the FD&C Act, including development of an "appropriate formulation" (presentation) that can be used to directly and accurately administer MSB11455 (pegfilgrastim-fpgk) to pediatric patients who weight less than 45 kg and require doses that are less than 0.6

mL (6 mg), and conducting any necessary human factors studies to evaluate the ability of healthcare providers and/or caregivers to measure the appropriate doses.

Based on the foregoing, for MSB11455, the potential risks associated with dosing errors for pediatric patients weighing less than 45 kg can be addressed through fulfillment of the postmarketing requirement described above.

Authors:
Julie Weisman, MD
Clinical Reviewer

Tanya Wroblewski, MD
Clinical Team Leader

11. REMS and Postmarketing Requirements and Commitments

11.1. Recommendations for Risk Evaluation and Mitigation Strategies

None

11.2. Recommendations for Postmarket Requirements and Commitments

The following postmarketing requirement (PMR) and post-marketing commitment (PMC) will be requested:

PMR:

Submit pediatric assessments for Stimufend (pegfilgrastim-fpgk) as described in section 505B(a)(2)(A) of the FD&C Act, including development of an "appropriate formulation" (presentation) that can be used to directly and accurately administer Stimufend (pegfilgrastim-fpgk) to pediatric patients who weight less than 45 kg and require doses that are less than 0.6 mL (6 mg), and conducting any necessary human factors studies to evaluate the ability of healthcare providers and/or caregivers to measure the appropriate doses.
Draft Protocol Submission 01/2025
Study Completion: 06/2025
Final Report Submission 10/2025

PMC:

The following OBP post-marketing commitments (PMCs) have been discussed and agreed by the Applicant during the BLA review.

OBP-1: To complete method development and implement a method [redacted] for a [redacted] in-process control.

Final report submission date: July 2023

OBP-2: To complete a viral inactivation study [redacted] and to demonstrate that it is an effective step for inactivation of viruses that may be present.

Final report submission date: March 2023

OBP-3: To complete a real-time leachables study using the final container closure system [redacted] to identify any potential leachables at initial, 6 and 12 months under storage condition [redacted]

Final report submission date: March 2023

OBP-4: To complete a real-time leachables study using the final container closure system with MSB11455 drug substance to identify any potential leachables at initial, 6 and 12 months under storage condition [redacted]

Final report submission date: March 2023

OBP-5: To complete a real-time leachables study using the final container closure system with MSB11455 drug product to identify any potential leachables at initial, 6, 12, 24 and 36 months under storage condition between 2˚C -8˚C.

Final report submission date: March 2025

Authors:

Julie Weisman, MD — Clinical Reviewer

Tanya Wroblewski, MD — Clinical Team Leader

12. Division Director (OCP) Comments

Not applicable.I concur with review team's clinical pharmacology assessment of MSB11455.

Author:

Shirley Seo, PhD
Director, Division of Cardiometabolic and Endocrine Pharmacology (DCEP)

13. Division Director (OB) Comments

Not applicable.

14. Division Director (OND - Nonclinical) Comments

I concur with Dr. Carlson's nonclinical assessment of MSB11455.

Author:
Todd Bourcier, PhD
Director, Division of Pharmacology/Toxicology

15. Division Director (OND - Clinical) Comments

Not applicable.

16. Appendices

16.1. References

Crawford, Jeffrey, et al. "Reduction by granulocyte colony-stimulating factor of fever and neutropenia induced by chemotherapy in patients with small-cell lung cancer." New England Journal of Medicine 325.3 (1991): 164-170.

16.2. Financial Disclosure

Covered Clinical Study (Name and/or Number): EMR200621-001

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 22		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		

Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: Significant payments of other sorts: Proprietary interest in the product tested held by investigator: Significant equity interest held by investigator in S Sponsor of covered study:		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)
Was a list of clinical investigators provided:	Yes ☐	No ☐ (Request list from Applicant)
Total number of investigators identified: _____		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): _____		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): _____		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in S Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial	Yes ☐	No ☐ (Request details from Applicant)

interests/arrangements:		
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) _____		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

