CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761084Orig1s000

MULTI-DISCIPLINE REVIEW

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

BLA 761084

CROSS DISCIPLINE TEAM LEADER REVIEW

Date: May 24, 2022

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

Subject: Cross Discipline Team Leader (CDTL) Memorandum
BLA 761084, Resubmission after Complete Response
Proposed Biosimilar Product Applicant: Kashiv BioSciences, LLC

Product Information

Proposed Proprietary Name[1]: Fylnetra

Proposed Non-proprietary Name: pegfilgrastim-pbbk

Code Name: TPI-120

TPI-120 is a proposed biosimilar to US-licensed Neulasta (pegfilgastrim) also referred to as US-Neulasta

Dosage Forms, Strength, Presentation:

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

Pharmacologic Class: Leukocyte growth factor

Mechanism of Action: TPI-120 is a colony-stimulating factor that acts on hematopoietic cells by binding to specific cell surface receptors, thereby stimulating proliferation, differentiation, commitment, and end cell functional activation.

Proposed Indications:

- 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.

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

Regulatory History

This application was originally submitted on August 11, 2020. A complete response letter for product quality, microbiology, and device deficiencies was issued on August 11, 2021. The CR letter also reported that the inspection of the Kashiv BioSciences facility intermediate product and drug substance manufacturing site, which is required for approval of the BLA, could not take place due to travel restrictions due to the COVID-19 pandemic. On November 29, 2021, Kashiv submitted responses to address the deficiencies and additional comments identified in the CR letter. A pre-license inspection of the Kashiv BioSciences facility was conducted between January 10, 2022 and January 14, 2022.

Chemistry, Manufacturing and Controls (CMC), Product Quality Microbiology, and Facility Assessment Review (summarized from OPQ reviews)

The Office of Biotechnology Products (OBP), OPQ, CDER recommends approval of STN 761084 for Fylnetra, manufactured by Kashiv BioSciences (see primary assessment dated April 15, 2022). According to OBP's assessment, based on the totality of information and data provided, Kashiv adequately addressed all the OBP-noted deficiencies and additional comments outlined in the CR letter. Sufficient analytical data was provided in the application to support that Flynetra is highly similar to US-licensed Neulasta, notwithstanding minor differences in clinically inactive components, and that the strength, dosage form, and route of administration of Flynetra are the same as those of US-licensed Neulasta. A total of 13 lots of US-licensed Neulasta and 12 lots of TPI-120 drug product were originally used in the assessment. All lots for each product were used in the assessment of very high and high risk quality attributes, while only a subset of lots were used in the analysis of low risk quality attributes. The assessment included analysis of independent TPI-120 drug product lots generated from clinical and commercial processes. The selected US-licensed Neulasta lots span the shelf-life of the product (24 months) and TPI-120 lots ranged from < 1 -17 months. Kashiv Biosciences updated the assessment for certain evaluations with additional lots of TPI-120 (1) and US-licensed Neulasta (5) to support the original dataset.

This BLA was also reviewed from product quality microbiology perspective and sterility assurance perspective. According to OPMA's assessment, based on the totality of information and data provided, Kashiv adequately addressed all the microbiology deficiencies (media fill studies and bacterial retention study for the sterilizing-grade filter) and additional comments outlined in the CR letter. For full details, see Product Quality Microbiology/Facility Assessment dated April 18, 2022. All CR issues were addressed and TP-120 is recommended for Approval.

A pre-license inspection was conducted from January 10, 2022 through January 14, 2022 at the drug substance (DS) manufacturing facility for theragrastim and TPI-120 (FEI 30112896553: 440

S. Dearborn Street, Chicago, Illinois. The inspection concluded with the issuance of a five-item FDA Form 483 and a field recommendation of approve for BLA 761084. The FDA's compliance review of the firm's response concurred with the field recommendation and recommended approval for BLA 761084. A compliance inspection of the (b) (4) manufacturing facility for theragrastim drug product (DP) (b) (4) was conducted (b) (4). The FDA field investigation team conveyed deficiencies to the representative of the facility. The facility's response to these deficiencies was reviewed and found satisfactory. The current status of this facility is compliant since August 10, 2021. For full details, see OPMA Review and OPQ Summary Reviews. The data submitted in this application are adequate to support the conclusion that the manufacture of Fylnetra is well-controlled and leads to a product that is pure and potent. All CR issues were addressed and TP-120 is recommended for Approval.

Devices/Center for Devices and Radiological Health (CDRH) Review: FDA issued a CR letter that included deficiencies relating to CDRH issues. The firm submitted a Type 1 meeting request with CDRH response completed October 2021. The deficiency requested activation force data for T=0 and over a shelf as well as needle safety override force data to support shelf life. The firm provided design verification and validation for needle safety activation force of T= 30 months real time and needle safety lockout force/override force/safe mode challenge with T-30 month real time and CDRH states that the Sponsor has adequately addressed the issues raised in the CR letter. Please refer to the review by Courtney Evans and Porsche Bennett in Office of Product Evaluation and Quality, Office of Health Technology 3 for additional details.

Nonclinical Pharmacology/Toxicology Review: No additional pharmacology/toxicology information is included in this resubmission. Pharmacology/Toxicology Memorandum (Todd Bourcier,) concluded there remain no residual uncertainties from the pharmacology/toxicology assessment that would preclude approval of this BLA.

Clinical Pharmacology/Biopharmaceutics Review: There was no new clinical pharmacology information included in this submission and no residual uncertainties based on the clinical pharmacology analysis.

Clinical/Statistical Review: There was no new clinical information included in this submission and no residual uncertainties based on the clinical safety analysis. There was no clinical/statistical review for this submission.

Refer to the Biosimilar Multi-disciplinary Evaluation and Review (BMER) dated April 21, 2022 (DARRTS Reference ID: 4968781) that was completed for the original BLA submission for detailed information.

Labeling:

During the review of labeling the subject of applicability of 21 CFR 610.61(r) arose and the regulation stated does not apply to BLA 761084. Thus, "potency is a factor" do not apply to

Fylnetra because lot variability is not a concern for Fylnetra because the manufacturing process is appropriately controlled to ensure consistency and quality of the final product. For further background information, please refer to the memorandum from Janice Weiner, J.D., M.P.H., CDER/Office of Regulatory Policy, Division of Regulatory Policy I.

Please refer to the labeling review by Virginia Kwitkowski in DARRTs.

Post Marketing Requirements and Commitments: Three post marketing commitments (PMCs) will be issued related to manufacturing and controls. The PMCs can be addressed post-market rather than pre-market because the risk is minimal (e.g., verification of data under similar conditions, manufacturing process analysis, and long-term data needed).

1. Perform a real-time drug product (DP) shipping study from DP manufacturing site to Kashiv BioSciences and to the distribution center to confirm validation of the commercial TPI-120 DP shipping conditions, such as described in protocol PTL-2374 (Section 3.2.P.3.5). The final study report should include assessments for the impact of real-time shipping on (i) product quality (comparison of product pre- and post-shipment), (ii) temperature for the duration of transport, and (iii) physical damage to the DP containers.
2. Perform a study to evaluate the impact of the removal of kanamycin from the (b) (4) manufacturing process. If the data support removal of kanamycin, a plan for the removal of kanamycin from the manufacturing process is expected to be provided. The plan should include an evaluation of consistency of the fermentation process and comparability of the (b) (4) manufactured with and without kanamycin. The results should be reported per 21 CFR 601.12.
3. Re-assess the (b) (4) acceptance criteria for testing of drug substance (DS) and drug product (DP) at release and on stability when 10 commercial DS and DP batches have been manufactured and tested. The final study report should include sufficient information and data to support the acceptance criteria, and all relevant protocols (e.g., qualification and requalification protocols of reference standards) as well as DS and DP specifications should be updated as needed.

There will be one post marketing requirement:

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

The pediatric submission of your pediatric study will be deferred until October 31, 2025, because this product is ready for approval for use in adults and the pediatric study has not been completed.

Your deferred pediatric study required under section 505B(a) of the Federal Food, Drug, and Cosmetic Act is a required postmarketing study. The status of this postmarketing study must be reported annually according to 21 CFR 601.28 and section 505B(a)(4)(C) of the Federal Food, Drug, and Cosmetic Act. This required study is listed below.

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

1.1. Conclusions on Licensure

The Applicant is seeking licensure of TPI-120 as a biosimilar product to US-Neulasta for the following indication which has been previously approved for US-Neulasta and for which TPI-120 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.

In considering the totality of the evidence submitted, the data submitted by the Applicant show that TPI-120 is highly similar to US-licensed Neulasta, notwithstanding minor differences in clinically inactive components and that there are no clinically meaningful differences between TPI-120 and U.S.-licensed Neulasta in terms of safety, purity and potency of the product. The Applicant has provided adequate scientific justification for extrapolation of data and information to support licensure of TPI-120 for the proposed indication.

This BLA for TP-120, a proposed biosimilar product to US-licensed Neulasta, is recommended for approval.

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/

TANYA M WROBLEWSKI
05/25/2022 03:08:59 PM

BIOSIMILAR MULTI-DISCIPLINARY EVALUATION AND REVIEW

Application Type	351(k) BLA
Application Number	761084
Submit Date	August 11, 2020
Received Date	August 11, 2020
BsUFA Goal Date	August 11, 2021
Division/Office	DNH/OCHEN/OND
Review Completion Date	8/11/2021
Product Code Name	TPI-120
Proposed Non-Proprietary Name[1]	Pegfilgrastim-pbbk
Proposed Proprietary Name[1]	(b) (4)
Pharmacologic Class	Leukocyte Growth Factor
Applicant	Kashiv BioSciences, LLC
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	Complete Response

[1] Section 8 of the Biosimilar Mutli-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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Reviewers of Biosimilar Multi-Disciplinary Evaluation and Review

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Nonclinical Pharmacology/Toxicology Reviewer(s)	Fred Alavi
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Clinical Pharmacology Reviewer(s)	Anusha Ande
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Clinical Reviewer(s)	Hyon-Zu Lee
Clinical Team Leader(s)	Tanya Wroblewski
Clinical Statistics Reviewer(s)	Lola Luo
Clinical Statistics Team Leader(s)	Yeh-Fong Chen
Cross-Discipline Team Leader(s) (CDTL(s))	Tanya Wroblewski
Designated Signatory Authority	Albert Deisseroth

Additional Reviewers of Application

CMC – OPRO RBPM	Andrew Shiber
CMC – Team Leader (Application Technical Lead)	Brian Janelsins
CMC – OBP Reviewer	Anshu Rastogi
CMC – OBP Biosimilar Policy	Joel Welch/Marlene Schultz-DePalo
CMC – OBP Labeling Reviewer	James T. Barlow
CMC – Facility Team Leader	Peter Qiu
CMC – Micro Team Leader for Drug Substance and Drug Product	Dupeh Palmer
CMC - Drug Substance	Michael Shanks
CMC - Drug Product	Yarery Smith
OPDP	Rebecca Falter
Patient Labeling (DMPP)	Sharon Mills/Barbara Fuller
OSE/DEPI	Steven Bird/Fang Tian
OSE/DMEPA	Hina Mehta/Stephanie DeGraw
OSE/DRM	Peter Waldron/Mallika Mundkur
ICCR	Alan Stevens/Carolyn Dorgan/Rumi Young/Porsche Bennett

Other	

CMC=Chemistry, Manufacturing, and Controls
OBP=Office of Biotechnology Products
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
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
FDA	Food and Drug Administration
FISH	Fluorescence In Situ Hybridization
GCP	Good Clinical Practice
GMR	Geometric Mean Ratio
ICH	International Conference on Harmonization
IND	Investigational New Drug
ITT	Intention to Treat
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
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
SGE	Special Government Employee
SOC	System Organ Class
SOP	Standard Operating Procedures
TEAE	Treatment-Emergent Adverse Events
ULOQ	Upper Limit of Quantitation

1. Executive Summary

1.1. Product Introduction

- Proposed Proprietary Name: (b) (4)
- Proposed Non-proprietary Name: Pegfilgrastim-pbbk
- Code Name: TPI-120
  TPI-120 is a proposed biosimilar to US-licensed Neulasta (pegfilgrastim) (also referred to as US-Neulasta).
- Dosage Forms, Strength, Presentation: Injection (6mg/0.6mL in a single dose prefilled syringe)
- Pharmacologic Class: Leukocyte growth factor
- Mechanism of Action: TPI-120 is a colony-stimulating factor that act on hematopoietic cells by binding to specific cell surface receptors, thereby stimulating proliferation, differentiation, commitment, and end cell functional activation.
- 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 6mg 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

Not applicable.

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

The activity of US-licensed Neulasta is mediated by binding to the granulocyte colony stimulating factor (G-CSF) receptor and activation of downstream pathways in order to regulate the myeloid lineage. It stimulates the production of neutrophil precursors, and the differentiation and release of mature neutrophils form the bone marrow (1). US-licensed Neulasta 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).

TPI-120 is a pegylated recombinant granulocyte colony stimulating factor (PEG-GCSF. Comparative analytical testing included multiple orthogonal assays relevant to mechanism of action of US-Neulasta which demonstrated that TPI-120 and US-licensed Neulasta have the same mechanism of action, to the extent known.

The Applicant proposes to develop a preservative-free solution for injection (0.6 mL) containing 6 mg of pegfilgrastim-pccg (10 mg/mL) in a prefilled syringe.

The proposed dosage form, strength, and route of administration are the same as US-licensed Neulasta, and the conditions of use for which the applicant is seeking licensure have been previously approved for US-licensed Neulasta. The applicant is not seeking the following indication for US-Neulasta: to increase survival in patients acutely exposed to myelosuppressive doses of radiation. This indication is protected by orphan exclusivity until November 23, 2022.

1.4. Inspection of Facilities

Following an evaluation of an inspection performed at Kashiv Biosciences (FEI 3011289655) manufacturing facility at Chicago, IL, our field investigator observed objectionable conditions at the facility and conveyed that information to the representative of the facility at the close of the inspection. Satisfactory resolution of the remaining objectionable conditions, and verification by FDA, is required before this application may be approved. We recommend you contact your manufacturing facility if more information is needed.

We will continue to monitor the public health situation as well as travel restrictions. We are actively working to define an approach for scheduling outstanding inspections, once safe travel may resume and based on public health need and other factors. For more information, please see the FDA guidances related to COVID 19. These guidances can be found at https://www.fda.gov/emergency-preparedness-and-response/coronavirus-disease-2019-covid-19/covid-19-relatedguidance-documents-industry-fda-staff-and-other-stakeholders.

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

Not applicable. A non-U.S.-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 demonstrating that TPI-120 is highly similar to US-Neulasta, notwithstanding minor differences in clinically inactive components. The information provided in the current submission supports the demonstration that TPI-120 has the same strength as that of US-licensed Neulasta. • TPI-120 has the same dosage form and route of administration of US-Neulasta
Residual Uncertainties and Outcomes	• There are no residual uncertainties from the product quality assessment.
Nonclinical Studies	
Summary of Evidence	• A 90-day rat study designed to compare TPI-120 to Neulasta at a similar dose level (1000 µg/kg Once weekly) found no notable differences in expected hematology and related hematopeotic tissues in rats.
Residual Uncertainties and Outcomes	• There are no residual uncertainties from the pharmacology/toxicology assessment.
Clinical Pharmacology Studies	
Summary of Evidence	• In study TPI-CL-109-A, PK similarity was demonstrated between TPI-120 and US-Neulasta in healthy subjects. The 90% CI of the GMR for the primary PK endpoints C_{max} and AUC_{0-inf} were within the pre-specified margin of 80-125%. • In study TPI-CL-109-A, PD (ANC) similarity was demonstrated between TPI-120 and US-Neulasta in healthy subjects. The 90% CI of the GMR for the primary PD endpoints ANC E_{max} and $AUEC_{0-t}$ were within the pre-specified margin of 80-125%. • In study ADL-CL-112, a similar incidence of ADA formation was observed for TPI-120 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.

Residual Uncertainties and Outcomes	There are no residual uncertainties based on the clinical pharmacology analysis.
Clinical Studies	
Summary of Evidence	• In the comparative safety analyses of Studies TPI-CL-109A and ADL-CL-112, there were no substantial differences in adverse events, laboratory values, vital signs, or ECG changes. • In the comparative analysis of adverse events of special interest in Studies TPI-CL-109A and ADL-CL-112, there were no substantial differences in allergic reactions, musculoskeletal events, or injection site reactions. • The analysis of safety supports a demonstration of no clinically meaningful differences between TPI-120 and US-licensed Neulasta.
Residual Uncertainties and Outcomes	• There are no residual uncertainties based on the clinical safety analysis.
Extrapolation of Data to Support Licensure as a Biosimilar	
Summary of Evidence	The clinical team has determined that the Applicant has provided adequate scientific justification (based on mechanism of action, PK, immunogenicity, and toxicity) to support extrapolation of data and information submitted to support licensure of TPI-120 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.

1.7. Conclusions on Licensure

The Applicant is seeking licensure of TPI-120 as a biosimilar product to US-Neulasta for the

following indication which has been previously approved for US-Neulasta and for which TPI-120 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.
In considering the totality of the evidence submitted, the data submitted by the Applicant show that TPI-120 is highly similar to US-licensed Neulasta, notwithstanding minor differences in clinically inactive components and that there are no clinically meaningful differences between TPI-120 and U.S. licensed Neulasta in terms of safety, purity and potency of the product. The Applicant has provided adequate scientific justification for extrapolation of data and information to support licensure of TPI-120 for for the proposed indication.