Covered Clinical Study (Name and/or Number): EMR200621-003

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 14		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: Significant payments of other sorts: Proprietary interest in the product tested held by investigator: Significant equity interest held by investigator in S Sponsor of covered study:		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

16.3. Office of Clinical Pharmacology Appendices

16.3.1. Summary of Bioanalytical Method Validation and Performance

16.3.1.1. Pharmacokinetics

For the PK/PD similarity study EMR200621-001, serum US-Neulasta and serum MSB11455 concentrations measured using a validated ELISA method (TM.1600) were suitable for assessment of PK similarity. Both the method validation entitled "Validation of an ECL immunoassay for the quantitation of pegfilgrastim biosimilar (MSB11455) and Neulasta® in human serum between 100 pg/ml and 5000 pg/ml" and sample analysis for the study were performed (b) (4) In this method, mouse anti-human G-CSF (b) (4) coated in 96-well plate was used to capture serum pegfilgratim and SULFO-TAGGED™ Streptavidin (Meso Scale Discovery, Rockville, MD) was used to detect the bound analytes. Table 3 shows the summary of ELISA method performance in quantification of serum MSB11455 and serum US-Neulasta during the method validation.

Table 16. Summary of the bioanalytical method validation and in-study performance for measurement of serum MSB11455 and US-Neulasta

Bioanalytical method review summary	Validation of an ECL immunoassay for the quantitation of MSB11455 and US-Neulasta in human serum
Materials used for calibration curve & concentration	MSB11455 Lot No.: BA039674PS Expiration: 25 Nov 2018
Validated assay range	100 pg/mL - 5000 pg/mL
Material used for QCs & concentration	MSB11455 Lot No.: BA039674PS Expiration: 25 Nov 2018 Source: Fresenius Kabi US-Neulasta Lot No:1057373 Expiration: 31 Jan 2018 Source: Amgen Inc. USA Lower Limit of Quantitation (LLOQ) QC: 100 pg/mL Low Quality Control Sample (QCL): 300 pg/mL Mid Quality Control Sample (QCM): 1000 pg/mL High Quality Control Sample (QCH): 3750 pg/mL Upper Limit of Quantitation (ULOQ) QC: 5000 pg/mL
Minimum required dilutions (MRDs)	1:5
Source & lot of reagents (LBA)	Human G-CSF Duo set kit (b) (4) • Capture Antibody (mouse anti-human G-CSF) • Detection Antibody (biotinylated anti-G-CSF antibody)

	Reagent Additive 1 (Normal Goat Serum) Lot: 329700 Source: (b) (4) SULFO-TAG™ Streptavidin Lot Number: W0016082S Source: Meso Scale Discovery		
Regression model & weighting	Regression Model: 4-parameter logistic Weighting: $1/[concentration]^2$		
Validation Parameters	Method Validation Summary		Acceptability
Calibration curve performance during accuracy & precision	No of standard calibrators from LLOQ to upper limit of quantitation (ULOQ)	8	Yes
	Cumulative accuracy (%bias) from LLOQ to ULOQ MSB11455	-4.00% to 6.00%	Yes
	Cumulative precision (%CV) from LLOQ to ULOQ MSB11455	≤ 3.06%	Yes
QCs performance during accuracy & precision	Cumulative accuracy (%bias) in 5 QCs MSB11455 US-Neulasta	 -5.62% – 7.06% -3.58% – 11.6%	Yes
	Inter-batch %CV MSB11455 US-Neulasta	 ≤ 7.08% ≤ 4.83%	Yes
	Percent total error (TE) MSB11455 US-Neulasta	 ≤ 13.0% ≤ 16.8%	Yes
Selectivity & matrix effect	Ten total lots tested. Range of observed bias at LLOQ: MSB11455: -38 to 1% (8/10 lots within -25.0 to 25.0%) US-Neulasta: -20.4 to 5% (10/10 lots within -25.0 to 25.0%)		Yes
Interference & specificity	Not evaluated		NA
Hemolysis effect	Six total lots tested. Range of observed bias at LLOQ: MSB11455: -23.9 to -9.60 (6/6 lots within -25.0 to 25.0%)*		Yes