However, data submitted in this application are not sufficient to support a conclusion that the manufacture of TPI-120 is well-controlled and will lead to a product that is safe, pure, and potent for the duration of the shelf-life. Therefore, a Complete Response is recommended. The Complete Response Letter will outline the deficiencies summarized below and the information and data required to support approval.

These deficiencies include 1) inadequate protocols for assessing the requalification of reference standards (b) (4); (2) inadequate qualification of the working reference standard (b) (4) (3) inadequate validation of the drug product filling operation at (b) (4); (4) inadequate strategy to control sequence variants in TPI-120; (5) inadequate validation of the purity by CEX-HPLC method (STM-0282) (b) (4); and (6) inadequate data to support comparability of drug product to maximum allowed levels of (b) (4) present in the primary container closure system.

Author:
Tanya Wroblewski
Cross Discipline Team Leader

2. Introduction and Regulatory Background

2.1. Summary of Presubmission Regulatory Activity Related to Submission

Relevant presubmission regulatory history pertaining to this BLA are summarized in the table

below.

Table 2 Regulatory History

November 24, 2014	IND 120048 for TPI-120, a proposed biosimilar to US-Neulasta, was opened.
December 15, 2014	Biosimilar Biological Product Development (BPD) Type 2 meeting was held to discuss the development program of TPI-120. -With regard to the proposed comparative clinical pharmacology (PK/PD) study, it was agreed that generally, a double-blind, randomized, controlled, crossover, comparative pharmacokinetic (PK) and pharmacodynamic (PD) study in healthy subjects is an acceptable study design to support a demonstration of PK and PD similarity for a proposed biosimilar to US-licensed Neulasta.
October 5, 2016	A second BPD Type 2 meeting was held to discuss the overall design of the comparative PK/PD and immunogenicity studies. -With regard to the Human Factor (HF) study, the FDA asked that the Applicant should submit a comprehensive risk analysis or plans for a HF validation study. If it is determined that an HF validation study is not needed for TPI-120, risk analysis and justification for not conducting the HF validation study should be submitted for review under the IND.
January 19, 2017	Another BPD Type 2 meeting was held to discuss the testing plan to establish analytical similarity between TPI-120 and US-licensed Neulasta.
September 1, 2017	The FDA issued an "Agreed Initial Pediatric Study Plan (iPSP)" to IND 120048 for the proposed indication "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." No pediatric clinical studies are planned. The Applicant is planning to fulfill PREA requirements by satisfying the statutory requirements for showing biosimilarity and by providing adequate scientific justification under the BPCI Act for extrapolating the pediatric information from US-licensed Neulasta, the reference product, to TPI-120. The Applicant requested deferral for development of appropriate pediatric presentation.
October 20, 2017	The FDA communicated to the Applicant that the proposal to combine the immunogenicity results from Studies ADL-CL-112 and TPI-CL-109A is not acceptable.

[Source: FDA compilation]

2.2. Studies and Publicly Available Information Submitted by the Applicant

Table 3 TPI-120: Comparative Nonclinical Studies

Study Number	Study Title	Dose Regimen/Route/Duration	Population
13-04551-G7	A 90-Day Repeat Subcutaneous Dose Toxicity Study of PEG-Theragrastim in Rats with a 14-Day Recovery Period"	1000 mcg/kg SC once weekly for 13 weeks.	Sprague Dawley rats

[Source: Applicant's submission]

Table 4 Listings of Clinical Studies Relevant to this BLA

Study ID/ country	Study Design	Regimen	Objectives	No. of Subjects/ Status
PK/PD Similarity Study				
TPI-CL-109-A	Randomized, double blind, single-dose, two-period crossover comparative pharmacology study comparing TPI-120 and US-Neulasta administered through subcutaneous (SC) route in healthy adult subjects	Single 2 mg dose of TPI-120 or US-Neulasta was administered SC on Day 1 of each period with a washout period of 34 days.	To compare PK/PD and safety.	Randomized: 120 subjects Completed: 109 subjects Study is completed
Comparative Clinical Study				
ADL-CL-112	Randomized, single blind, repeat-dose, two cycle, parallel-arm comparative immunogenicity study comparing TPI-120 to US-Neulasta in healthy adult subjects	Single 6 mg dose of TPI-120 or US-Neulasta was administered SC on Day 1 for 2 cycles separated by 21 days.	To compare the incidence of treatment-emergent anti-drug antibody (ADA) and safety.	Randomized: 230 subjects Completed: 216 subjects Study is completed

[Source: Applicant's submission]

Authors:
Hyon-Zu Lee, Pharm.D.
Clinical reviewer

Tanya Wroblewski, M.D.
Clinical team leader

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 quality and integrity of the submitted data and analyses were adequate. In study TPI-CL-109-A, data were reviewed/verified by the Clinical Research Associate and the PK section of final report was audited by (b) (4). In study ADL-CL-112, data were handled and processed based on the principles of GCP. The study was audited by the Quality Assurance department.

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 submission contained financial certification form 3454 signed by Michael Washabaugh, PhD, the Chief Scientific Officer, dated April 24, 2018 certifying that there were no financial arrangements with investigators involved in the two clinical studies TPI-CL-109-A and ADL-CL-112. The document included a list of investigators and sub-investigators that indicated the financial disclosures were collected and that no financial interests was reported for the 28 clinical investigators who participated in the covered studies.

The Applicant reported that none of the clinical investigators were full or part-time employees of the Applicant for the covered studies.

Authors:
Hyon-Zu Lee, Pharm.D.
Clinical reviewer

Tanya Wroblewski, M.D.
Clinical team leader

4. Summary of Conclusions of Other Review Disciplines

4.1. Chemistry, Manufacturing and Controls (CMC)

TPI-120 is a polyethylene glycol (PEG) modified non-glycosylated form of recombinant human granulocyte colony-stimulating factor (rhG—CSF) with an additional N-terminal methionine to enforce expression in *E. Coli.* Linear PEG is covalently attached to the G-CSF intermediate, which is composed of 175 amino acid residues with one free cysteine (Cys) residue at position 18 and two intramolecular disulfide linakges; the disulfide bonds from a loop-like structure that maintains the biologicall active conformation of the protein.

Sufficient analytical data are provided to support that TPI-120 is highly similar to US-licensed Neulasta, notwithstanding minor differences in clinically inactive components.

However, data submitted in this application are not sufficient to support a conclusion that the manufacture of TPI-120 is well-controlled and will lead to a product that is safe, pure, and potent for the duration of the shelf-life. Therefore, from a product quality perspective, the Office of Pharamaceutical Manufacturing (OPMA) and OBP are recommending a Complete Response letter be issued to Kashiv to outline the deficiencies summarized below and the information and data that will be required to support approval. These deficiencies include (i) inadequate protocols for assessing the requalification of reference standards (b) (4) (ii) inadequate qualification of the working reference standard (b) (4); (iii) inadequate information and data to support the cell-based potency assay (b) (4) (iv) inadequate validation of the drug product filtration and filling operation at (b) (4); (v) inadequate strategy to control sequence variants in TPI-120; (vi) inadequate validation of the purity by CEX-HPLC method (STM-0282) (b) (4) and (vii) inadequate data to support compatibility of drug product to maximum allowed levels of (b) (4) present in the primary container closure system.

From the product quality microbiology perspective and sterility assurance perspective and is recommended for approval, however manufacturing facility assessment recommendation is to

withhold. The Drug Substance manufacturint site, Kashiv Biosciences LLC is not acceptable and an inpsecton of the Kashiv Biosciences Drug Substance site is required before this application can be approved. The following are the microbiology complete response issues identified by OPMA:

Information regarding media fill studies is inadequate. Please update Section 3.2.P.3.5 of the BLA with the following:
a. Summarized results (media fill date, container closure, filled volume, duration, number of units filled/incubated/rejected, positive) from the three initial media fill validation runs and the latest requalification run that was performed to validate the syringe line filling process relevant to the drug product.
b. Description of the hold periods (date, temperature, duration) simulated in each media fill run.
c. Description of confirmatory growth promotion test. Include a list of microorganisms used in the test.

The bacterial retention study for the sterilizing-grade filter was performed using the drug substance, which is not adequate. Please update BLA section 3.2.P.3.5 with the following:
a. Protocol and data from the validation studies using three different lots of the sterilizing filter intended for commercial production using the final drug product solution.
b.Study/report # and the date of the study.
c. Comparison of validation test parameters with those used during routine operation (i.e., temperature, filtration time, filtration pressure, flow volume, and flow rate, etc.)
d. Description of the challenge microorganism, membrane lot numbers, pore size rating, pre- and post-filtration bubble point, challenge (CFU/cm2).
e. Demonstration of viability of the challenge organism in the presence of drug product.

4.2. Clinical Microbiology

Not applicable

4.3. Devices

4.3.1. Center for Devices and Radiological Health (CDRH)

CDRH concluded that the device constitutent parts of the combination product are not approvable with the following complete response deficiencies.

Complete Response 1:
You provided a design verification (DV) plan (DCP-0037), DV protocol (PTL-1712), and T=0, 6,24, and 36 month reports, as well as a (b) (4) safety device verification summary (DCP-0025) which were assessed for adequacy of testing to support verification of the device and proposed shelf

life. However, youd did mot provide adequate data for needle safety performance to support verication of the design and the proposed shelf life for the following reasons:

1. In the prefilled synringe design verification protocol, PTL-171, section 6.6 details the deliverable volume and autonomic safety device activation. Thirty samples were tested for deliverable volume and activatin force sequentlly and another 30 samples were soley tested for activation foce. However, automatic safety device activation was conducted for an attribute method and as such quantitative data was not measured to verify that the activation forces met specification. As such, the acceptance criteria for activation force testing as detailed in section 6.6 is inadequate.

   Section 6.9 details how you will test safety device activation force using a variable method. However, in section 6.9.2.2-6.9.2.3 of the protocol, it is stated to (b) (4) " which is not a representative method of forces that would be required to activate the needle guard. As such, the method for testing activation force as detailed in section 6.9 is inadequate.

2. You reference DCP-0025, attachment 1 to demonstrate that needle safety activation foce meets a 95% confidence level/99%/reliability criteria. While your firm's vendor, (b) (4) appears to have tested activation force to demonstrate a confidence and reliability of 95/99%, the testing does not appear to have been conducted with the to-be-marketed configuration of TPI-120 containing the TPI-120 drug solution. Since the activation foce may be impacted by the pre-filled syringe glide force, this testing must be conducted in the final finished combination product. Additionally, the AQL testing represents T+0 and does not asses performance of aged product. As such, you have not provided sufficient data to support a confidence and reliability of 95/99% for needle safety activation force to support verification of the design and the proposed shelf life.

3. You reference (b) (4) testing to demonstrate control of needle safety override force over shelf life. However, while (b) (4) conducted testing on the needle safety feature, which includes compression force esting, the testing appears to only be conducted for T=). Additionally, while (b) (4) performs AQL testing before releasing each lot in which Kashiv performs verification of Certificate of Conformance, lot release testing also represents only T=0 timpeoint. Thus, you have not provided adequate data to support needle safety override performance over the proposed shelf life.

Per FDA's Guidance for Industry and FDA Staff, "Medical Devices with Sharps Injury Prevention Features" bench testing should be conducted to assess the force to activate and deactivate the safety feature (i.e. activation force and override force). As such, the following data is required to support design verification and the proposed shelf life of TPI-120:

1. Provide design verification and shelf life testing to demonstrate needle safety activation force performance meets specification. Please ensure forces are evaluated after sequential shelf-life, shipping and drop/freefall, with final finished combination product, utilizing a variable method that is representative of forces that a user would experience to activate the needle guard (i.e. measured after depressing the drug product out of the syringe), meeting a confidence and reliability of 95/99%.
2. Provide test data for needle safety override force over shelf life.

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

DMEPA concluded that TPI-120 has the same intended users, use environments, dosing and route of administration as US-licensed Neulasta (BLA 125031) for its febrile neutropenia indication. The Applicant submitted a use-related risk analysis (URRA), which identified and evaluated the tasks involved in the use of the TPI-120 prefilled syringed (PFS), the errors that users might commit, the tasks they might fail to perform, and the potential negative consequences of use errors.

DMEPA reviewed the URRA for the proposed product and did not identify any new or unique risks for the TPI-120 PFS as compared to the US-licensed Neulasta PFS. The DMEPA reviewers noted that users are not required to activate the needle guard manually (as compared to the US-licensed Neulasta PFS).

DMEPA determined that the Applicant does not need to submit a human factors validation study for review at this time. Any changes to the URRA would warrant further review. Additionally, as a biosimilar, the proposed labeling for TPI-120 is, in relevant part, substantially the same as the labeling for US-licensed Neulasta regarding administration of doses less than 0.6mL (6mg).

4.4. Office of Study Integrity and Surveillance (OSIS)

The Division of New Study Drug Integrity (DNDSI) within the Office of Study Integrity and Surveillanance (SOSI) determined that inspections are not warranted at this time for the sites listed below. The rationale for this decision is that OSIS inspected the analytic site (b) (4) which falls within the surveillance interval. The final classification for the inspections was No Action Indicated (NAI). OSIS inspected the analytical site (b) (4) which falls within the surveillance interval and final classification for the inspection was No Action Indicated. Therefore, based on the rationale

described above, inspections are not warranted at this time.

4.5. Office of Scientific Investigations (OSI)

An OSI audit was not requested for this application.

Author:
Tanya Wroblewski
Cross Discipline Team Leader

5. Nonclinical Pharmacology and Toxicology Evaluation and Recommendations

5.1 Nonclinical Executive Summary and Recommendation

TPI-120 toxicity profile was compared to the referenced product, US-Neulasta, at a single dose level of 1000 µg/kg/week SC in a 90-day study in SD rat study with a 14-day recovery phase. Toxicological assessments were made at interim Day 30 (recovery group Day 44) and at the end of the study on Day 93 (recovery group Day 107). Per drug pharmacology, both products affected the hematology parameters in rats as early as interim day 30 and prominently on Day 93. Changes in the hematology parameters consisted of increases in white blood cells, neutrophil and platelet volume and decreases in red blood cells and lymphocytes. The hematological changes generally recovered by the end of a 14-day recovery phase. Hematological changes corresponded to microscopic changes in the tissues involved in hematopoiesis i.e. spleen, liver and bone marrow. The microscopic changes consisted of mild multifocal to moderate diffuse extramedullary hematopoiesis in spleen, bone marrow and liver. Both products also increase prothrombin time that persisted during recovery. The increase in serum ALP and BUN only partially recovered. Immunological assessment found only two samples (a control and US-Neulasta) that were positive for anti-human PEG-GCSF. The toxicokinetic analysis of TPI-120 and US-Neulasta did not reveal any substantial differences between the two products. TPI-120 exposure however, tended to be more variable than US-Neulasta. The t1/2 for TPI-120 ranged from 5.5 to 12.1 hr versus 7.9 to 8.9 hr for US-Neulasta. Overall, the 90-day rat study did not distinguish any notable toxicological or toxicokinetic differences between TPI-120 and the reference product, US-Neulasta, in the 90 day study in SD rats.

5.1.1. Nonclinical Residual Uncertainties Assessment

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

5.2. Product Information

Product Formulation

TPI-120 (6 mg/0.6 mL) is provided as sterile aqueous, clear, colorless and preservative free solution (pH 4.0). Each 0.6 mL syringe contains 6 mg TPI-120 (based on protein weight) , acetate (0.35 mg), sorbitol (30 mg), polysorbate 20 (0.02 mg) and sodium (0.02 mg) in water for injection, USP.

Comments on Novel Excipients

All the excipients in the TPI-120 fomulation are compendial.

Comments on Impurities/Degradants of Concern

There are no impurities or degradants with toxicological safety concern.

Authors:

Fred Alavi, PhD
Pharmacologist

Pedro Del Valle, PhD
Supervisory Pharmacologist

6. Clinical Pharmacology Evaluation and Recommendations

6.1. Clinical Pharmacology Executive Summary and Recommendation

The applicant submitted pharmacokinetic (PK), pharmacodynamic (PD), and immunogenicity data from two clinical studies in healthy subjects to support a demonstration of no clinically meaningful differences between TPI-120 and US-Neulasta.

Study TPI-CL-109-A was a single-center, randomized, single-dose, double-blinded, 2-period crossover, comparative study, to evaluate the PK and PD (absolute neutrophil count [ANC]) similarity of TPI-120 and US-Neulasta following a single 2 mg subcutaneous (SC) dose in healthy adult subjects (N=109). The results of the study TPI-CL-109-A established the PK and PD similarity between TPI-120 and US-Neulasta based on the primary PK (C_{max}, $AUC_{0-\infty}$, and AUC_{0-t}) and PD (observed ANC E_{max} and $AUEC_{0-t}$) endpoints.

Study ADL-CL-112 was a multi-center, randomized, single-blind, repeat-dose, 2-cycle, parallel-arm, comparative immunogenicity study to evaluate the immunogenicity of TPI-120 and US-Neulasta following multiple doses of 6 mg administered subcutaneously (2 doses, with a gap of 21 days between the 2 cycles/periods) in healthy subjects (N=230). The observed antidrug antibodies (ADA) formation was similar between TPI-120 and US-Neulasta. The study results

demonstrated non-inferiority of TPI-120 over US-Neulasta for the confirmed treatment induced ADA positive status.