	US-Neulasta: -22.2 to -2.5% (4/5 lots within -25.0 to 25.0%) <u>Range of observed bias at QCH:</u> MSB11455: -9.3 to -0.80% (6/6 lots within -20.0 to 20.0%) US-Neulasta: 0.26 to 6.40 % (6/6 lots within -20.0 to 20.0%) * Two human serum samples spiked with MSB11455 at LLOQ did not meet the acceptance criteria in original evaluation. Those two samples were repeated, confirmed and met the overall acceptable criteria. Data demonstrated in tables 13, 14 and 15 of report number 10219-071217.	
Lipemic effect	Five total lots tested. <u>Range of observed bias at LLOQ:</u> MSB11455: -20.8 to -6.9 (5/5 lots within -25.0 to 25.0%)* US-Neulasta: -24.6 to 6.0% (5/5 lots within -25.0 to 25.0%) <u>Range of observed bias at QCH:</u> MSB11455: -8.00 to 1.33% (5/5 lots within -20.0 to 20.0%)** US-Neulasta: -3.73 to 8.27 % (5/5 lots within -20.0 to 20.0%) * Two human serum samples spiked with MSB11455 at LLOQ did not meet the acceptance criteria in original evaluation. After, repeated analysis and confirmation still did not meet the acceptance criteria. Therefore, 5 additional lots were tested, and all 5 additional lots met the acceptance criteria. **One sample spiked with MSB11455 at QCH did not meet the acceptance criteria in original evaluation. Upon reanalysis the sample met the acceptance criteria.	Yes
Dilution linearity & hook effect	<u>Range of %bias for dilution linearity samples within the range of quantitation (up to 2500-fold dilution):</u> MSB11455: -10.2 to -5.40% US-Neulasta: -5.4 to -3.40% <u>Hook Effect:</u>	Yes

	All hook effect samples tested produced values above the ULOQ for MSB11455 and Neulasta.	
Bench-top/process stability	17 hours at ~25°C: MSB11455: QCL: -8.67% (-80°C), -10.7% (-20°C) QCH: -3.73% (-80°C), -5.60% (-20°C) US-Neulasta: QCL: -3.00% (-80°C), -3.00% (-20°C) QCH: 1.60% (-80°C), 3.73% (-20°C) 17 hours at 4°C: MSB11455: QCL: 0 (-80°C), -1.33% (-20°C) QCH: 4.00% (-80°C), -0.533% (-20°C) US-Neulasta: QCL: 7.67% (-80°C), 7.33% (-20°C) QCH: 8.00% (-80°C), 10.4% (-20°C)	Yes
Freeze-Thaw stability	6 cycles: MSB11455: QCL: 2.67% (-80°C), -3.67% (-20°C) QCH: -6.40% (-80°C), -9.60% (-20°C) US-Neulasta: QCL: 7.67% (-80°C), 4.00% (-20°C) QCH: 1.07% (-80°C), 1.07% (-20°C)	Yes
Long-term storage	-20°C at 364 days*: MSB11455: QCL: -17.7%; QCH: -17.6% US-Neulasta: QCL: -4.33%; QCH: -11.2% -80°C at 364 days*: MSB11455: QCL: -8.33%; QCH: -12.5% US-Neulasta: QCL: -2.33%; QCH: -4.53% *Data available from 22 days to 364 days for MSB11455 and Neulasta® at -20°C as well as -80°C	Yes
Parallelism	Not evaluated	N/A
Carry over	Not evaluated	N/A
Method Performance in Study EMR200621-001 Determination of study drug in human serum samples from protocol EMR200621-001		
Assay passing rate	• Runs conducted: 22 • All passed for validation	Yes
Standard curve performance	• Standard Curve Range: 100 – 5000 pg/mL • $R^2 \geq 0.98$ • Cumulative bias range: -0.80 to 0.88% • Cumulative precision: ≤ 4.82% CV	Yes
QC performance	• Cumulative bias range: -3.00 to -1.00%	Yes

	• Cumulative precision: ≤ 7.80% CV • Including values outside acceptance range criteria: ± 20.0% bias for all QC samples	
Method reproducibility	96.2% of repeat values for Pegfilgrastim were within the reproducibility criteria	Yes
Study sample analysis/ stability	The interval from first sample draw date to last analysis date was 261 days. Adequate long-term stability (364 days) has been established to cover the storage period	