Overall, the results from study TPI-CL-109-A and study ADL-CL-112 support the demonstration of no clinically meaningful differences between TPI-120 and US-Neulasta and add to the totality of the evidence to support a demonstration of biosimilarity between TPI-120 and US-Neulasta (Table 5)

Table 5: Clinical Pharmacology Major Review Issues and Recommendations

Review Issue	Recommendations and Comments
Pharmacokinetics Similarity	• In study TPI-CL-109-A, PK similarity was demonstrated between TPI-120 and US-Neulasta. The 90% CI of the GMR for the primary PK endpoints C_{max} and AUC_{0-inf} were within the pre-specified margin of 80-125%.
Pharmacodynamics Similarity	• In study TPI-CL-109-A, PD (ANC) similarity was demonstrated between TPI-120) and US-Neulasta. The 90% CI of the GMR for the primary PD endpoints ANC E_{max} and $AUEC_{0-t}$ were within the pre-specified margin of 80-125%.
Immunogenicity	• In study ADL-CL-112, a similar incidence of ADA formation was observed for TPI-120 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.

6.1.1. Clinical Pharmacology Residual Uncertainties Assessment

The clinical studies adequately demonstrated PK and PD similarity of TPI-120 to US-Neulasta and showed similar incidence of ADA formation between TPI-120 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-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 (TPI-CL-109-A) comparing TPI-120 to US-Neulasta® in healthy subjects. The study design (TPI-CL-109-A) 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.
- In healthy subjects, subcutaneous (SC) doses of 2 to 6 mg are in the linear range for PK. This dose range is also in the sensitive portion of the dose response curve for PD (ANC) assessments.
- A cross-over study design was used to assess the PK/PD similarity of TPI-120 and US-Neulasta. Refer to Section 7.2 for more detailed description on study design.
- A target washout period of at least 34 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 Endpoint

In Study TPI-CL-109-A, 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 TPI-120 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, 2, 4, 6, 8, 10, 12, 16, 20, 24, 36, 48, 72, 120, 168, 216, 264, 336, and 504 hours post-dose during each study period
- PD – blood samples for ANC measurements were collected at pre-dose, and 1, 4, 8, 16, 24, 48, 72, 120, 168, 216, 264, 336, and 504 hours post-dose during each study period.
- ADA – blood samples for anti-study drug antibodies were collected at four times during the study: pre-dose (Day 1 within 10 minutes prior to dosing) and Day 22 (± 60 minutes) of each study period.

Bioanalytical method for PK measurements and performance

See section 16.4.1.1. for details

PK similarity assessment

PK similarity between TPI-120 and US-Neulasta was demonstrated in the single-dose crossover study TPI-CL-109-A. The 90% CI of the GMR for PK (C_{max} and AUC_{0-inf}) endpoints were within 80-125% (Error! Reference source not found.). The geometric mean concentration-time profiles and a summary of the calculated PK parameters are shown in Error! Reference source not found. and Figure 1.

Figure 1: Mean concentrations (pg/mL) versus time (hours) from study TPI-CL-109-A

A. Linear Scale

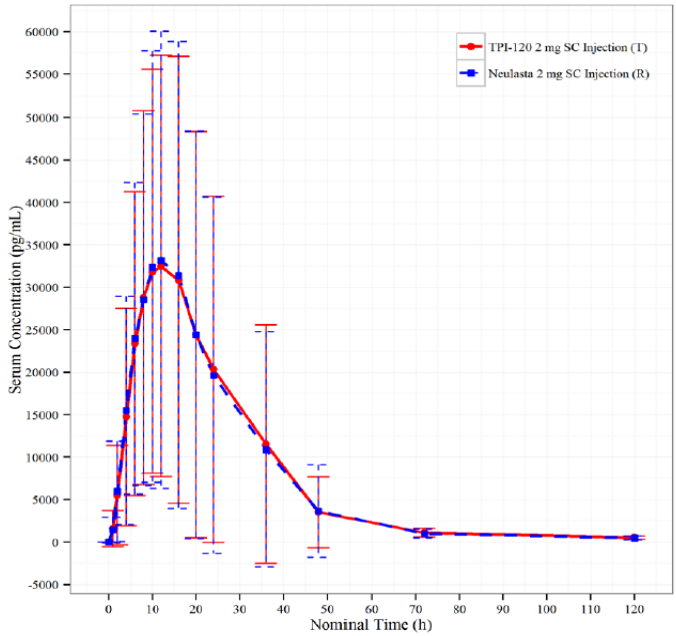


Table 6. Summary of statistical analyses for assessment of PK similarity (Study TPI-CL-109-A)

Parameter	Statistic	TPI-120 (n=108)	**US-Neulasta** (n=108)	Geometric Mean Ratio* (90% CI)
				TPI-120 vs **US-Neulasta®**
AUC_{0-inf} (pg*h/mL)	Geometric Mean	745724	694362	107 (96.5, 119.4)
AUC_{0-t} (pg*h/mL)	Geometric Mean	737613	672765	109 (98.1, 122.4)
C_{max} (pg/mL)	Geometric Mean	26859	24611	109 (95.5, 124.7)

*Presented as percent. Source: Reviewer's analysis

PD Similarity Assessment

PD (ANC) similarity between TPI-120 and US-Neulasta was demonstrated in the single-dose crossover study TPI-CL-109-A (Figure 2). The 90% CIs of the GMR for PD endpoints (ANC E_{max} and AUE_{0-t}) were within 80-125% (

Table 7).

Figure 2: Mean ANC concentration (x 10^9/L) vs. time (hr) from Study TPI-CL-109-A (Error bars – Standard deviation)

A. Linear Scale

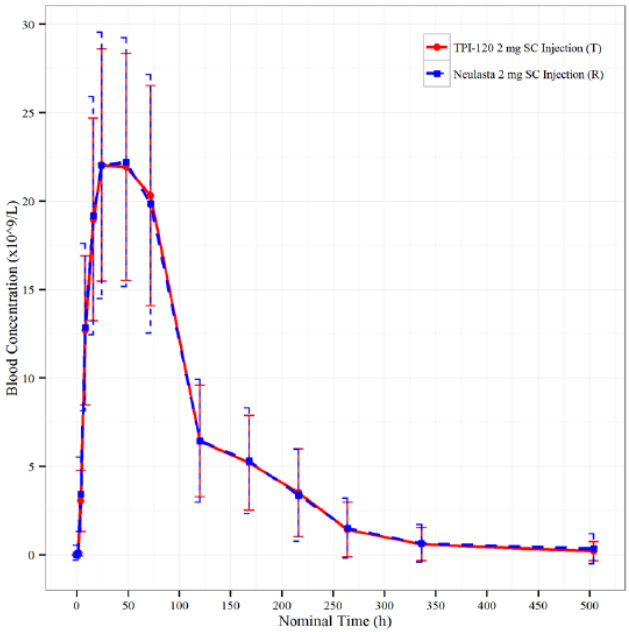


Table 7. Summary of statistical analyses for assessment of PD (biomarker) similarity (Study TPI-CL-109-A)

Parameter	Statistic	TPI-120 (n=109)	**US-Neulasta** (n=109)	Geometric Mean Ratio* (90% CI)
				TPI-120 vs **US-Neulasta**
AUE_{0-t} (10^9*h/L)	Geometric LS Mean	2636	2609	101.03 (96.9, 105.3)
ANC Emax (10^9/L)	Geometric LS Mean	22.6	22	102.72 (98.55, 107.07)

*Presented as percent. Source: Reviewer's analysis

6.4. Clinical Immunogenicity Studies

- Immunogenicity Assessment in study ADL-CL-112

Design features of the clinical immunogenicity assessment

The applicant conducted an immunogenicity study (ADL-CL-112) 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 TPI-120 and US-Neulasta in healthy adult subjects. Overall, 230 healthy adult subjects were randomized in either of the treatment arms, TPI-120 or US-Neulasta (n= 115/ treatment arm).

The primary objective of this study was to compare incidence of treatment-emergent anti-drug antibody (ADA) incidence rates between TPI-120 (Test) and US-Neulasta (Reference), over a course of 2 SC injections of 6 mg in healthy adult volunteers. The primary endpoint for immunogenicity was to estimate and compare the treatment-emergent ADA incidence rates for TPI-120 and US-Neulasta to evaluate potential differences between the 2 products.

The secondary objectives of the study were to compare the safety, antibody titer, prevalence, and neutralizing activity of TPI-120 and US-Neulasta. The secondary immunogenicity endpoints included the characterization of ADA for anti-PEG and anti-G-CSF backbone specificity and evaluation for persistence/duration and neutralizing activity. The secondary safety endpoints included physical examinations, vital signs measurements, 12-lead electrocardiograms (ECGs), AEs, injection site reactions, and clinical laboratory tests. Based on the study design described above, study ADL-CL-112 is considered adequate to assess immunogenicity risk.

The study design consisted of two treatment periods (TPI-120 and US-Neulasta). Each randomized subject received 1 SC dose of 6 mg (6mg/0.6 mL TPI-120 or US-Neulasta) administered on Day 1 of Period 1 (study day 1) followed by 1 SC dose of 6 mg administered on Day 1 of Period 2 (study day 22) with a gap of 21 days between the 2 cycles/periods.

Blood samples for immunogenicity assessments were collected at day 1 pre-dose (baseline), day 8 ± 1 of period 1, day 21 ± 1 of period 1 prior to administration of the dose on Day 1 of Period 2 (Study Day 22), day 8 ± 1 of period 2 (Study Day 29 ± 1), day 37 ± 1 of period 2 (Study Day 58 ± 1). Additional blood samples were collected for subjects whose final blood sample (on Study Day 58) was confirmed to be positive for ADA (for either drug product). Single or multiple follow-ups were done as per the sole discretion of the PI on a case-by-case basis until the particular subject's ADA levels returned to pre-dose baseline titers or below.

Safety (physical examination, vital signs, oral temperature, ECG, AEs, biochemistry, hematology, and urinalysis) were assessed through Day 37 of Period 2 (Study Day 58).

Immunogenicity endpoints

The primary endpoint was the relative ADA incidence between TPI-120 and US-Neulasta. Any confirmed positive samples were also evaluated for ADA titer, ADA persistence/duration, and neutralizing activity. These aspects were evaluated qualitatively to determine if any differences are clinically meaningful. Anti-PEG antibody response was also to be evaluated and compared as secondary immunogenicity endpoint.

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 TPI-120 and US-Neulasta in the study samples. The sensitivity of the ADA assay was 11 ng/mL for anti-pegfilgrastim antibodies and 99 ng/mL for anti-PEG antibodies (specificity assay). Drug tolerance was evaluated with anti-pegfilgrastim antibody and TPI-120 and US-Neulasta. For TPI-120, the assay is tolerant up to 0.250 µg/mL of TPI-120 at 20.0 and 40.0 ng/mL, 1.00 µg/mLof TPI-120 at 100 ng/mL and ≥ 1.50 µg/mL at 500 ng/mL. For US-Neulasta, the assay is tolerant ≥ 1.50 µg/mL of US-Neulasta at 100 and 500 ng/mL. There was no positive response for the 20.0 and 40.0 ng/mL. The sensitivity of the Nab assay was 202 ng/mL for TPI-120 drug control and 247 ng/mL for US-Neulasta drug control. 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 ADL-CL-112 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 (pre-dose), day 8 ± 1 and day 21 ± 1
- Period 2: Day 1 (Study Day 22), day 8 ± 1 (Study Day 29 ± 1), day 37 ± 1 (Study Day 58 ± 1)

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

Table 8. Immunogenicity results for binding ADA and nAb in Study ADL-CL-112.

	N	Anti-[drug] antibody		Nab
		Baseline	Treatment-Induced	
TPI-120	115	1/115 (0.9%)	8/114 (7.0%)	0
US-Neulasta	115	6/115 (5.2%)	16/108 (14.8%)	1/108 (0.9%)

Source: Applicant's analysis

These results indicate that overall, only 7% of the subjects had confirmed detectable serum anti-study drug antibodies following TPI-120 administration compared to 14.8% of subjects following US-Neulasta.

Neutralizing antibodies

Only one subject showed neutralizing activity of the antibody post-dose, and it was observed following US-Neulasta administration.

Anti-PEG antibodies

At pre-dose, 1 subject tested positive (0.9%) for anti-PEG antibodies in each treatment arm (TPI-120 and US-Neulasta). None of the subjects treated with TPI-120 showed specificity for the inactive PEG component, while 9 subjects (8.3%) treated with US-Neulasta showed specificity to PEG.

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

A sensitivity analysis including subjects tested positive to ADA (N = 108) was performed using the PK data from study TPI-CL-109-A. The 90% CI of the GMR for PK endpoints were within 80-125% for both the analysis including and excluding the subjects tested positive to ADA (

Table 9).

Table 9: Summary of statistical analyses for assessment of PK similarity (TPI-CL-109-A) with and without ADA

Parameter	Geometric Mean Ratio* (90% CI)	Geometric Mean Ratio* (90% CI)
	TPI-120 vs **US-Neulasta** without ADA	TPI-120 vs **US-Neulasta** with ADA
$AUC_{0\text{-inf}}$ (pg*h/mL)	107 (97, 118.2)	107 (96.5, 119.4)
$AUC_{0\text{-t}}$ (pg*h/mL)	108 (97.3, 119.4)	109 (98.1, 122.4)

C_{max} (pg/mL)	107 (94.8, 121.7)	109 (95.5, 124.7)

*Presented as percent. Source: Reviewer's Analysis

Thus, it can be concluded that the ADA status did not impact PK parameters for TPI-120. Furthermore, there was no impact of ADA on PD or safety of TPI-120.

Also, refer to Section 7.2.2 for more information about the study and the results from the noninferiority test. The review team concluded that the non-inferiority of TPI-120 to US-Neulasta with respect to treatment-emergent ADA+ response was demonstrated because the lower bound of 90% CI for the proportion difference was above the NI margin of -10%.

Overall, in study ADL-CL-112, a similar incidence of ADA formation was observed for TPI-120 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.
Authors:

Anusha Ande, Ph.D.
Clinical Pharmacology Reviewer

Shirley Seo, Ph.D.
Division Director

7. Statistical and Clinical Evaluation and Recommendations

7.1. Statistical and Clinical Executive Summary and Recommendation

The BLA submission contained a double-blind, randomized, single-dose, two-period, PK/PD crossover study (TPI-120-CI-109-A) and a randomized, parallel, non-inferiority, immunogenicity study (ADL-CL-112) to support the licencure of TPI-120 as a biosimilar product to US-Neulasta for the same approved indication (i.e., 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 the Hematopoietic Syndrome of Acute Radiation Syndrome indication due to an Orphan Drug Exclusivity that expires on November 13, 2022.

The safety evaluation of TPI-120 was based on a total of 350 subjects who participated in the comparative studies [TPI-CL-109-A crossover study: 120 subjects (TPI-120: 119 subjects, US-Neulasta: 111 subjects), ADL-CL-112: 230 subjects (TPI-120: 115 subjects, US-Neulasta: 115 subjects)].

In study ADI-CL-112, among subjects who had positive anti-drug antibody postdose, all subjects in both treatments (TPI-120: 100%, US-Neulasta: 100%) experienced treatment emergent

adverse events (TEAEs). TEAEs that occurred in more than 1 subject in the TPI-120 arm were back pain, headache, myalgia, nausea and pain in extremity.

The overall safety profile of TPI-120 was similar to that of US-Neulasta. The safety results from the comparative clinical studies supports demonstration of no clinically meaningful differences between TPI-120 and US-Neulasta.

7.1.1. Statistical and Clinical Residual Uncertainties Assessment

There are no residual uncertainties based on the clinical safety evaluation.

7.2. Review of Comparative Clinical Studies with Statistical Endpoints

7.2.1. TPI-CL-109-A

Title: A Randomized, Double-Blind, Single-Dose, Two-Period Crossover Comparative Pharmacology Study Comparing TPI-120 and Neulasta® administered through subcutaneous route in Healthy Adult Subjects.

Study Initiation Date (first subject visit): March 3, 2017
Study Completion Date (Last Subject Last Visit): January 18, 2018
Study Site: The study was conducted at one site in the US.

Study Design and Endpoints

This study was a single-center, double-blind, randomized, single-dose, two-period crossover study to compare PK and PD of TPI-120 (T: test product) to US-Neulasta (R: reference product) in healthy adult subjects. Subjects were to receive 2 mg of study treatment (T or R) by subcutaneous injection. Treatments were administered to all subjects in a crossover fashion.

Study treatment:

- Treatment R: 0.2 mL of 10 mg/mL solution for injection (2 mg) of US-Neulasta (Amgen Inc., USA)
- Treatment T: 0.2 mL of 10 mg/mL solution for injection (2 mg) of TPI-120 (Adello Biologics, LLC, USA)

A total of 122 subjects were to be randomized (stratified by body weight: 50 kg-75 kg vs 75.1 kg-100 kg) to one of the two treatment sequences (TR or RT) (61 subjects per sequence) with 34 days washout between study treatments. At each period, study drugs were to be administered to each subject as a 2 mg SC injection according to the randomization scheme.

Table 10 TPI-CL-109-A: Subject Treatment Assignment

	N	Period 1	Period 2
Sequence 1	**61**	Treatment R	Treatment T
Sequence 2	**61**	Treatment T	Treatment R

[Source: CSR]

The recommended dose for US-Neulasta is 6 mg. (b) (4) The elimination of pegfilgrastim is non-linear with respect to dose; serum clearance of pegfilgrastim decreases with increasing dose. Pegfilgrastim appears to be mainly eliminated by neutrophil mediated clearance, which becomes saturated at higher doses. A lower dose may be more likely to be located in the (sensitive for differences) steep and linear part of the dose-response curve of the PD endpoint, ANC and reduce the likelihood of decreased serum clearance due to the saturation of the neutrophil-mediated clearance pathway of pegfilgrastim.

Pegfilgrastim has a half-life of up to 80 hours. A washout period of 34 days was used in the study to avoid the potential for drug carry-over effects for both the PK (> 10 half-lives i.e. 33.3 Days) and PD (blood cell counts completely normalize by Day 34).

Drug administration was performed on the morning of Day 1, after subjects had undergone a overnight fast of at least 10 hours. The study drug was administered approximately 0.5 to 1 hour after a light breakfast. Subjects were to be confined from at least 10 hours before dosing and for 36-hours after dosing for post-dose blood draws. Return visits were scheduled for Days 3, 4, 6, 8, 10, 12, 15, and 22.

Population: Healthy male or female subjects 19 - 55 years of age (inclusive), with body mass index (BMI) between 19 and 30 kg/m^2 (inclusive), and body weight not < 50 kg or > 100 kg. A subject had no be a non-smoker. Inclusion criteria included WBC count > 4.0 x 10^9/L and < 1.5 x ULN, ANC > 2.0 x 10^9/L and < 1.5 times ULN, platelet count > 150 x 10^9/L, AST < 2.5 x ULN, ALT < 2.5 x ULN, serum bilirubin < 1.5 x ULN, and serum creatinine < 1.5 x ULN; absence of febrile (defined by a documented oral temperature of 101.5 °F or greater) or infectious illness within 1 week of first dosing. Female subjects of childbearing potential and male subjects and their partners of childbearing potential, agreed to pregnancy prevention throughout the duration of the study (through the follow-up visit), and agreed to use an effective method of contraception.

Objectives:

The primary objective was to compare the PK and PD of TPI-120 with US-Neulasta following a single 2 mg dose in a crossover design with a washout period of at least 34 days in healthy adult subjects.

The secondary objective was to assess and compare the safety and tolerability of TPI-120 to US-Neulasta.

Endpoints:

Primary endpoints:

- For PK analyses: AUC_{0-t}, AUC_{0-inf}, and C_{max};
- For PD analyses: $AUEC_{0-t}$ and E_{max} calculated using baseline-corrected absolute neutrophil count (ANC) data.

Secondary endpoints:

- For PK analyses: Residual area [Calculated as $100*(1- AUC_{0-t} / AUC_{0-inf})$], time of observed C_{max} (T_{max}), elimination half-life ($T_{½ el}$), elimination rate constant (K_{el});
- For PD analyses: For ANC baseline-corrected: T_{maxE}, time of observed E_{max}; For ANC baseline-uncorrected: $AUEC_{0-t}$, E_{max}, and T_{maxE};
- Safety parameters, i.e., adverse events (AEs), laboratory evaluations (biochemistry, hematology, coagulation and urinalysis), vital signs, 12-lead electrocardiogram (ECG), immunogenicity evaluation, and physical examination.

Schedule of Events

Table 11 TPI-CL-109-A: Schedule of Assessment

PROCEDURE	Screening (Days -28 to -1)	Days (To be considered for both study periods)											Study Exit (Day 22 + 3 after last dose in period 2 or early withdrawal)
		C-I*	1	2	3	4	6	8	10	12	15	22	
Informed Consent	X[1]												
Demographic Data	X												
Medical and Medication Histories	X												
Review of AEs and Concomitant Medications		X	X	X	X	X	X	X	X	X	X	X	X
Physical Examination	X	X											X
Body Measurements[2]	X	X											
Vital Signs[3]	X	X	X	X	X	X	X	X	X	X	X	X	X
Oral Temperature[4]	X	X	X	X	X	X	X	X	X	X	X	X	X
ECG[5]	X		X										X
Biochemistry[6]	X							X				X	X
Hematology	X	X						X				X	X
HIV and Hepatitis	X												
Urinalysis	X												X
Urine Alcohol Test	X	X											
Urine Drug Screen	X	X											
Serum Pregnancy Test	X	X										X	X
FSH (postmenopausal females only)	X												
Urine Cotinine Test	X	X											
Review of Inclusion/Exclusion criteria	X	X											
Coagulation	X												X
Injection Site Evaluation[7]			X	X									
Confinement[8]		X	X	X									
Ambulatory Visits	X				X	X	X	X	X	X	X	X	X
Study Drug Administration			X										
Blood Sampling for PK[9]			X	X	X	X	X	X	X	X	X	X	
Blood Sampling for ANC/WBC[10]			X	X	X	X	X	X	X	X	X	X	
Blood Sampling for Anti-PEG—rhG CSF Antibodies[11]			X									X	

*C-I : Check in (Day -1) - All check-in plus pre dose activities except pre dose vital signs prior to respective study period needs to be completed within 24 hours prior to dosing. Pre dose vital signs need to be carried out within 3 hours prior to dosing for the respective study period.

1. Informed consent must be obtained from all subjects prior to any study-related assessments.
2. Height and body weight will be measured and BMI will be calculated at screening. Body weight will be measured at check-in (Day -1).
3. Blood pressure, heart rate, and respiratory rate: at screening, check-in (Day -1) and 0.25, 0.5, 2, 4, 12 (Day 1), 24, 36 (Day 2), 48 (Day 3), 72 (Day 4), 120 (Day 6), 168 (Day 8), 216 (Day 10), 264 (Day 12), 336 (Day 15), and 504 (Day 22) hours post-dose, and at study exit (Day 22 + 3 after the last injection). Post dose vital signs measurements taken up to 24 hours would be having ± 10 minutes of window period to avoid unnecessary deviation. The subject must remain in a seated position for 5 minutes before vital signs are obtained. Vital signs should be measured in sitting position.
4. Oral body temperature: at screening, check in (Day -1), pre-dose and 4, 6, 12 (Day 1), 24, 36 (Day 2), 48 (Day 3), 72 (Day 4), 120 (Day 6), 168 (Day 8), 216 (Day 10), 264 (Day 12), 336 (Day 15), and 504 (Day 22) hours post-dose, and at study exit (Day 22 + 3 after the last injection). Post dose oral body temperature measurements taken up to 24 hours would be having ± 10 minutes of window period to avoid unnecessary deviation.
5. ECG: at screening, 5 hours post-dose (±30minutes), and at study exit (Day 22 + 3 after the last injection).
6. Biochemistry: at screening, Day 8 (liver panel only, i.e., AST, ALT, LDH, alkaline phosphatase, and uric acid), Day 22, and at study exit (Day 22 + 3 after last injection).
7. Injection site evaluation: approximately 1, 2, 4, and 24 hours post-dose. If applicable, extend injection site evaluation until the reaction is resolved.
8. Subjects will be confined from at least 10 hours before drug administration (Day -1) until after the 36-hour post-dose blood draw (Day 2).
9. Blood samples for PK: pre-dose and at 1, 2, 4, 6, 8, 10, 12, 16, 20 (Day 1), 24, 36 (Day 2), 48 (Day 3), 72 (Day 4), 120 (Day 6), 168 (Day 8), 216 (Day 10), 264 (Day 12), 336 (Day 15), and 504 (Day 22) hours post-dose.
10. Blood sampling for ANC/WBC determination: pre-dose and at 1, 4, 8, 16 (Day 1), 24 (Day 2), 48 (Day 3), 72 (Day 4), 120 (Day 6), 168 (Day 8), 216 (Day 10), 264 (Day 12), 336 (Day 15) and 504 (Day 22) hours post-dose.
11. Blood sampling for anti-PEG-rhG-CSF antibody detection: Total 4 blood samples would be taken during the entire study: pre-dose (Day 1 of each study period within 10 minutes prior to dosing) & Day 22 of each study period (± 60 minutes from the reference dosing time).

[Source: Protocol]

Statistical Methodologies

A target of 122 healthy adult subjects were to be randomized (with 106 subjects to complete the study) to receive one of the two treatment sequences. The power for the sample size was conducted under the following assumptions:

- A 2x2 crossover design comparing the test and reference products;
- Difference of 5% geometric mean ratio between the test and reference products;

- Utilizing the estimate of 52% as the highest intrasubject CV% for AUC, approximately 106 subjects would be required to complete a 2x2 randomized crossover study to conclude similarity with 80% power. This estimate assumes that the geometric mean ratio of the natural log-transformed parameters of interest fall within 0.95-1.05 and the two, one-sided 90% CIs fall within the boundary of 80.00-125.00%;
- Sample size calculation was performed based on natural log-transformed data;
- Schuirmann's two one-sided tests procedure was used at the 5% level of significance;
- Sample size required was selected for achieving an 80% power for establishing biosimilarity.

A total of 53 subjects per sequence were required for achieving 80% power for establishing PK and PD similarity between TPI-120 and US-Neulasta assuming that there is a 5% difference based on Schuirmann's two one-sided tests procedure at the 5% level of significance and the biosimilarity limits of (80.00%, 125.00%). Sixteen more subjects were to be dosed to account for possible dropouts (15%) for a total of 122 subjects.

Statistical analyses were to be performed on the PK and PD parameters under the two-period crossover design.

Criteria for PK similarity: The 90% CIs of the geometric mean ratios (T/R) of least-squares means from the ANOVA of the natural log-transformed AUC_{0-t}, AUC_{0-inf}, and C_{max} had to within 80.00% to 125.00% to conclude in favor of biosimilarity.

Criteria for PD similarity: For baseline-corrected ANC, the 90% CIs of the geometric mean ratios (T/R) of least-squares means from the ANOVA of the natural log-transformed $AUEC_{0-t}$ and E_{max} had to be within 80.00% to 125.00% to conclude in favor of biosimilarity.

Subject Disposition

Study TPI-CL-109-A was a two-period crossover study. A total of 120 subjects (TPI-120/US-Neulasta: 60 subjects, US-Neulasta/TPI-120: 60 subjects) were randomized in the study.

The Safety Population was comprised of a total of 120 subjects who received at least one dose of study treatment (a total of 119 subject received TPI-120; and a total of 111 subjects received US-Neulasta during both periods). A total of 109 subjects (90.8%) completed both treatment periods and 11 subjects (9.2%) withdrew from the study. Of the 11 subjects who prematurely discontinued the study, one subject (0.9%) discontinued after last treatment with US-Neulasta (due to schedule conflict) and 10 subjects (8.4%) discontinued after last treatment with TPI-120.

Table 12 TPI-CL-109-A: Subject Disposition

	TPI-120/US-Neulasta (n=60)	US-Neulasta/TPI-120 (n=60)	Total (n=120)
Randomized population	60 (100%)	60 (100%)	120 (100%)
Safety population	60 (100%)	60 (100%)	120 (100%)
Received both TPI-120 and US-Neulasta	51 (85.0%)	59 (98.3%)	110 (91.7%)
Only received TPI-120	9 (15.0%)	0	9 (7.5%)
Only received US-Neulasta	0	1 (1.6%)	1 (0.8%)
Completed all periods	51 (98.3%)	58 (96.7%)	109 (90.8%)
Discontinued	9 (1.6%)	2 (3.3%)	11 (9.2%)#
Reasons for study discontinuation			
Physician decision	4 (6.7%)	0	4 (3.3%)
Adverse event	1 (1.6%)	0	1 (0.8%)
Non-compliance	1 (1.6%)	0	1 (0.8%)
Withdrawal by subject	0	1 (1.6%)	1 (0.8%)
Other	3 (5.0%)*	1 (1.6%)**	4 (3.3%)

* Includes subjects unable to make follow up visits, transportation issues, and use of medications other than hormonal contraceptives/hormone replacement therapy and/or thyroid replacement therapy.
**Schedule conflict (after receiving US-Neulasta).
Of the 11 subjects who discontinued the study, 1 subject discontinued after last treatment with US-Neulasta (due to schedule conflict); and 10 subjects discontinued after last treatment with TPI-120.
[Source: ADSL.xpt]

Protocol Deviations:
In study TPI-CL-109-A, all 120 subjects had at least one protocol violation. A total of 415 protocol violations were reported. The majority of protocol violations were in the category of Other (226, the majority of which were blood draws collected outside of the time window allowed), followed by Vital Signs (128 deviations, the majority of which were measurements not completed), and Pharmacokinetic (42 deviations, mainly PK blood collection collected outside of the time window allowed). The violations in the blood sampling schedule did not impact the statistical analyses since only the actual collection times were used in the PK and PD calculations. No deviations were reported to have met the criteria for IRB reporting and unlikely to have affected the overall safety results.

Demographics and Baseline Characteristics

See Table 18 in section 7.3.2.

Efficacy Results

Efficacy evaluations were not conducted in the study.

PK/PD Results

The primary objectives were to compare the PK and PD of TPI-120 with US-Neulasta following a single 2 mg dose in a crossover design with a washout period of at least 34 days in healthy adult subjects. For results of the primary endpoint, see Section 6.

7.2.2. ADL-CL-112

Title: A Randomized, Single Blind, Repeat-dose, Two Cycle, Parallel-Arm Comparative Immunogenicity Study Comparing TPI-120 to Neulasta® in Healthy Adult Subjects.

Study Initiation Date: March 25, 2017
Study Completion Date (Last Subject Last Visit): April 12, 2018
Study Site: The study was conducted at two sites in the US.

Study Design and Endpoints

The study was a multi-center, randomized, single-blind (blinded to subjects only), repeat-dose, 2-cycle, parallel-arm, comparative immunogenicity study in 230 healthy adult subjects (115 subjects per arm). Subjects were randomization using body weight as a variable. An adaptive study design was used which included an interim analysis. The original sample size of 102 subjects (51 per arm) was adjusted with the addition of 128 subjects based on the interim analysis results.

Subjects received a single dose of study drug 6 mg (6mg/0.6 mL TPI-120 or US-Neulasta) in 2 cycles separated by 21 days [one SC dose of study drug 6 mg on Day 1 of Period 1 (Study Day 1) followed by one SC dose of 6 mg administered on Day 1 of Period 2 (Study Day 22)]. Subjects were confined from at least 10 hours prior to dosing and until 36 hours postdose on Day 2 in each cycle. Subjects were to return for all subsequent blood draws and assessments.

- Test Treatment A: 6 mg (6 mg/0.6 mL solution) in a single-dose prefilled syringe for manual use only of TPI-120, (Adello Biologics LLC, USA).
- Reference Treatment B: 6 mg (6 mg/0.6 mL solution) in a single-dose prefilled syringe for manual use only of US-Neulasta(pegfilgrastim), (Amgen Inc., USA).

Population: Healthy male or female subjects, 19 to 55 years of age (inclusive), with BMI between 19 and 30 kg/m^2, and body weight of 50 kg to 100 kg. Subjects had to be a non-smoker (no use of tobacco or nicotine products within 3 months prior to dosing). Inclusion criteria included WBC > 4.0 x 10^9/L and < 1.5 x ULN, ANC > 2.0 x 10^9/L and < 1.5 x ULN, platelet count > 150 x 10^9/L, AST < 2.5 x ULN, ALT < 2.5 x ULN, serum bilirubin < 1.5 x ULN and serum creatinine < 1.5 x ULN at the time of screening. Subjects had to be afrebrile (defined by oral temperature of <101.5 °F) and absence of infectious illness within 1 week of first dosing. Female subjects of childbearing potential and male subjects and their partners of childbearing

potential, agreed to pregnancy prevention throughout the duration of the study (through the follow-up visit), and agreed to use an effective method of contraception.

Subjects who had positive test for hepatitis B, hepatitis C, or human immunodeficiency virus (HIV); history of allergic reactions to pegfilgrastim, filgrastim, E. coli-derived proteins, or other related drugs; hereditary fructose intolerance; clinically significant ECG or vital sign abnormalities; history of pulmonary infiltrate or pneumonia (radiologically confirmed) within 6 months; past exposure to recombinant human G-CSF products and/or a known history of prior treatment with blood-cell colony stimulating factors, interleukins, or interferons; subjects who were on a special diet or who had self-reported a weight loss of more than 15 pounds within 1 month; history of any clinically significant disease or condition that were excluded from the study. Subjects who had received any vaccination (including influenza) within 90 days prior to initial dosing were also excluded.

Prescription and over-the-counter medications were prohibited throughout the study with the exception of hormonal contraceptives/HRT and/or thyroid replacement therapy.

Objectives:

The primary objective was to compare the incidence of treatment-emergent anti-drug antibody (ADA) incidence rates between TPI-120 (Test) and US-licensed Neulasta (Reference), over a course of two SC injections of 6 mg in healthy adult volunteers.

The secondary objectives were to compare the safety, antibody titer, prevalence, and neutralizing activity of TPI-120 and US-licensed Neulasta.