16.3.1.2. Pharmacodynamics

For pharmacodynamics (PD) determination The Applicant provided the details of the bioanalytical method used to determine Absolute Neutrophil Count (ANC) over time in the blood of the subjects included in the EMR200621-001 study. The ANC was derived from measurements of the total number of WBC and is part of a larger blood panel (complete blood count (CBC)). CBC determination was conducted at two pathological laboratories in Australia accredited by the Australian National Association of Testing Authorities (NATA)/RCPA Laboratory Accreditation Program. Whole blood samples were analyzed using automated Sysmex hematology analyzers: Sysmex XE 5000 (b) (4) and Sysmex XN 9000 (b) (4)
Both analyzers work on the fluorescence flow cytometric analysis principle. A lysis reagent initially perforates the cell membranes while leaving the cells largely intact. A fluorescence marker labels the intracellular nucleic acids (mostly RNA) in the second step. The prepared sample is then analyzed using fluorescence flow cytometry. The measurement signals related to side scatter (SSC) and side fluorescence (SFL) are analyzed and depicted in a scattergram. Cells with similar cytochemical properties fall within the same area in the scattergram and can be separated using an advanced software algorithm.
Periodic calibration of the autoanalyzers was not required as per the manufacturer's instructions. Instrument calibration was performed during installation, the calibration outcome and QC verification of each instrument are summarized in tables 4 and 5.

Table 4. Summary of the calibration performed during instrument installation (b) (4)

Instrument S/N	End of installation	Calibration Material SCS-1000		Outcome	QC Material E-Check Level 2		WBC Result	WBC Target
		Lot	Expiry		Lot	Expiry		
(b) (4)		21780525	30-Jul-2012*	Passed	21700811	09-Sep-2012	7.0	6.99 +/- 0.42

(b) (4)	21780525	30-Jul-2012*	Passed	21700811	09-Sep-2012	6.99	6.99 +/- 0.42

Table 5. Summary of the calibration performed during instrument installation (b) (4)

Instrument S/N	End of installation	Calibration Material XN-CAL		Outcome	QC Material XN Check Level 2		WBC Result	WBC Target
		Lot	Expiry		Lot	Expiry		
(b) (4)		62262101	18-Sep-2016	Passed	61931102	02-Oct-2016	6.98	7.03 +/- 0.42
		62262101	18-Sep-2016	Passed	61931102	02-Oct-2016	7.02	7.03 +/- 0.42
		62002101	21-Aug-2016	Passed	61371102	07-Aug-2016	6.70	6.74 +/- 0.4
		62002101	21-Aug-2016	Passed	61371102	07-Aug-2016	6.96	6.74 +/- 0.4
		62002101	21-Aug-2016	Passed	61371102	07-Aug-2016	6.74	6.74 +/- 0.4
		61722101	24-Jul-2016	Passed	61371102	07-Aug-2016	6.87	6.74 +/- 0.4
		61722101	24-Jul-2016	Passed	61931102	07-Aug-2016	6.87	6.74 +/- 0.4
		61722101	24-Jul-2016	Passed	61371102	07-Aug-2016	6.84	6.74 +/- 0.4
		61722101	24-Jul-2016	Passed	61371102	07-Aug-2016	6.77	6.74 +/- 0.4
		61722101	24-Jul-2016	Passed	61371102	07-Aug-2016	6.78	6.74 +/- 0.4

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/s/

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08/29/2022 11:50:53 AM

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08/29/2022 03:54:00 PM
Approval recommendation from the nonclinical perspective

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

PHARMACOLOGY/TOXICOLOGY BLA REVIEW AND EVALUATION

Application number:	761173
Supporting document/s:	eCTD
Applicant's letter date (CDER Stamp Date):	3/27/2020
Product:	MSB11455 (pegylated granulocyte colony-stimulating factor; pegfilgrastim)
Indication:	Decrease the incidence of infection, as manifested by febrile neutropenia
Applicant:	Fresenius Kabi USA, LLC
Review Division:	Nonmalignant Hematology
Reviewer:	David B. Carlson, PhD
Supervisor/Team Leader:	Todd Bourcier, PhD
Division Director / Deputy Director:	Ann Farrell, MD Albert Deisseroth, MD
Project Manager:	Courtney Hamilton, PharmD, BCPS
Review Completion Date:	12/21/2020