Endpoints:

- The primary endpoint was the relative ADA incidence between TPI-120 and US-licensed Neulasta. Any confirmed positive samples were also evaluated for ADA titer, ADA persistence/duration, and neutralizing activity. These aspects were evaluated qualitatively to determine if any differences are clinically meaningful. Anti-PEG antibody response was also to be evaluated and compared as secondary immunogenicity endpoint.

- Safety endpoints included physical examinations, vital signs measurements, 12-lead electrocardiograms (ECGs), AEs, injection site reactions, and clinical laboratory tests (hematology, coagulation, serum chemistry, and urinalysis).

Schedule of Events

Table 13 ADL-CL-112: Schedule of Assessment

Procedure	S[a]	Study event in Cycle 1 & Cycle 2						Study Exit[m]
Study Day		C-I[b]	1	2	4	8 ± 1	15 ± 1	58 ± 1
Informed Consent	X							
Inclusion/Exclusion Criteria	X	X						
Demographic Data	X							
Body measurement[c]	X	X[d]						
Medical History	X							
Physical Examination	X	X[d]				X		X[n]
Vital Signs (HR, BP, RR)[f]	X	X[d]	X	X	X	X		X[n]
Oral Temperature[g]	X	X[d]	X	X	X	X		X[n]
ECG[h]	X	X[d]	X					X[n]
Hematology[e]	X	X[d]				X		X[n]
Serum Chemistry[e]	X					X		X[n]
Urinalysis[e]	X	X[d]				X		X[n]
Coagulation	X							X[n]
Urine Alcohol Test, Urine Cotinine, and Urine Drug Screen	X	X[d]						
Hepatitis B, C & HIV Testing	X							
Serum Pregnancy Test (female only)	X	X[d]						X[n]
FSH (PMP female only)	X							
Injection site evaluation[i]			X	X				
Telephonic safety follow up call							X	
AEs and Concomitant Medication Monitoring		X	X	X	X	X	X	X
Pegfilgrastim Injection			X					
Blood sampling for Anti- PEG-rhG-CSF Antibodies[j,o]			X			X		X
Confinement[k]		X	X	X				
Ambulatory Visits[l]					X	X		X

C-I = Check-in, ConMeds = Concomitant medication,
Hem = Hematology, S = Screening

Note:
a. Within 28 days of the first study drug administration.
b. Subjects were admitted to the CRU at the time indicated by the CRU.
c. Height and body weight were measured and BMI was calculated at screening. Body weight was measured at check-in (Day -1).
d. Performed within 24 hours prior to dosing.
e. Laboratory specifications as per concerned CRO's SOP.
f. Blood pressure, respiratory rate, and heart rate: predose, and 0.25, 0.5, 2, 4, 6 12 (Day 1), 24, 36 (Day 2), 72 (Day 4), 168 (Day 8 ± 1) hours postdose in each Cycle. Postdose vital signs measurements taken up to 24 hours had ± 10 minutes of window period to avoid unnecessary deviation. The subject remained in a seated position for 5 minutes before vital signs were obtained. Vital signs were measured in sitting position.
g. Oral temperature: predose and 0.25, 0.5, 2, 4, 6, 12 (Day 1), 24, 36 (Day 2), 72 (Day 4), 168 (Day 8 ± 1) hours postdose in each Cycle. Postdose oral body temperature measurements taken up to 24 hours had ± 10 minutes of window period to avoid unnecessary deviation.
h. ECG: predose and approximately 5 hours postdose (± 30minutes), and at study exit (Day 58 ± 1) or prior to early termination.
i. Injection site evaluation: approximately 0.5, 2, 4, 6, 12 (Day 1), 24 (Day 2) hours postdose in each cycle.
j. Samples for Immunogenicity assessment: First collection prior to administration of the dose on study Day 1 (Day 1 of Cycle 1), second collection on Study Day 8 ± 1, third collection on Study day 21 ± 1 prior to administration of the dose on study Day 22 (Day 1 of Cycle 2), fourth collection on Study Day 29 ± 1, and fifth collection on Study Day 58 ± 1.
k. Subjects were confined from at least 10 hours before drug administration (Day -1) until after the 36-hour (Day 2).
l. On these days, subjects returned daily to the CRU at the time determined by the CRU, to complete activities and assessments for the day.
m. Subjects returned to the CRU on Study Day 58 ± 1 for follow-up procedures, and to determine if any AE had occurred since the last study visit. Subjects who terminated the study early underwent the follow-up study procedures at the time of early withdrawal or within approximately 14 days after the last participation and may have been further contacted if the Investigator or designee deemed necessary.
n. Performed at the follow-up visit or prior to early termination.
o. Any subjects with a positive ADA were followed-up until ADA levels returned to baseline.

[Source: CSR]

Statistical Methodologies

A target of 230 subjects (115 per arm) was required for achieving 80% power for establishing biosimilarity between the test and reference products at 5% significance level for the one-sided non-inferiority test. The following assumptions were used:

- The ADA incidence rate of US-Neulasta and TPI-120 is 1%
- The mean ADA rate difference between the two products is zero
- Non-inferiority margin is 10%
- One-sided test with 5% significance level
- 80% statistical power

The null hypothesis of the NI comparison was that difference in proportion of ADA+ response in US-Neulasta arm minus the proportion in TPI-120 arm was less than the NI margin of -10% and non-inferiority would be demonstrated if the lower bound of the 90% confidence limits is greater than -10%.

The proportion of the treatment-emergent ADA+ response was calculated as the number of subjects with confirmed treatment-emergent ADA+ response in a treatment arm divided by the number of evaluable subjects in that treatment arm.

The rate difference between TPI-120 and US-Neulasta was defined as:

$$\delta = \pi_1 - \pi_2$$

Where $\pi_1$is the ADA+ rate of TPI-120, and π_2 is the ADA+ rate of US-Neulasta.

The primary statistical hypotheses were the following:

$$H_0: \delta \geq 0.10 \text{ vs. } H_1: \delta < 0.10$$

The above hypotheses were equivalent as follows:

$$H_0: \pi_2 - \pi_1 \leq -0.10 \text{ vs. } H_1: \pi_2 - \pi_1 > -0.10$$

Confidence intervals (CIs) were calculated using the Farrington-Manning method in the primary analysis and the null hypothesis would be rejected (i.e., TPI-120 is not inferior to US-Neulasta) if the lower bound of the one-sided 95% CI of the difference was above non-inferiority margin (-0.10).

The study had an adaptive size interim analysis plan.

- To adjust the sample size based on the incidence rate observed in the first cohort; and
- The samples remaining blinded for aligning the statistical power over 80% in testing the difference in immunogenicity rates between the test and reference was less than 10% in the final analysis.

A Bayesian framework was used to re-estimate the sample size needed for the entire study.

1. The parameter of interest, θ (ADA+ response in this study), will be assumed to follow some non-informative prior distribution. The outcome is assumed to follow a distribution dependent on θ.
2. The posterior distribution of θ will be calculated using Bayes rule with data incorporated
3. The mean of the posterior distribution will be used to re-calculate the sample size needed.

The estimation of nature ADA+ response during the interim analysis used Bayesian Beta-Binomial Model (BBBM). This model is illustrated below:

> When k incidences occur from a n subject trial, the k incidences follow the binomial distribution with the nature response rate as the probability θ, i.e., k\ θ ~ Bin (n, θ).
>
> The conjugate Bayesian updates for Binomial distribution will be:
>
> - Prior: θ ~ Beta (α, β), where Beta is the beta distribution
> - Observed data: k\ θ ~ Bin (n, θ), then
> - Posterior: θ\n, k, α, β ~ Beta (α+k, β+n-x)

The Sponsor chose to use a non-informative prior, Jeffreys prior, to allow for a wider range for the parameter of interest which can control potential errors and lead to unbiased conclusions. Jeffreys prior is a non-informative prior distribution that is invariant under reparameteration of the parameter. For binomial distributions: k\ θ ~ Bin (n, θ), Jeffreys prior of θ is

$$\frac{1}{\pi}\theta^{-1/2}(1-\theta)^{-1/2}$$

The posterior response was estimated using the BBBM model and θ has the following posterior distribution: θ\k, n ~ Beta (k+1/2, n-k+1/2)

The interim analysis was performed on the treatment-emergent ADA incidence rate by an independent statistician. The study had one interim stage (i.e., the first subset with 102 subjects), with the blinded incidence rate to realign the sample size. The pre-determined second subset was then initiated and more subjects were recruited to complete the study with the adjusted sample size.

The results of the interim analysis was used as a guide to terminate the study if any treatment-emergent neutralizing antibody was observed in the TPI-120 arm, or if results from the first cohort clearly suggested that TPI-120 had increased ADA+ incidence rate compared to US-Neulasta. During the interim analysis, confirmed ADA+ subjects were unblinded to determine whether the difference in immunogenicity rates was ≤ 10%.

Subjects were considered to be ADA positive if a treatment-emergent seroconversion was observed from Day 1 to a specific and measurable ADA titer at any subsequent post baseline visit. Subjects with at least two consecutive postdose ADA positive samples were considered as having a persistent antibody response. Subjects with only one ADA positive sample were described as having a transient antibody response. Subjects were considered 'Neutralizing Positive', if they were positive for the TPI-120 neutralizing assay and/or the G-CSF neutralizing

assay. Subjects were considered 'Confirmatory Positive', if they were positive for the TPI-120 confirmatory assay and/or the US-Neulasta confirmatory assay.

The table below summarizes the results of the interim analysis. The overall ADA+ response was 3/46 or 6.5% (Table 15). The ADA+ response for US-Neulasta was 2/23 or 8.7%. The ADA+ response for TPI-120 was 1/23 or 4.3%. Based on these results, the sample size was increased by additional 116 subjects (58 subjects per arm). To account for a 10% dropout rate, a total of 128 additional subjects were recruited. Also see section 6.4.

Table 14 ADL-CL-112: Interim Analysis Results

	Treatment	
Incidence	TPI-120 N (%)	US-Neulasta N (%)
Predose	23	23
Day 81		
Overall Negative	22 (95.7)	23 (100.0)
Confirmatory Positive	1 (4.3)	0 (0.0)
Day 22		
Overall Negative	20 (100)	19 (90.5)
Confirmatory Positive	0 (0.0)	2 (9.5)
Day 29		
Overall Negative	18 (100)	19 (95.0)
Confirmatory Positive	0 (0.0)	1 (5.0)

Source: Table 2 of the Sponsor's SAP

Subject Disposition

Study ADL-CL-112 enrolled a total of 230 subjects (TPI-120: 115 subjects, US-Neulasta: 115 subjects) and all 230 subjects received at least one dose of study treatment (Safety Population).

For the evaluation for treatment-emergent immunogenicity, all subjects who received at least one dose of the study drug, had at least one immunogenicity blood sample collected, and had a treatment-emergent response were included. A total of 222 subjects (TPI-120: 114 subjects, US-Neulasta: 108 subjects) were included in the immunogenicity analyses. A total of 8 subjects were excluded from the immunogenicity analyses due to not providing any postdose immunogenicity samples (1 subject) and positive immune response at predose (7 subjects).

Table 15 ADL-CL-112: Analysis Populations

	TPI-120 (n=115)	US-Neulasta (n=115)	Total (n=230)
Randomized population	115 (100%)	115 (100%)	230 (100%)

Immunogenicity population	114 (99%)	108 (94%)	222 (97%)
Safety population	115 (100%)	115 (100%)	230 (100%)

[Source: ADSL.xpt and CSR]

Of the 230 enrolled subjects, a total of 216 subjects (94%) completed the study; 14 subjects (6%) withdrew from the study prematurely, mostly due to personal reasons (3%).

Table 16 ADL-CL-112: Subject Disposition

	TPI-120* (n=115)	US-Neulasta** (n=115)	Total (n=230)
Randomized	115 (100%)	115 (100%)	230 (100%)
Completed	107 (93%)	109 (95%)	216 (94%)
Discontinued early	8 (7%)	6 (5%)	14 (6%)
Reasons for study discontinuation			
Adverse event	1 (1%)	1 (1%)	2 (1%)
Failed check-in laboratory	0	1 (1%)	1 (<1%)
Failed drug/alcohol Laboratory	1 (1%)	0	1 (<1%)
Non-compliance	1 (1%)	0	1 (<1%)
Other	1 (1%)	0	1 (<1%)
Personal reasons	4 (3%)	4 (3%)	8 (3%)

*A single SC dose of 6 mg/0.6 mL TPI-120 on Cycle 1 Day 1 and Cycle 2 Day 1
**A single SC dose of 6 mg/0.6 mL US-Neulasta® (pegfilgrastim) on Cycle 1 Day 1 and Cycle 2 Day 1
[Source: ADSL.xpt]

Protocol Deviations:
Protocol deviations that were reported for the first site in study ADL-CL-112 included out-of-window, missed safety assessments, and sample processing errors. The safety assessments deviations were not considered to have a significant impact on study conclusions since for all affected subjects, safety assessments were also performed at earlier and later time points. The sample processing errors involved immunogenicity samples that were frozen approximately 5 minutes late on Day 8. For the majority of subjects, the immune response observed on Day 8 was consistent with the treatment-emergent response observed at other time points during that dosing interval (i.e., the immune response on Day 8 was consistent with the immune response observed on Day 21 prior to the second dosing). The impact of this deviation on the conclusion of the study was considered minor.

Protocol deviations that were reported for the second site included the following administrative errors: failure to capture which arm was used for vital sign assessments for Subject (b) (6), failure to fully document injection details (e.g., injection site) when recording dosing for Subject (b) (6) in Period 2, and failure to capture actual time of study assessments performed on Day 3 for Subject (b) (6). These deviations were determined to have a minor impact on the study conclusions.

All protocol deviations that occurred in study ADL-CL-112 were considered minor and none of deviations were determined to have affected the results/conclusions of the study.

Demographics and Baseline Characteristics

See Table 19 in Section 7.3.2.

Efficacy Results

Efficacy evaluations were not conducted in this study.

Immunogenicity Results

In total, out of the 230 subjects enrolled in the study, 222 subjects were included in the analyses, of which 114 were administered TPI-120 and 108 were administered US-Neulasta. Eight (8) subjects (Subjects (b) (6)) were excluded from the immunogenicity analyses. One (1) subject (Subject (b) (6)) was excluded for not providing any post-dose immunogenicity samples and the remaining 7 subjects were excluded for having a positive immune response at pre-dose.

Subjects is ADA+ if a treatment-emergent seroconversion is observed from the baseline time point (Day 1) to a specific and measurable ADA titer at any subsequent post baseline visit during the sampling period.

The results of the non-inferiority comparison of TPI-120 to US-Neulasta with respect to proportion of ADA+ response at any subsequent post-dose visits. Since the lower bound of 90% confidence limit of the difference (US-Neulasta - TPI-120) is above -10% for all post-dose visits, the non-inferiority was demonstrated (Table 17 and Figure 3).

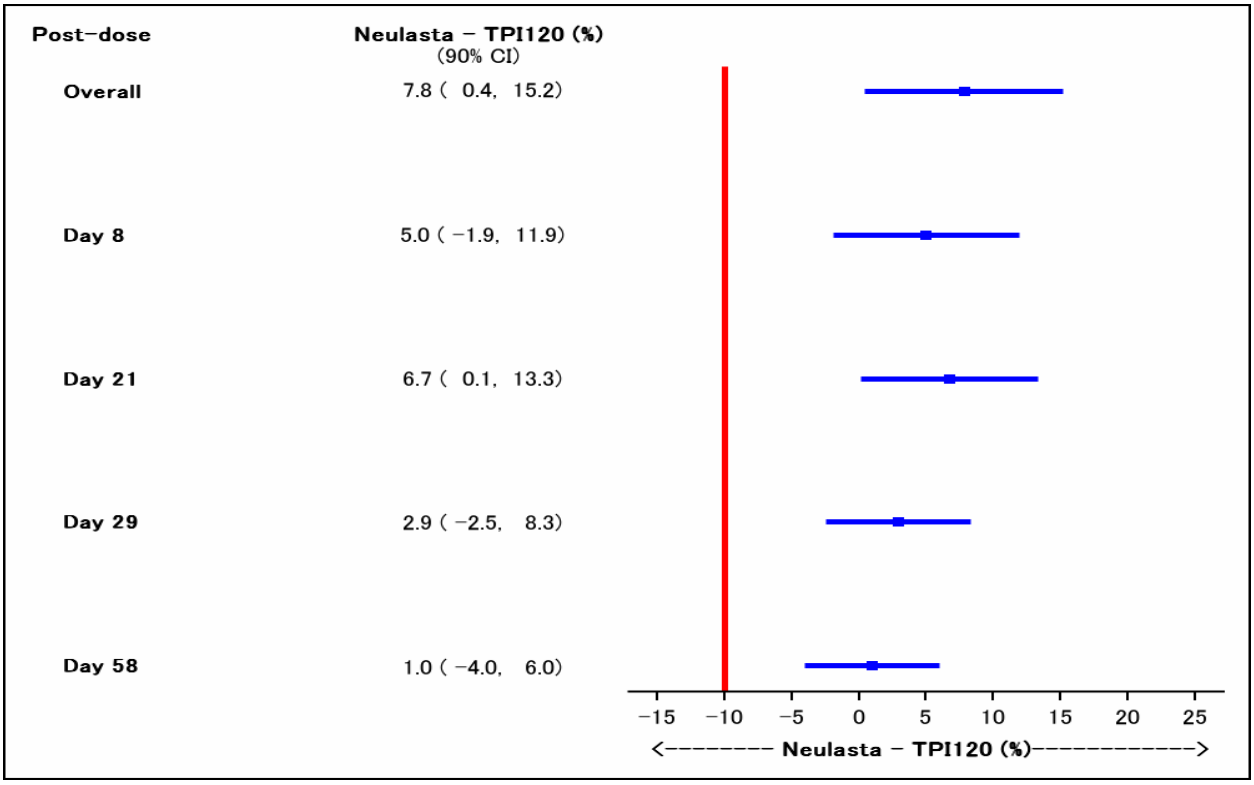
Table 17: Study Results of the Non-inferiority Test for ADA+ Response