Disclaimer

Except as specifically identified, all data and information discussed below and necessary for approval of BLA 761173 are owned by Fresenius Kabi or are data for which Fresenius Kabi has obtained a written right of reference. Any information or data necessary for approval of BLA 761173 that Fresenius Kabi does not own or have a written right to reference constitutes one of the following: (1) published literature, or (2) a prior FDA finding of safety or effectiveness for a listed drug, as described in the drug's approved labeling. Any data or information described or referenced below from reviews or publicly available summaries of a previously approved application is for descriptive purposes only and is not relied upon for approval of BLA 761173.

Review Notes and Abbreviations

Tables and figures in this review are from the applicant's electronic BLA submission. Maximum recommended human dose (MRHD); human granulocyte colony-stimulating factor (G-CSF); U.S. licensed Neulasta® (US-Neulasta); Maximum Daily Intake (MDI); Permissible Daily Exposure (PDE); pre-filled syringe (PFS); polyethylene glycol (PEG).

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1 Executive Summary

1.1 Introduction

MSB11455 is a recombinantly expressed pegylated filgrastim (human granulocyte colony-stimulating factor (G-CSF)) with an identical sequence to U.S. listed pegfilgrastim. The applicant considers the proposed pegfilgrastim biosimilar to Neulasta® (US-Neulasta) and is seeking licensing under Section 351(k) of the Public Health Service Act. No nonclinical data were submitted to the BLA. The applicant is relying on chemical analyses and in vitro potency data to demonstrate biosimilarity to the reference listed product for administration in a pre-filled syringe to decrease the incidence of infection as manifested by febrile neutropenia in chemotherapy patients.

1.2 Brief Discussion of Nonclinical Findings

No nonclinical data were submitted to the BLA to support the final clinical formulation of MSB11455. FDA agreed with the applicant in a Biosimilar Product Development Type 2 meeting that nonclinical in vivo pharmacology and toxicology data from studies with (b) (4), an early, non-commercial small-scale batch precursor product to the final MSB11455 product, were not directly relevant to the final proposed clinical formulation.[1] The applicant provided a justification that those nonclinical data were not necessary to establish similarity of MSB11455 to the US-listed pegfilgrastim.[2] A biosimilarity determination will be established with comparative analytical data, in vitro potency and G-CSF receptor binding, and clinical studies.

All MSB11455 excipients are compendial, qualitatively and quantitatively similar to the excipients in US-Neulasta, and there are no novel excipients in the formulation.

There are no impurities or degradants of concern. The applicant's risk assessment of extractable and leachable impurities identified five compounds of potential concern from standard use and accelerated degradation conditions. Maximum Daily Intake (MDI) from each of the potential extractable and leachable compounds were well below the calculated Permissible Daily Exposure (PDE), confirming negligible risk for any extractable or leachable impurity in MSB11455. No elemental impurities were measured in extractable or leachable studies at levels that posed a safety concern. Similarly, drug substance specifications limit elemental impurities to negligible levels and all potential process-related elemental impurities measured during drug substance batch analyses were below PDEs established from ICH impurity guidances.

[1] IND 113717, Memorandum of Meeting Minutes, 5/9/2019 (Biosimilar Product Development Type 2 Meeting, 4/10/2019)
[2] BLA 761173, Response to Information Request, 5/21/2020

While nonclinical studies conducted with (b) (4) were not necessary to establish physicochemical and biological similarity of the final MSB11455 to US-Neulasta, the in vivo pharmacology and toxicology data were informative in the development of the final drug product. The (b) (4) data showed the proposed pegfilgrastim was pharmacologically and toxicology similar to US-Neulasta. Pharmacodynamic activity consistent with listed pegfilgrastim was seen in neutropenic mice treated subcutaneously with (b) (4) prior to treatment with cyclophosphamide, as evidenced by increased total white blood cells and absolute neutrophil counts for several days post-treatment. A four-week rat toxicity study with (b) (4) showed similar pharmacodynamic activity and toxicity of the proposed pegfilgrastim and listed pegfilgrastim. Expected pharmacodynamic effects of increased white blood cells, neutrophils, lymphocytes, eosinophils, and myeloid:erythroid ratio were seen in the (b) (4) and other pegfilgrastim treated groups. Toxicity was similar across pegfilgrastim groups and generally consistent with exaggerated pharmacology, including increased hematopoiesis (bone marrow, spleen) and splenomegaly. Spleen enlargement in rats is consistent with labeled clinical postmarket adverse events and a Warning/Precaution for enlarged spleen or splenic rupture (US-Neulasta).[3] Toxicokinetic profiles in rats were consistent across the pegfilgrastim treatment groups.

The quality review assessed all of the data provided to establish similarity of MSB11455 to US-Neulasta, including biological activity-based in vitro cell proliferation for potency and receptor affinity and binding assays. From a nonclinical perspective, the data show similar pharmacologic activity of MSB11455 and US-Neulasta based on G-CSF receptor binding affinity, specific activity, and relative potency.

1.3 Recommendations

1.3.1 Approvability

Approval is recommended from a nonclinical perspective.

1.3.2 Additional Non Clinical Recommendations

None.

1.3.3 Labeling

Proposed nonclinical sections of the label are identical to the reference U.S. listed pegfilgrastim (Neulasta®) label. No new nonclinical data were submitted and no changes are recommended to the proposed label.

[3] See Neulasta® at https://www.accessdata.fda.gov/scripts/cder/daf/

2 Drug Information

2.1 Drug

2.1.1 CAS Registry Number

208265-92-3

2.1.2 Generic Name

Pegfilgrastim

2.1.3 Code Name

MSB11455 ((b) (4) pegylated Granulocyte Colony-Stimulating Factor (G-CSF)

2.1.4 Chemical Name

N-(3-hydroxypropyl) methionyl colony-stimulating factor (human), 1-ether with alpha-methylomega-hydroxypoly (oxyethylene)

2.1.5 Molecular Formula/Molecular Weight

175 amino acid protein, approximately 19 KDa plus 20 KDa polyethylene glycol (PEG)

2.1.6 Structure (or Biochemical Description)

Figure 1 – Amino acid structure (MSB11455)

Amino Acid Sequence of MSB11455

$^{1}\underline{\mathbf{M}}$TPLGPASSL^{10} PQSFLLKCLE^{20} QVRKIQGDGA^{30} ALQEKL$\underline{\mathbf{C}}^{37}$ATY^{40} KL$\underline{\mathbf{C}}^{43}$HPEELVL^{50}

LGHSLGIPWA^{60} PLSS$\underline{\mathbf{C}}^{65}$PSQAL^{70} QLAG$\underline{\mathbf{C}}^{75}$LSQLH^{80} SGLFLYQGLL^{90} QALEGISPEL^{100}

GPTLDTLQLD^{110} VADFATTIWQ^{120} QMEELGMAPA^{130} LQPTQGAMPA^{140}FASAFQRRAG^{150}

GVLVASHLQS^{160}FLEVSYRVLR^{170}HLAQP^{175}

Note: bold, underlined text indicates pegylated Met1 and locations of cysteine-cysteine disulfide bonds.

2.1.7 Pharmacologic class

Leukocyte growth factor

2.2 Relevant IND/s, NDA/s, and DMF/s

IND 113717 – MSB11455 ((b) (4) pegfilgrastim; pegylated Granulocyte Colony-Stimulating Factor (G-CSF)) proposed biosimilar to US-Neulasta®

2.2 Drug Formulation

MSB11455 drug product is formulated as a clear, colorless, ready-to-use, disposable, single-use, fixed dose (6 mg/0.6 mL), pH 4.0 pre-filled syringe (PFS) assembled with a passive “Safe’n’Sound®” needle guard system. The excipients in the pegylated recombinant filgrastim are identical and quantitatively similar to those in US-Neulasta, including acetate, sorbitol, sodium, and polysorbate 20 (Table 1). The commercial scale manufacturing of MSB11455 in the drug product for marketing was used for comparative analytical and clinical study batches to determine similarity to US-Neulasta. (b) (4)