Post-dose	Risk Difference (%)	90% Confident Limit
Overall	7.8	0.4, 15.2
Day 8	5.0	-1.9, 11.9
Day 21	6.7	0.1, 13.3

Day 29	2.9	-2.5, 8.3
Day 58	1.0	-4.0, 6.0

Source: Reviewer's Analysis

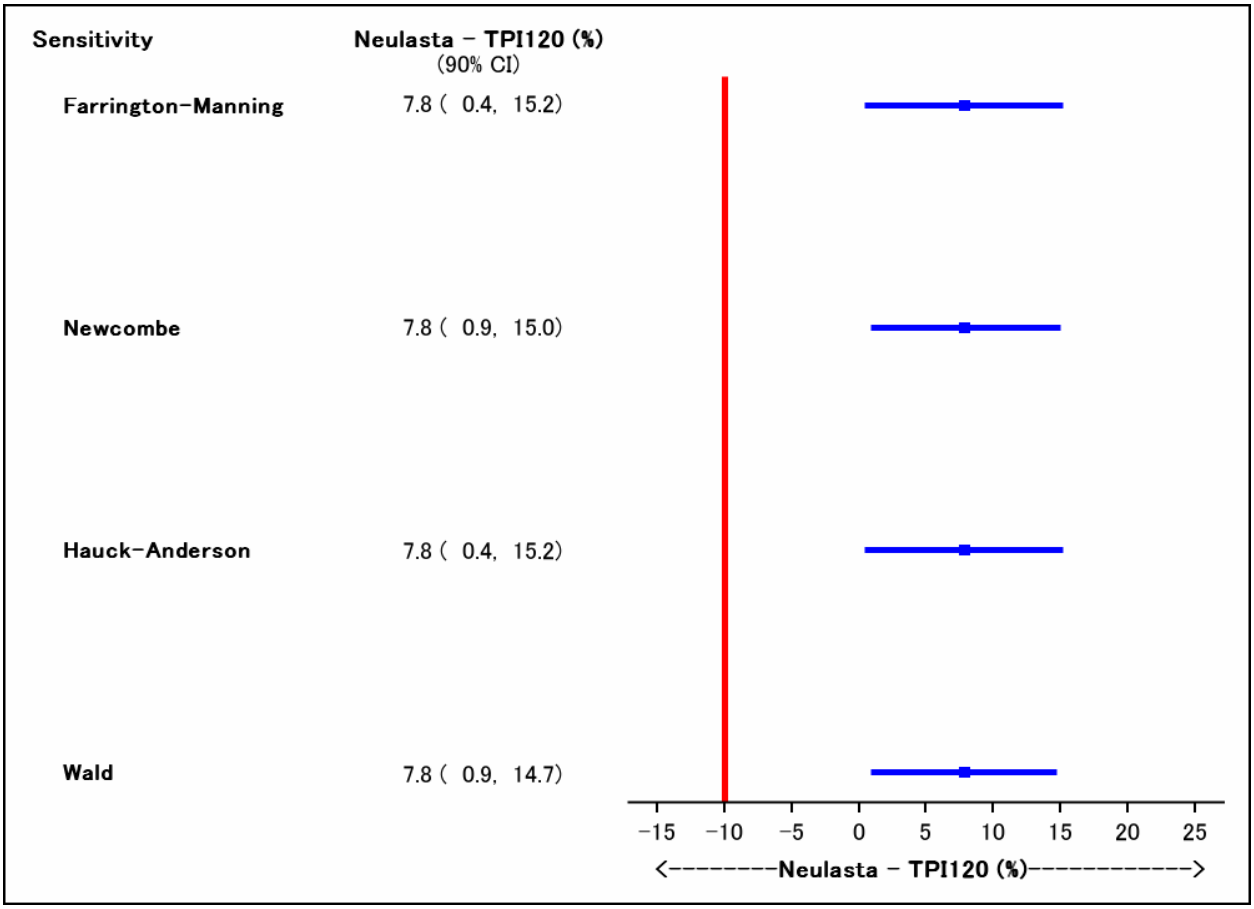
Figure 3: Forest Plot for the Difference in Proportion of Treatment-emergent ADA+ Response



Source: Reviewer's Analysis

Sensitivity Analysis:
The 90% confident limit of the difference (US-Neulasta - TPI-120) in proportion of treatment-emergent ADA+ response was also calculated using other statistical tests as sensitivity analyses to assess the robustness of the primary analysis result (Figure 4).

Figure 4: Forest Plot for the Sensitivity Analyses



Source: Reviewer's Analysis

Conclusion:
The non-inferiority of TPI-120 to US-Neulasta with respect to treatment-emergent ADA+ response was demonstrated because the lower bound of 90% CI for the proportion difference was above the NI margin of -10%. In addition, the results from the sensitivity analyses agreed with the primary analysis result.

7.3. Review of Safety Data

7.3.1. Methods

The overall safety database consisted of a total of 350 subjects (TPI-CL-109-A: 120 healthy volunteers, ADL-CL-112: 230 healthy volunteers). In studies TPI-CL-109-A and ADL-CL-112, subjects received 2 mg and 6 mg of study treatment, respectively. The safety review included the following:

- Electronic submission of the clinical study report and other relevant portions of the BLA;

- Safety data were audited or reproduced;
- Regulatory history; and
- Existing labels

With regard to safety issues for US-Neulasta and biosimilars, see Section 2.1.

Clinical Studies Used to Evaluate Safety

See sections 7.2.1 and 7.2.2 for description of the clinical studies.

The design of the clinical studies and the safety database (including study treatment exposure) were adequate for a biosimilar application (to US-Neulasta). The Safety Population was comprised of subjects who received at least one dose of study treatment. There were no major concerns regarding data integrity. The overall quality of data was acceptable for safety evaluation.

However, even though comparisons across studies should be conducted with caution, the reported incidences of TEAEs in study TPI-CL-109-A were lower compared to study ADL-CL-112 and other studies of pegfilgrastim product possibly due to lower dose of study treatment. In addition, the BLA submission did not contain safety analyses for AEs of special interests.

Population Demographics

The safety database of TPI-120 was comprised of a total of 234 healthy adult subjects from the PK/PD and immunogenicity comparative studies (TPI-CL-109-A: 119 subjects, ADL-CL-112: 115 subjects) and adequate for evaluation of a biosimilar drug product to US-Neulasta. See section 7.3.2 for demographics and baseline characteristics of the safety population.

Categorization of Adverse Events

Adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA) terminology. Grade Mapping of the verbatim AE terms to MedDRA Preferred Term and System Organ Class (SOC) was acceptable. The severity of AEs was categorized as mild, moderate or severe. The laboratory results were categorized as low, high, normal or abnormal.

The definitions of AEs and SAEs in the protocol were adequate. A treatment emergent AE (TEAE) was defined as an AE that started or worsened at the time of or after study drug administration. An AE that occurred during the washout period between drugs was considered treatment-emergent to the last drug given. All AEs regardless of the causality, were monitored until the event has resolved, returned to baseline or stabilized at a level acceptable to the Investigator and Medical Monitor, until there is a satisfactory explanation for the changes observed, or until the subject is lost to Follow-up.

Safety Analyses

The BLA submission contained safety analyses from individual studies and integrated safety analyses of TEAEs by treatment, severity and relationship to study treatment. A pre-351(k) BLA meeting was not held. Table 20 summarizes the overall safety results that occurred in studies ADL-CL-112 and TPI-CL-109A. TEAEs that occurred in >10% of subjects in the TPI-120 arm in study ADL-CL-112 were headache, back pain, myalgia, local administration reactions, arthalgia, nausea, erythema, abdominal pain, and injection site pain which were mostly consistent with the most frequent TEAEs reported in the TPI-120 arm in study TPI-CL-109A. Combined evaluation of TEAEs of studies TPI-CL-109A and ADL-CL-112 did not reveal a new safety signal of TPI-120.

7.3.2. Relevant Characteristics of the Population Evaluated for Safety

Relevant Characteristics of the Population Evaluated for Safety

TPI-CL-109-A:
Study TPI-CL-109-A was a two-period crossover study. A total of 120 subjects (TPI-120/US-Neulasta: 60 subjects, US-Neulasta/TPI-120: 60 subjects) received at least one dose of study treatment (TPI-120: 119 subject, US-Neulasta: 111 subjects) as shown in Table 12. Overall, 50% of the subjects were males and 57% were White. The median age for all subjects was 37 years (range, 20 to 55).

The baseline demographics and characteristics between the two sequences were generally balanced, except that the median age in the TPI-120/US-Neulasta was 35 years (range, 20 to 55) versus 40.5 years (range, 21 to 55) in the US-Neulasta/TPI-120 sequence; and smaller proportion of subjects were White (50%) in the TPI-120/US-Neulasta versus 63% in the US-Neulasta/TPI-120 sequence.

Table 18 TPI-CL-109-A: Demographics and Baseline Characteristics (Safety Population)

	TPI-120/US-Neulasta (n=60)	US-Neulasta/TPI-120 (n=60)	Total (n=120)
Age (years)			
Median	35	40.5	37
Range	20, 55	21, 55	20, 55
Sex			
Female	31 (52%)	29 (48%)	60 (50%)
Male	29 (48%)	30 (52%)	60 (50%)
Race			
White	30 (50%)	38 (63%)	68 (57%)
Black or African American	22 (37%)	15 (25%)	37 (31%)

	TPI-120/US-Neulasta (n=60)	US-Neulasta/TPI-120 (n=60)	Total (n=120)
Asian	2 (3%)	4 (7%)	6 (5%)
Other	6 (10%)	3 (5%)	9 (7%)
Weight (kg)			
Median	75	73	74
Range	53, 98	51, 99	51, 99
Height (cm)			
Median	167	169	168
Range	152, 186	149, 190	149, 190
Body mass index (kg/m^2)			
Median	27	26	26
Range	20, 30	21, 30	20, 30

[Source: ADSL.xpt]

ADL-CL-112:

In study ADL-CL-112, 61% of subjects were females and 82% were White. The median age for all subjects were 33 years (range, 19 to 55). The baseline demographics and characteristics were generally balanced between the two treatment arms.

Table 19 ADL-CL-112: Demographics and Baseline Characteristics (Safety Population)

	TPI-120 (n=115)	US-Neulasta (n=115)	Total (n=230)
Age (years)			
Median	32	34	33
Range	19, 55	19, 55	19, 55
Sex			
Female	72 (63%)	68 (59%)	140 (61%)
Male	43 (37%)	47 (41%)	90 (39%)
Race			
White	89 (77%)	99 (86%)	188 (82%)
Black or African American	14 (12%)	14 (12%)	28 (12%)
Asian	4 (3%)	0	4 (2%)
Other	8 (7%)	2 (2%)	10 (4%)
Weight (kg)			
Median	70	72	71
Range	51, 98	50, 99	50, 99
Height (cm)			
Median	166	167	167

	TPI-120 (n=115)	US-Neulasta (n=115)	Total (n=230)
Range	147, 188	151, 189	147, 189
Body mass index (kg/m^2)			
Median	26	26	26
Range	19, 30	20, 30	19, 30

[Source: ADSL.xpt]

7.3.3 Safety Results

The table below summarizes the overall safety results of studies TPI-CL-109-A and ADL-CL-112. The overall safety profile was similar between two treatments in both studies. The reported incidences of TEAEs in study TPI-CL-109-A were lower compared to those of study ADL-CL-112 and other studies of pegfilgrastim products possibly due to lower dose of the study treatment.

Table 20 TPI-CL-109-A and ADL-CL-112: Overall Summary of Safety (Safety Population)

	Study TPI-CL-109-A*		Study ADL-CL-112**	
	TPI-120 (n=119)	US-Neulasta (n=111)	TPI-120 (n=115)	US-Neulasta (n=115)
All TEAEs	60 (50%)	56 (50%)	108 (94%)	109 (95%)
Treatment related	47 (40%)	49 (44%)	108 (94%)	108 (95%)
Severe TEAEs	6 (5%)	2 (2%)	0	0
All deaths	0	0	0	0
TESAEs	0	0	0	0
TEAEs leading to treatment discontinuation	1 (0.8%)	0	1 (0.9%)	1 (0.9%)
AEs of special interests	0	1 (0.9%)	13 (11.3%)	10 (8.7%)

*Study treatment 2 mg
**Study treatment 6 mg
[Source: ADAE.xpt]

Exposure

TPI-CL-109-A:
In study TPI-CL-109-A, the dose of study treatment was 2 mg. A total of 119 and 111 subjects received at least one dose of TPI-120 and US-Neulasta, respectively, across the two sequence groups.

Table 21 TPI-CL-109-A: Exposure of Study Treatment (Safety Population)

	Study TPI-CL-109-A	
	TPI-120	US-Neulasta

	(n=119)	(n=111)
Study period 1 (n)	60	60
Median (mg)	2.0	2.0
Range (mg)	2.0-2.0	2.0-2.0
Study period 2 (n)	59	51
Median (mg)	2.0	2.0
Range (mg)	2.0-2.0	2.0-2.0

[Source: EX.xpt]

ADL-CL-112:
In study ADL-CL-112, the dose of study treatment was 6 mg. A total of 230 subjects (TPI-120: 115 subjects, US-Neulasta: 115 subjects) received at least one dose of the study drug. The majority of subjects (TPI-120: 93%, US-Neulasta: 96%) received the planned two doses of the study drug on Day 1 of Periods 1 and 2 (Study Days 1 and 22).

Table 22 ADL-CL-112: Exposure of Study Treatment (Safety Population)

	Study ADL-CL-112	
	TPI-120 (n=115)	US-Neulasta (n=115)
Subjects treated		
1 day	8 (7%)	5 (4%)
2 days	107 (93%)	110 (96%)

[Source: EX.xpt]

Deaths

No deaths were reported among subjects who participated in studies TPI-CL-109-A and ADL-CL-112.

Serious Adverse Events

No SAEs were reported in studies TPI-CL-109-A and ADL-CL-112.

Treatment Emergent Adverse Events

TPI-CL-109-A:
Overall, a total of 82 subjects (68%) of the 120 subjects who received at least one dose of the study treatment experienced an TEAE during the two crossover periods. The incidences of TEAEs were similar between the two treatments (TPI-120: 50.4%, US-Neulasta: 50.5%). The overall reported incidences of TEAEs were lower compared to study ADL-CL-112.

The most frequently reported TEAEs (≥ 5%) after the TPI-120 treatment were back pain, headache and myalgia. Most of the AEs were mild or moderate in severity. Severe AEs were reported in a total of 8 subjects [6 subjects (5%) after treatment with TPI-120 and 2 subjects (2%) after treatment with US-Neulasta (see below under Significant Adverse Events section).

The incidence of TEAES that were considered related to study treatment (including possibly or probably related) were also similar between the two treatments [TPI-120: 47 subjects (39.5%) , US-Neulasta: 49 subjects (44.1%)].

Table 23 TPI-CL-109-A: Summary of TEAEs in ≥ 2 Subjects in the TPI-120 Treatment Arm (Safety Population)

FMQ*	Study TPI-CL-109-A	
	TPI-120 (n=119)	US-Neulasta (n=111)
All subjects	60 (50.4%)	56 (50.5%)
Back pain	30 (25.2%)	31 (27.9%)
Headache	18 (15.1%)	17 (15.3%)
Myalgia	6 (5.0%)	2 (1.8%)
Pain in extremity	4 (3.4%)	6 (5.4%)
Arthralgia	3 (2.5%)	2 (1.8%)
Local administration reaction	2 (1.7%)	4 (3.6%)
Abdominal pain	2 (1.7%)	0
Upper respiratory tract infection	2 (1.7%)	0
Pain	2 (1.7%)	1 (0.9%)

*Grouped Terms by FDA Medical Query (FMQ).
Incidences are based on the number of subjects, not the number of events. Although a subject may have had 2 or more clinical AEs, the subject is counted only once in a category. The same subject may appear in different categories.
[Source: ADAE.xpt and ADSL.xpt]

ADL-CL-112:

In study ADL-CL-112, the incidence of TEAEs was similar between the two arms (TPI-120: 94%, US-Neulasta: 95%). The most frequently reported TEAEs (≥ 10%) in the TPI-120 arm were headache, back pain, myalgia, local administration reactions, arthralgia, nausea, erythema, abdominal pain and injection site pain. The majorty of subjects had TEAES that were considered related to study treatment (including possibly or probably related) [TPI-120: 108 subjects (93.9%), US-Neulasta: 108 subjects (93.9%)].

All TEAEs were mild or moderate in severity. No severe TEAEs were reported.