Table 1 – Drug product/substance compositions

Composition of MSB11455 Drug Product

Component	Function	Quality Grade	Quantity per mL	Nominal Quantity per Syringe
Pegfilgrastim	Active ingredient	In-house	10.0 mg	6.0 mg
(b) (4) Sorbitol	(b) (4)	USP-NF, Ph. Eur.	50.0 mg	30.0 mg
(b) (4)		USP-NF, Ph. Eur.		(b) (4)
Polysorbate 20		USP, Ph. Eur.	0.03 mg	0.02 mg
(b) (4)		USP, Ph. Eur.		(b) (4)
Water for Injection		USP, Ph. Eur.		

Ph. Eur. = European Pharmacopoeia; USP = United States Pharmacopoeia; USP-NF = United States Pharmacopoeia National Formulary; q.s. = quantum satis (for as much as required).

(b) (4)

2.4 Comments on Novel Excipients

All excipients are compendial and qualitatively and quantitatively similar to the excipients in US-Neulasta (see Table 1). There are no novel excipients in the formulation. As part of the quality assessment, an in vitro potency cell proliferation assay established similar biological activity of the final drug product formulation to US-Neulasta, confirming an appropriate excipient formulation for MSB11455 biosimilarity to the referenced US-Neulasta.

2.5 Comments on Impurities/Degradants of Concern

There are no impurities or degradants of concern. The applicant performed a risk assessment of extractable and leachable compounds in the drug substance in the planned marketing of drug product in pre-filled syringes. Five compounds of concern were identified from extractable and leachable studies simulating conditions of use and accelerated degradation conditions (Table 2, Table 3). Maximum Daily Intake (MDI) from each of the potential extractable and leachable compounds, calculated in the risk assessment based on potential worst-case exposures at the clinical maximum recommended human dose (MRHD) of MSB11455, was well below the calculated Permissible Daily Exposure (PDE) based on public toxicity data for individual compounds (Table 4). No elemental impurities were measured in extractable or leachable studies at levels that posed a safety concern. There are no safety concerns for any potential extractable or leachable compounds in the drug substance based on the applicant's risk assessment and the calculated MDI < PDE predicting negligible risk for each compound.

Table 2 – Extractables summary

Summary of Extractables

Table 3 – Leachables summary

Summary of Leachables safety assessment

(b) (4)

Table 4 – Applicant's safety summary of potential extractables and leachables

Non-Clinical Safety Assessment

(b) (4)

Toxicity and exposure risks were assessed for potential process-derived impurities in the drug substance. (b) (4) The FDA's quality review assessed the potential biological impurities (i.e., proteins, DNA, endotoxins, etc.). The elemental impurities of potential concern in the drug substance were identified by the applicant following ICH Q3D guidelines (b) (4) Drug substance specifications limit elemental impurities to negligible levels and all potential process-related elemental impurities measured during drug substance batch analyses were below PDEs established from ICH Q3D guidance (Table 5).

Table 5 – Drug substance process-related elemental impurity limits

(b) (4)

2.6 Proposed Clinical Population and Dosing Regimen

The proposed therapeutic indications and dosing regimen for MSB11455 are similar to the listed US-Neulasta. In short, MSB11455 will be administered subcutaneously once per chemotherapy cycle to patients with cancer receiving myelosuppressive chemotherapy.

2.7 Regulatory Background

Initial review cycle for the proposed biosimilar BLA.

3 Studies Submitted

No nonclinical data were submitted. Relative potency data determined in a validated in vitro proliferation assay with M-NFS-60 murine myelogenous leukemia cells were included in the quality biosimilarity assessment. Receptor affinity and binding kinetics data determined by Surface Plasmon Resonance (SPR) were included in the quality biosimilarity assessment.