Table 24 ADL-CL-112: Summary of TEAEs in ≥ 5% of Subjects in TPI-120 Treatment Arm (Safety Population)

FMQ*	Study ADL-CL-112	
	TPI-120 (n=115)	US-Neulasta (n=115)
All subjects	108 (93.9%)	109 (94.8%)
Headache	75 (65.2%)	75 (65.2%)
Back pain	61 (53.0%)	61 (53.0%)
Myalgia	46 (40.0%)	48 (41.7%)
Local administration reactions	25 (21.7%)	29 (25.2%)
Arthralgia	19 (16.5%)	14 (12.2%)
Nausea	19 (16.5%)	16 (13.9%)
Erythema	15 (13.0%)	15 (13.0%)
Abdominal pain	14 (12.2%)	11 (9.6%)
Injection site pain	12 (10.4%)	13 (11.3%)
Pain in extremity	11 (9.6%)	11 (9.6%)
Injection site erythema	10 (8.7%)	13 (11.3%)
Oropharyngeal pain	9 (7.8%)	4 (3.5%)
Dizziness	8 (7.0%)	10 (8.7%)
Fatigue	8 (7.0%)	5 (4.4%)
Pain	7 (6.1%)	12 (10.4%)
Dyspepsia	6 (5.2%)	4 (3.5%)
Pruritus	6 (5.2%)	6 (5.2%)
Vomiting	6 (5.2%)	10 (8.7%)

*Grouped Terms by FDA Medical Query (FMQ).
Incidences are based on the number of subjects, not the number of events. Although a subject may have had 2 or more clinical AEs, the subject is counted only once in a category. The same subject may appear in different categories.
[Source: ADAE.xpt and ADSL.xpt]

Dropouts and/or Discontinuations

TPI-CL-109-A:
In study, TPI-CL-109-A, one subject experienced an TEAE (upper respiratory infection) after receiving TPI-120 2 mg SQ injection that resulted in study treatment withdrawal. The narrative of the subject is presented below:

The subject (b) (6) was a 30-year-old white male who experienced upper respiratory tract infection approximately 25 days after receiving TPI-120 2 mg SQ injection in Period 1. This

TEAE was considered significant since it led to subject discontinuation from the study. The TEAE was mild in severity and considered to be not related to the study treatment. This event resolved after 3 days without any intervention. There were no relevant medical history findings for this subject.

ADL-CL-112:

A total of 2 subjects (TPI-120: 1 subject due to QT interval prolongation, US-Neulasta: 1 subject due to thrombocytopenia and decreased neutrophil and WBC counts) withdrew from study treatment due to TEAEs. The narratives are presented below:

Subject (b) (6) (a 26-year-old male Native Hawaiian/ Pacific Islander and Hispanic/Latino) in the TPI-120 arm experienced (mild) prolonged QT interval approximately 20 days following treatment in Period 1. At onset the QTcF value was 471 msec (change from baseline was + 23 msec). The event was considered to be clinically significant, the treatment was withdrawn and the subject was discontinued. The early termination value recorded 1 day later was 472 msec. The event was unresolved at end of study and lost to follow-up. The event was considered to be unlikely related to the study drug.

Subject (b) (6) (a 26-year-old Black/African American male) in the US-Neulasta arm experienced mild thrombocytopenia approximately 11 days following treatment in Period 1. The platelet levels ranged from 86,000/µL to 100,000/µL (reference range: 151,000/µL – 361,000 /µL) before resolving approximately 5 days later with a value of 168,000/µL. Generally, results for hemoglobin, hematocrit, and red blood cells were within normal limits or slightly below the reference range. The event was considered not related to the study drug and the study drug was discontinued. This subject also experienced the mild AEs of decreased neutrophil count and decreased WBC count approximately 16 days following treatment in Period 1. Neutrophil counts ranged from 1,000/µL to 1,600/µL. The Investigator considered the result to be clinically significant, study treatment was withdrawn and the subject was discontinued. The WBC value ranged from 3,100/µL to 3,700/µL (reference range: 4,100/µL – 11,500/µL). The PI considered the events not related to the study drug.

In addition, one subject (b) (6) in the US-Neulasta arm was withdrawn due to positive choriogonadotropin Beta test on Day -1 of Period 2. The subject was advised to follow-up with obstetrics. At the time of this report, the subject was healthy and well.

Significant Adverse Events

TPI-CL-109-A:

A total of 8 subjects [6 subjects (5%) after the last dose of TPI-120 and 2 subjects (2%) after the last dose of US-Neulasta] experienced severe AEs during study TPI-CI-109-A. The most frequently reported severe AE was back pain (TPI-120: 4%, US-Neulasta: 2%).

Table 25 TPI-CL-109-A: Incidence of Severe AEs (Safety Population)

Preferred Term	TPI-120* (n=119)	US-Neulasta* (n=111)
All subjects	6 (5%)	2 (2%)
Back pain	5 (4%)	2 (2%)
Dysmenorrhoea	1 (0.8%)	0
Arthralgia	1 (0.8%)	0
Limb injury	0	1 (0.9%)

*Severe AEs that occurred after the last study treatment.
[Source: ADEA.xpt]

ADL-CL-112:
No severe AEs were reported in study ADL-CL-112.

Laboratory Findings

TPI-CL-109-A:
Hematology:
No meaningful differences in hematology parameters were observed between the TPI-120 and US-Neulasta treatments. The median values of neutrophils and leukocytes increased after the administration of each study drug on Day 8, and returning close to baseline values on Day 22. No subjects had elevated leukocyte count of ≥ 100 $x10^9$/L or leukocytosis as a TEAE during the study.

The median platelet count decreased on Day 8, followed by increase on Day 22 in both arms.

Table 26 TPI-CL-109-A: Summary of Hematology Laboratory Tests (Safety Population)

		TPI-120 (n=119)	US-Neulasta (n=111)
Neutrophils ($x10^9$/L)	Baseline	4.1	3.8
	Day 8	7.9	8.2
	Day 22	2.8	3.0
Leukocytes ($x10^9$/L)	Baseline	6.9	6.6
	Day 8	12.2	12.3
	Day 22	5.2	5.3
Hemoglobin (g/L)	Baseline	13.3	13.1
	Day 8	13.9	13.7
	Day 22	13.5	13.6
Platelets ($x10^9$/L)	Baseline	260.0	258.0
	Day 8	219.0	219.0

		TPI-120 (n=119)	US-Neulasta (n=111)
	Day 22	296.5	308.5

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

Biochemistry:
In study TPI-CL-109-A, no meaningful differences in biochemistry parameters were observed between the two treatments. The mean values for biochemistry parameters were within normal range at each time points (baseline, Day 8, Day 22 and study exit) and no meaningful changes from baseline to each timepoint were observed over time in the two treatments.

ADL-CL-112:
Hematology:
In study ADL-CL-112, results of hematology parameters were also similar between the two arms. As observed in study TPI-CL-109-A, the median values of neutrophils and leukocytes increased after the administration of each study drug on Day 8 in both periods, and returning close to baseline by follow-up visits (Day -1 and Day 37). One subject (b) (6) in the US-Neulasta arm developed leukocytosis that resolved. No cases of leukocyte count of ≥ 100 $x10^9$/L were reported.

The median platelet count decreased on Day 8 in both periods, returning close to baseline by Period 2 Day 37 in both arms.

Table 27 ADL-CL-112: Summary of Hematology Laboratory Tests (Safety Population)

		TPI-120 (n=115)	US-Neulasta (n=115)
Neutrophils ($x10^9$/L)	Baseline	4.1	3.9
	Period 1 Day 8	10.9	10.3
	Period 2 Day -1	3.6	3.7
	Period 2 Day 8	15.0	13.2
	Period 2 Day 37	3.3	3.0
Leukocytes ($x10^9$/L)	Baseline	6.9	6.7
	Period 1 Day 8	15.9	14.5
	Period 2 Day -1	6.2	6.0
	Period 2 Day 8	20.1	18.3
	Period 2 Day 37	5.8	5.6
Hemoglobin (g/L)	Baseline	13.8	13.9
	Period 1 Day 8	14.0	14.0
	Period 2 Day -1	13.0	13.3
	Period 2 Day 8	13.7	13.9
	Period 2 Day 37	13.5	13.5

		TPI-120 (n=115)	US-Neulasta (n=115)
Platelets ($x10^9$/L)	Baseline	269.0	258.0
	Period 1 Day 8	198.0	196.0
	Period 2 Day -1	322.5	327.5
	Period 2 Day 8	246.0	242.0
	Period 2 Day 37	267.0	266.0

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

Biochemistry:
The median values for biochemistry parameters at each time points were also similar between the two arms in study ADL-CL-112. No meaningful differences in biochemistry parameters were reported between the two arms.

Vital Signs

In study TPI-CL-109-A, the mean values for all timepoints and all parameters for vital signs were within normal range. No relevant differences were observed between the two treatments.

In study ADL-CL-112, the mean vital sign results remained generally within normal limits with no remarkable observations in mean change from baseline values. A total of 5 subjects who received TPI-120 (and none in the US-Neulasta arm) experienced mild increased heart rate events. Onset was approximately 1.5 days from dosing for all events. All events resolved within 1.5 days. All events were considered possibly or probably related to the study drug. Out-of-range heart rates were observed in the range of 101 bpm to 125 bpm. All events resolved with heart rates ranging from 92 to 99 bpm.

Electrocardiograms

TPI-CL-109-A:
The mean values for all timepoints and all parameters were within the normal range. No relevant differences were observed between results of subjects who received the TPI-120 treatment compared with the US-Neulasta treatment. No subject had QTcF intervals greater than 480 msec and no subject had a change or an increase in QTcF interval greater than 60 msec.

ADL-CL-112:
In study ADL-CL-112, one subject (b) (6) discontinued due to a prolonged QTcF interval following treatment with TPI-120 (see the Dropouts and/or Discontinuations section). In addition, a total of 28 subjects [TPI-120: 14 subjects (12%), US-Neulasta: 14 subjects (12%)] had isolated post treatment QTcF interval abnormalities including either a value > 450 msec, a

change from baseline > 30 msec, or both a > 450 msec interval with a >30 msec baseline change (but not greater than QTcF intervals of 480 msec or an increase greater than 60 msec).

A total of 7 subjects reported mild palpitations [TPI-120: 5 subjects (4%), US-Neulasta: 2 subjects (2%)]. Onset ranged from approximately 1 day to 55.7 days with most occurring 2.9 days following treatment. All events resolved within 4 days.

A total of 5 subjects reported mild chest pain events [TPI-120: 3 subjects (3%), US-Neulasta: 2 subjects (2%)]. Onset ranged from approximately 1 day to 2.25 days. All events resolved within 3.5 days. The chest pain events were not associated with ECG changes.

Product Specific Safety Concerns

Safety analyses for AEs of special interests (AESIs) were not included in the BLA submission. However, the toxicities of G-CSFs include allergic reactions, splenic rupture, acute respiratory distress syndrome (ARDS), leukocytosis, thrombocytopenia, capillary leak syndrome, sickle cell crises (in patients with sickle cell disorders), potential for tumor growth stimulatory effects on malignant cells, aortitis and glomerulonephritis. In addition, based on the AE profile of G-CSFs, preferred terms under the Musculoskeletal and Connective Tissue Disorders SOC and injection site reactions were also analyzed.

In studies TPI-CL-109-A and ADL-CL-112, no cases of splenic rupture, ARDS, capillary leak syndrome, sickle cell crises, neoplasms, aortitis or glomerulonephritis were reported.

In study ADL-CL-112, one subject (b) (6) in the US-Neulasta arm experienced mild leukocytosis that resolved; another subject (b) (6) in the US-Neulasta arm experienced mild thrombocytopenia that resolved. No other cases of leukocytosis or thrombocytopenia were reported in studies TPI-CL-109-A and ADL-CL-112.

In study TPI-CL-109-A, one subject after treatment with US-Neulasta developed injection site rash that was moderate in severity. No other cases of AESIs was found in the submitted dataset for the study. The incidence of AESIs (TPI-120: 0%, US-Neulasta: 0.9%) in study TPI-CL-109-A appears low (possibly due to lower dose).

In study ADL-CL-112, the incidences of AESIs were similar between the two treatments (TPI-120: 11%, US-Neulasta: 9%). All AESIs were mild in severity that resolved.

The table below summarizes the incidence of AESIs that occurred in studies TPI-CL-109-A and ADL-CL-112.

Table 28 TPI-CL-109-A and ADL-CL-112: Summary of AEs of Special Interest (Safety Population)

Preferred Term	Study TPI-CL-109-A*		Study ADL-CL-112**	
	TPI-120 (n=119)	US-Neulasta (n=111)	TPI-120 (n=115)	US-Neulasta (n=115)
All subjects	0	1 (0.9%)	13 (11.3%)	10 (8.7%)
Potential allergic reactions				
Injection site rash	0	1 (0.9%)	0	0
Injection site pruritus	0	0	5 (4.4%)	1 (0.9%)
Dermatitis (contact)	0	0	2 (1.7%)	1 (0.9%)
Injection site papule	0	0	1 (0.9%)	0
Injection site reaction	0	0	1 (0.9%)	0
Injection site swelling	0	0	1 (0.9%)	0
Local swelling	0	0	1 (0.9%)	0
Pruritus (generalized)	0	0	1 (0.9%)	2 (1.7%)
Rash (erythematous)	0	0	1 (0.9%)	1 (0.9%)
Eye/ear irritation/pruritus	0	0	1 (0.9%)	2 (1.7%)
Urticaria	0	0	0	2 (1.7%)
Leukocytosis	0	0	0	1 (0.9%)
Thrombocytopenia	0	0	0	1 (0.9%)

*Study treatment 2 mg
**Study treatment 6 mg
[Source: ADAE.xpt]

Musculoskeletal Disorders:

The overall incidences of TEAEs in the Musculoskeletal and Connective Tissue Disorders SOC were similar between the two treatments in study TPI-CL-109-A (TPI-120: 30%, US-Neulasta: 32%) and study ADL-CL-112 (TPI-120: 82%, US-Neulasta: 83%). The overall reported incidences in study TPC-CL-109-A were lower than in study ADL-CL-112.

A total of 7 subjects in study TPI-CL-109-A (TPI-120: 5 subjects, US-Neulasta: 2 subjects) had severe AEs. All other cases were either mild or moderate in severity. In study TPI-CL-109-A, the most frequently reported AEs (≥10%) in the musculoskeletal and connective tissue disorders SOC were back pain (TPI-120: 25%, US-Neulasta: 28%) while in study ADL-CL-112, those were back pain (TPI-120: 52%, US-Neulasta: 53%), myalgia (TPI-120: 37%, US-Neulasta: 37%) and arthralgia (TPI-120: 17%, US-Neulasta: 12%).

Table 29 TPI-CL-109-A and ADL-CL-112: Summary of TEAEs in the Musculoskeletal Connective Tissue Disorders that Occurred ≥ 2% in Any Arm (Safety Population)

System Organ Class Preferred Term	Study TPI-CL-109-A*		Study ADL-CL-112**	
	TPI-120	US-Neulasta	TPI-120	US-Neulasta

	(n=119)	(n=111)	(n=115)	(n=115)
Musculoskeletal and Connective Tissue Disorders	36 (30.3%)	36 (32.4%)	94 (81.7%)	95 (82.6%)
Back pain	30 (25.2%)	31 (27.9%)	60 (52.2%)	61 (53.0%)
Myalgia	0	0	43 (37.4%)	43 (37.4%)
Arthralgia	3 (2.5%)	2 (1.8%)	19 (16.5%)	14 (12.2%)
Pain in extremity	4 (3.4%)	6 (5.4%)	11 (9.6%)	11 (9.6%)
Musculoskeletal chest pain	0	0	8 (7.0%)	6 (5.2%)
Neck pain	0	0	6 (5.2%)	10 (8.7%)
Muscle spasm	0	0	4 (3.5%)	7 (6.1%)
Musculoskeletal discomfort	0	0	3 (2.6%)	5 (4.3%)
Musculoskeletal pain	0	0	3 (2.6%)	5 (4.3%)
Spinal pain	0	0	3 (2.6%)	1 (0.9%)

*Study treatment 2 mg
**Study treatment 6 mg
[Source: ADAE.xpt]

Injection Site Reactions (ISRs):
The overall incidences of injection site reactions were similar between the two treatments in studies TPI-CL-109-A (TPI-120: 2%, US-Neulasta: 4%) and ADL-CL-112 (TPI-120: 22%, US-Neulasta: 25%).

The Applicant reported that a total of 10 subjects (TPI-120: 1 subject, US-Neulasta: 9 subjects) experienced injection site reactions in study TPI-CL-109-A, however, the results could not be verified by the datasets.

In study ADL-CL-112, the most frequently reported AEs were injection site pain (TPI-120: 10%, US-Neulasta: 11%) followed by injection site erythema (TPI-120: 9%, US-Neulasta: 11%). According to the Applicant, injection site pain AEs occurred immediately postdose to approximately 21 days, the majority occurring immediately following dosing. Events resolved within 1.4 days. Injection site erythema events occurred within 1.3 days of dosing and all events resolved within 2.7 days.

All injection site reactions were mild or moderare in intensity in studies TPI-CL-109-A and ADL-CL-112.

Table 30 TPI-CL-109-A and ADL-CL-112: Summary of Injection Site Reactions that Occurred **≥2%** in Any Arm (Safety Population)

	Study TPI-CL-109-A*		Study ADL-CL-112**	
	TPI-120 (n=119)	US-Neulasta (n=111)	TPI-120 (n=115)	US-Neulasta (n=115)
All injection site reactions	2 (1.7%)	4 (3.6%)	25 (21.7%)	29 (25.2%)

Injection site pain	0	1 (0.9%)	12 (10.4%)	13 (11.3%)
Injection site erythema	1 (0.8%)	2 (1.8%)	10 (8.7%)	13 (11.3%)
Injection site pruritus	0	0	5 (4.3%)	1 (0.9%)
Injection site hemorrhage	0	0	2 (1.8%)	9 (7.8%)

*Study treatment 2 mg
**Study treatment 6 mg
[Source: ADAE.xpt]

7.3.3. Additional Safety Evaluations

The impact of immunogenicity on safety was assessed by reviewing the TEAEs reported in studies TPI-CL-109-A and ADL-CL-112 in subjects with confirmed positive anti-drug antibody results.

TPI-CL-109-A:
Immunogenicity evaluation was conducted for all subjects in the Safety Population in study TPI-CL-109-A. Among the 120 subjects who received G-CSF, a total of 50 subjects (42%) tested positive for ADA prior to and/or after treatment with TPI-120 or US-Neulasta. Of the 50 subjects, a total of 14 subjects [TPI-120: 6 subjects (5%), US-Neulasta: 8 subjects (7%)] were ADA positive at post-baseline. The overall incidences of TEAEs were similar between the two treatments (TPI-120: 67%, US-Neulasta: 63%) among subjects who were ADA positive post-baseline. TEAEs included headache, injection site erythema/rash, musculoskeletal discomfort/pain and back pain.

Table 31 TPI-CL-109-A: Incidence of TEAEs in Subjects with Positive Anti-drug Antibody Results

	Study TPI-CL-109-A*	
	TPI-120 (n=6)	US-Neulasta (n=8)
All	4 (67%)	5 (63%)
Injection site erythema	1 (17%)	1 (13%)
Headache	2 (33%)	1 (13%)
Musculoskeletal discomfort/pain	1 (17%)	1 (13%)
Back pain	0	1 (13%)
Injection site rash	0	1 (13%)

*Study treatment 2 mg
[Source: ADAE.xpt and IS.xpt]

ADL-CL-112:

In study ADL-CL-112, subjects who received at least one dose of the study drug and had a treatment-emergent response (i.e., a positive immune response at postdose time points only) were included in the immunogenicity evaluation.

Of the 230 enrolled subjects, a total of 222 subjects (TPI-120: 114 subjects, US-Neulasta: 108 subjects) were included in the analyses; and 8 subjects were excluded from the analyses for not providing any postdose immunogenicity samples (1 subject) and positive immune response at predose (7 subjects). Overall, a total of 24 subjects [TPI-120: 8 subjects (7.0%), US-Neulasta: 16 subjects (14.8%)] had confirmed detectable serum anti-drug antibodies at least once during the study following treatment with TPI-120 or US-Neulasta, respectively.

Among the 8 subjects who had confirmed detectable serum ADA following treatment with TPI-120, the majority (7 subjects) had specificity for TPI-120 only while 1 subject had specificity for US-Neulasta only. No subjects had specificity for the PEG component. No subjects developed neutralizing activity of the antibody.

Among the 16 subjects who had confirmed detectable serum ADA following treatment with US-Neulasta, the majority (11 subjects) had specificity for both TPI-120 and US-Neulasta while 5 subjects had specificity for TPI-120 only. Nine subjects (8.3%) were reported for specificity to PEG. One subject (0.9%) developed neutralizing activity of the antibody.

Among the subjects who had positive ADA postdose, all subjects in both treatments (TPI-120: 100%, US-Neulasta: 100%) experienced TEAEs. TEAEs that occurred in more than 1 subject in the TPI-120 arm were back pain, headache, pain in extremity, myalgia and nausea.

Table 32 ADL-CL-112: Incidence of TEAEs that Occurred in More >1 Subject in the TPI-120 Arm Among Subjects with Positive Anti-drug Antibody Results

Preferred Term	Study ADL-CL-112*	
	TPI-120 (n=8)	US-Neulasta (n=16)
All	8 (100%)	16 (100%)
Back pain	7 (88%)	10 (63%)
Headache	7 (88%)	10 (63%)
Pain in extremity	4 (50%)	5 (31%)
Myalgia	2 (25%)	7 (44%)
Nausea	2 (14%)	3 (19%)

*Study treatment 6 mg
[Source: ADAE.xpt and ADIS.xpt]

7.4. Clinical Conclusions on Immunogenicity

The overall immunogenicity evaluation included qualitative and quantitative measurement of anti-drug antibody (ADA) and neutralizing antibody (NAb) in healthy subjects (single dose PK and multiple dose safety), and an assessment of the impact of ADA on PK, PD (ANC), and safety. It is concluded that TPI-120 was similar to US-Neulasta in the production of ADA/NAb and their impact on PK, PD (ANC) and safety. Also refer to section 6.4 Clinical Immunogencity Studies for results of the immunogenicity assessments.

Authors:

Hyon-Zu Lee, Pharm.D. Clinical reviewer	Tanya Wroblewski, M.D. Clinical team leader
Lola Luo, PhD Statistical reviewer	Yeh-Fong Chen, PhD Statistical team leader

7.5. Extrapolation to Support Licensure of Non-Studied Indications

The Applicant is seeking licensure of TPI-120 as a biosimilar product to US-Neulasta for the following indication which has been previously approved for US-Neulasta and for which TPI-120 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 of data and information to support licensure of TPI-120 for the proposed indication above. See section 7.5.1 below for details as it pertains to the Applicant's justification for extrapolation.

7.5.1. Division of Nonmalignant Hematology (DNH)

The collective evidence from the comparative clinical studies supports demonstration of no clinically meaningful differences between TPI-120 and US-Neulasta in terms of safety, purity and potency based on similar PK, PD, safety and immunogenicity to support licensure of TPI-120 for the proposed indication (refer to Section 7.5).

- The Applicant provided data to support that TPI-120 has the same mechanism of action as US-Neulasta, to the extent known, which supports extrapolation for the sought indication. TPI-120 is highly similar to US-Neulasta notwithstanding minor differences in clinically inactive components.
- Similar PK and bio-distribution of TPI-120 was demonstrated to US-Neulasta in

the PD/PK Similarity Study (TPI-CL-109-A) as concluded in section 6.1. The comparative PK data indicate that TPI-120 has a PK profile similar to US-Neulasta for the sought indication for licensure.

- The immunogenicity profile of TPI-120 was comparable with US-Neulasta in the healthy volunteer studies as assessed by the incidences of anti-drug antibodies and the impact on PK, PD (ANC) and safety. The incidence of immunogenicity for TPI-120 would be expected to be similar to that of US-licensed Neulasta for the sought indication.
- The Applicant showed that the overall safety profile of TPI-120 was similar to that of US-Neulasta. The safety results from the comparative clinical studies supports demonstration of no clinically meaningful differences between TPI-120 and US-Neulasta. The safety profile of TPI-120 would be expected to be similar to that of US-licensed Neulasta for the sought indication.

DNH concludes that the Applicant has provided sufficient scientific justification (based on the mechanism of action, PK, immunogenicity and safety profile), and sufficient data and information, including clinical data, to support extrapolation of data and information in the application to support licensure of TPI-120 for the sought indication (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).

Authors:

Hyon-Zu Lee, Pharm.D.	Tanya Wroblewski, M.D.
Clinical reviewer	Clinical team leader

8. Labeling Recommendations

In view of the recommendation for a Complete Response, the labeling review was deferred until the next review cycle.

8.1. Proper Name

The Applicant's proposed nonproprietary name, pegfilgrastim-pbbk, was found conditionally acceptable by the Division of Medication Error Prevention and Analysis (DMEPA). Refer to DMEPA's memorandum dated 5/7/2021.

8.2. Proprietary Name

The proposed proprietary name, (b) (4), was found conditionally acceptable. Refer to review and letter issued by DMEPA on 12/23/2020 and 12/28/2020, respectively.

8.3. Other Labeling Recommendations

Not applicable.

Authors:
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Clinical reviewer

Tanya Wroblewski, M.D.
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9. Advisory Committee Meeting and Other External Consultations

There was no advisory committee meeting held for this application, as it was determined that there were no issues where the Agency needed input from the committee.

Author:
Tanya Wroblewski, M.D.
Clinical team leader

10.Pediatrics

In view of the recommendation for a Complete Response, any recommendations for PREA postmarketing requirement(s) were deferred until the next review cycle.
Authors:
Hyon-Zu Lee, Pharm.D.
Clinical reviewer

Tanya Wroblewski, M.D.
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

In view of the recommendation for a Complete Response, any recommendations for postmarket requirements and commitments was deferred until the next review cycle.

Authors:

Hyon-Zu Lee, Pharm.D.
Clinical reviewer

Tanya Wroblewski, M.D.
Clinical team leader

12.Comments to Applicant

13.Division Director (OCP) Comments

Not applicable.

14.Division Director (OB) Comments

Not applicable.

15.Division Director (OND - Nonclinical) Comments

16.Not applicable.Division Director (OND - Clinical) Comments

17.Not applicable.Appendices

17.1. Financial Disclosure

Covered Clinical Study (Name and/or Number): TPI-CL-109-A

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 11		
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) _____		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

Covered Clinical Study (Name and/or Number): ADL-CL-112

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 17		
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)

17.2. Nonclinical Appendices

17.2.1. None

17.3. Office of Clinical Pharmacology Appendices

17.3.1. Summary of Bioanalytical Method Validation and Performance

17.3.1.1. Pharmacokinetics

For the PK/PD similarity study TPI-CL-109-A, serum US-Neulasta and serum TPI-120 concentrations measured using a validated electrochemiluminescence (ECL) immunoassay (177006AQGX) were suitable for assessment of PK similarity. Both the method validation entitled "Validation of an immunoassay for the determination of TPI-120 and US-Neulasta (PEG-filgrastim) (100 to 5000 pg/ml) in human serum" and sample analysis for the study were performed at (b) (4) The assay consists of an ECL immunoassay, where mouse anti-human G-CSF is captured onto an uncoated Multi-array standard MSD plates for coating. The PEG-G-CSF in calibration standards, control blank, quality controls and samples is captured onto the coated plate. Following the incubation of the final reagent, the plate is washed followed by addition of MSD read buffer. The assay plate is then read using a MSD ECL plate reader. The electrochemiluminescence signal generated is relative to the amount of Pegylated human G-CSF present in the calibration standards, control blank, quality controls and samples tested. The concentration of the PEG-G-CSF from controls and

samples are back calculated from a non-linear regression of the standard curve established with TPI-120 (Pegylated human G-CSF from Sponsor). The method MRD is at 1/5 with sample diluted in assay diluent. Table x shows the summary of ECL method performance in quantification of serum TPI-120 and serum US-Neulasta during the method validation.

Table 33. Summary of the bioanalytical method validation and in-study performance for measurement of serum TPI-120 and US-Neulasta

Bioanalytical method review summary	Validation of an immunoassay for the determination of TPI-120 and US-Neulasta (PEG-filgrastim) (100 to 5000 pg/ml) in human serum
Materials used for calibration curve & concentration	TPI-120 Lot No.: 500-16023 & 150-16021 Expiration: 16 Jun 2018 & NA
Validated assay range	100 to 5000 pg/mL
Material used for QCs & concentration	TPI-120 Lot No.: 500-16023 & 150-16021 Expiration: 16 Jun 2018 & NA Source: Therapeutic Proteins International, LLC US-Neulasta Lot No: 1053071 Expiration: 31 Aug 2017 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 Duoset kit (R&D systems; Cat# DY214/ Lot #: 338704): • Capture Antibody (mouse anti-human G-CSF; 120 µg), Lot: GV2016021 • Detection Antibody (biotinylated goat anti-human G-CSF; 18 µg), Lot: ACN1216021 MSD SULFO-TAG labeled Streptavidin (500 µg/mL) Part Number: R32AD-1 Lot Number: W0016082S Source: Meso Scale Discovery

Regression model & weighting	Regression Model: 4-PL (Marquardt) Weighting: $1/y^2$		
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 TPI-120	 -1.81 to 1.44%	Yes
	Cumulative precision (%CV) from LLOQ to ULOQ TPI-120	 1.07 to 2.55%	Yes
QCs performance during accuracy & precision	Cumulative accuracy (%bias) in 5 QCs TPI-120 US-Neulasta	 -6.82 to 0.94% -15.70 to -3.63%	Yes
	Inter-batch %CV TPI-120 US-Neulasta	 2.63 to 6.14% 5.08 to 7.45%	Yes
	Percent total error (TE) TPI-120 US-Neulasta	 3.57 to 12.96% 11.08 to 21.77%	Yes
Selectivity & matrix effect	Ten total lots tested. Range of observed bias at LLOQ: TPI-120: 1.54 to 17.83% (10/10 lots within -25.0 to 25.0%) US-Neulasta: -3.85 to 8.77% (10/10 lots within -25.0 to 25.0%)		Yes
Interference & specificity	Not evaluated		NA
Hemolysis effect	Five total lots tested. <u>Range of observed bias at LLOQ:</u> TPI-120: -20.97 to -16.62% (5/5 lots within -25.0 to 25.0%) US-Neulasta: -18.75 to -10.12% (5/5 lots within -25.0 to 25.0%) <u>Range of observed bias at QCH:</u> TPI-120: -17.15 to -10.92% (5/5 lots within -20.0 to 20.0%) US-Neulasta: -29.62 to -12.01 % (4/5 lots within -20.0 to 20.0%)		Yes

Lipemic effect	Five total lots tested. Range of observed bias at LLOQ: TPI-120: -32.88 to -14.38% (4/5 lots within -25.0 to 25.0%) US-Neulasta: -21.35 to -2.43% (5/5 lots within -25.0 to 25.0%) Range of observed bias at QCH: TPI-120: -24.03 to -7.58% (4/5 lots within -20.0 to 20.0%) US-Neulasta: -27.43 to -12.81 % (4/5 lots within -20.0 to 20.0%)	Yes
Dilution linearity & hook effect	Range of %bias for dilution linearity samples within the range of quantitation (up to 8000-fold dilution): TPI-120: -8.76 to 2.14% US-Neulasta: -20.61 to -7.36% Hook Effect: No hook effect observed	Yes
Short-term stability CV (%)	TPI-120: 22.56 hours at RT QCL: 3.76%; QCH: 1.68% US-Neulasta: 11.11 hours at RT QCL: 3.73%; QCH: 3.13% TPI-120: 20.21 hours at 4°C QCL: 1.98%; QCH: 0.71% US-Neulasta: 20.21 hours at 4°C QCL: 0.82%; QCH: 1.21%	Yes
Freeze-Thaw stability CV (%)	4 cycles: TPI-120: QCL: 4.27% (-80°C), 9.84% (-20°C) QCH: 3.76% (-80°C), 4.78% (-20°C) US-Neulasta: QCL: 2.29% (-80°C), 2.22% (-20°C) QCH: 0.38% (-80°C), 1.68% (-20°C)	Yes
Long-term storage	-20°C at 91 days*: TPI-120: QCL: 5.2%; QCH: 2.41% US-Neulasta: QCL: 4.3%; QCH: 2.38% -80°C at 91 days*: TPI-120: QCL: 2.67%; QCH: 1.99% US-Neulasta: QCL: 0.44%; QCH: 1.28%	Yes

	*Data available from T=0 and 91 days for TPI-120 and US-Neulasta at -20°C as well as -80°C	
Parallelism	Not evaluated	N/A
Carry over	Not evaluated	N/A
Method Performance in Study TPI-CL-109-A Determination of TPI-120 in human serum samples from protocol TPI-CL-109-A		
Assay passing rate	• Runs conducted: 13 • All passed for validation	Yes
Standard curve performance	• Standard Curve Range: 100 – 5000 pg/mL • $R^2 \geq 0.98$ • Cumulative bias range: -1.47 to 0.90 • Cumulative precision: 1.88 to 3.46	Yes
QC performance	• Cumulative bias range: -10.06 to -9.70 • Cumulative precision: 5.15 to 5.82 • Including values outside acceptance range criteria: ± 20.0% bias for all QC samples	Yes
Method reproducibility	98.58% of repeat values for pegfilgrastim products were within the reproducibility criteria	Yes
Study sample analysis/ stability	The duration of sample storage (first collection date (PK1) to last extraction date) is 88 days which is within the validated stability period (91 days).	

17.3.1.2. Pharmacodynamics

Bioanalytical methods that were used to assess the PD biomarker(s) and/or the PD effect(s) of the study drug(s)
For pharmacodynamics (PD) determination, the applicant provided the validation report summary of the bioanalytical method used to determine Absolute Neutrophil Count (ANC) over time in the blood of the subjects was included in the TPI-CL-109-A 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)). Whole blood samples were analyzed using automated Sysmex hematology analyzers: Sysmex XN 3000 (b) (4)
Periodic calibration of the autoanalyzers was not required as per the manufacturer's instructions. The validation summary report contains information on the performance characteristics of the XN-3000 systems (Module 5.3.1.4 cbc-analzers-XN3000-sys-val-rep-109a.pdf). The validation studies have been reviewed and the performance of the analyzers is considered acceptable for patient testing.

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No nonclinical issues with approval.

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