3.3 Previous Reviews Referenced

Del Valle PL. IND 113717 Pharmacology/Toxicology Review and Evaluation, 01/10/2014

4 Pharmacology

4.1 Primary Pharmacology

As previously noted, no nonclinical data were submitted to the BLA to support the final clinical formulation of MSB11455. Nonclinical studies conducted with (b) (4) were not necessary to establish physicochemical and biological similarity of the final MSB11455 to US-Neulasta but the in vivo pharmacology data were informative in the development of the final drug product. Briefly, neutropenic mice were treated with (b) (4) by single subcutaneous injection prior to treatment with cyclophosphamide and showed a similarly robust pharmacodynamic response compared to US-Neulasta, as evidenced by increased total white blood cells and absolute neutrophil counts for several days post-treatment.[4]

The quality review assessed all of the data provided to establish similarity of MSB11455 to US-Neulasta, including the in vitro potency and receptor binding assays. Because the in vitro potency and receptor binding assays are pharmacologic in nature, the nonclinical reviewer independently verified the pharmacologic implications. The applicant's overall summary of in vitro potency and receptor binding "equivalence" of MSB11455 to US-Neulasta are shown in Table 6. In short, the applicant conducted multiple independent cell proliferation assays to assess similarity in an established in vitro potency assay and multiple receptor affinity and receptor binding assays to show similar kinetics between 13 different batches of MSB11455 and 21 different batches of US-Neulasta. From a nonclinical perspective, the data show similar biological activity of MSB11455 and US-Neulasta based on G-CSF receptor binding affinity, relative potency, and specific activity.

Table 6 – Biologically similarity assessment summary

Clinical Relevance	Level of Criticality	Similarity Analysis	Assay	Measurement	MSB11455 vs US-Licensed Neulasta (Equivalence [1]/ % within QR [2]/ RD)
Biological Activities					
MoA & Efficacy	Very High	RD	G-CSF-R Binding SPR	ka (x10^4 1/Ms)	Similar
		RD		kd (x10^{-5} 1/s)	Similar
		QR		KD (pM)	100%
		QR ET	Pegfilgrastim induced M-NFS-60 cell proliferation	Relative Potency (%EC_{50})	100% Equivalent
		QR ET		Specific Activity (x10^6 IU/mg)	100% [3] Equivalent

[1] EM was determined as 1.5σ_R of Neulasta data and results were determined as 90 % CI of mean difference between two products.

[2] The QR limits were set based on the range of the values obtained for reference product variation, expressed as X times Standard Deviation (SD). High similarity was considered to have been demonstrated if 90 % of data points were within the QR. X=3 unless otherwise indicated.

[3] X=2.

RD Visual comparison of raw data.

[4] Del Valle PL. IND 113717 Pharmacology/Toxicology Review and Evaluation. 1/10/2014

6 Toxicology

No nonclinical toxicology data were submitted to the BLA to support the final clinical formulation of MSB11455. Nonclinical studies conducted with an early batch of (b) (4) were not necessary to establish physicochemical and biological similarity of the final MSB11455 to US-Neulasta, but the in vivo toxicology data were informative in the development of the final drug product. A brief summary of the 4-week rat toxicology study conducted with (b) (4) earlier in the drug development process is included here for reference purposes:[5]

- 4-Week, once weekly sc injection, Sprague Dawley rats (GLP-compliant)
  - 1000 µg/week (b) (4) compared to US-Neulasta and EU-Neulasta
  - Summary
    - Similar pharmacodynamic and toxicological effects of (b) (4) compared to marketed pegfilgrastim (US-Neulasta, EU-Neulasta)
  - Pharmacodynamic summary
    - Pegfilgrastim treated groups showed pharmacodynamic effects of markedly increased white blood cells and neutrophils
      - Also increased lymphocytes, eosinophils, myeloid:erythroid ratio
  - Toxicology summary
    - Toxicity consistent with exaggerated pharmacology
    - Toxicity findings consistent across pegfilgrastim treatment groups and with expected pegfilgrastim-related effects
      - Increased hematopoiesis (bone marrow, spleen)
      - Increased alkaline phosphatase (3-fold)
      - Spleen macroscopic enlargement and increased organ weight
      - Slight increases in liver and mesenteric lymph node weights
    - Toxicokinetics consistent across pegfilgrastim treatment groups

[5] *IBID*

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/

DAVID B CARLSON
01/14/2021 12:05:31 PM
Approval recommendation from nonclinical perspective

TODD M BOURCIER
01/14/2021 12:06:57 PM
I concur