CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761111Orig1s000

MULTI-DISCIPLINE REVIEW

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

BIOSIMILAR MULTI-DISCIPLINARY EVALUATION AND REVIEW

Application Type	Original BLA
Application Number	761111
Submit Date	June 10, 2019
Received Date	June 10, 2019
BsUFA Goal Date	June 10, 2020
Division/Office	DNH/OCHEN
Review Completion Date	See stamped date
Product Code Name	PF-06881894 (also referred to as HSP-130)
Proposed Non-Proprietary Name[1]	Pegfilgrastim-apgf
Proposed Proprietary Name[1]	Nyvepria
Pharmacologic Class	Leukocyte growth factor
Applicant	Hospira, Inc., a Pfizer Company
Applicant 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.
Recommendation on Regulatory Action	Approval

[1] The proposed nonproprietary and proprietary names are conditionally accepted until the application is approved.

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CMC=Chemistry, Manufacturing, and Controls
OBP=Office of Biotechnology Products
OPDP=Office of Prescription Drug Promotion
OSIS= Office of Study Integrity and Surveillance
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

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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

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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

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1. Executive Summary

1.1. Product Introduction

Nyvepria (pegfilgrastim-apgf) (PF-06881894) is a proposed biosimilar product to U.S.-licensed Neulasta (pegfilgrastim) (hereafter referred to as US-Neulasta). PF-06881894 is a covalent conjugate of G-CSF (recombinant methionyl human granulocyte colony-stimulating factor [met-HuG-CSF]) and a single methoxypolyethylene glycol moiety of approximately 20,000 Daltons. G-CSF is a 175 amino acid protein cytokine containing a 4-helix bundle motif with 2 intramolecular disulfide bonds: Cys37-Cys43 and Cys65-Cys75 and a free cysteine at amino acid residue 18.

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

Endogenous and recombinant human G-CSF promote the growth and maturation of myeloid cells and the activation, proliferation, and differentiation of neutrophil progenitors. G-CSF also reduces the neutrophil maturation time, leading to a rapid release of neutrophils from the bone marrow into circulation. G-CSF functions through binding to the G-CSF receptor, which is the mechanism of action across the licensed indications of US-Neulasta. Nyvepria is proposed for the followingindication as previously approved for US-Neulasta:

- *Decrease the incidence of infection, as manifested by febrile neutropenia, in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a clinically significant incidence of febrile neutropenia.*

The Applicant notes that the US-Neulasta indication of "*Increase survival in patients acutely exposed to myelosuppressive doses of radiation (Hematopoietic Subsyndrome of Acute Radiation Syndrome)"* has orphan exclusivity status until 23 Nov 2022 and acknowledges that this indication is protected for PF-06881894 until the end of the orphan exclusivity period; thus, the Applicant does not seek approval of this indication in the current application.

Pegfilgrastim-apgf (PF-06881894) has the same dosage form, route of administration, and dosing regimen as that of US-Neulasta. Nyvepria is supplied as injection for subcutaneous use as a 6 mg/0.6 mL solution in a single-dose prefilled syringe.

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1.4. Inspection of Facilities

FDA's Office of Pharmaceutical Manufacturing Assessment (OPMA) and Office of Biotechnology Products (OBP) conducted pre-approval inspections of the manufacturing facilities for this BLA.

Hospira Zagreb, Croatia, a Division of Pfizer, is responsible for drug substance (DS) and drug product (DP) manufacturing (FEI 3010630287). A pre-approval inspection (PAI) for PF-06881894 DS and DP was conducted November 14-22, 2019. The Hospira Zagreb site is also responsible for packaging and labeling, and DS and DP release and stability testing. The inspection was system based and covered Quality, Facilities and Equipment, Production, Laboratory Control and Materials. A 2-item FDA Form 483 was issued at the conclusion of the inspection. Refer to the FDA Form 483 for a list of the 483 observations. The inspection was classified as voluntary action indicated (VAI).

A PAI for PF-06881894 filgrastim intermediate manufacturing site at Thebarton, Australia (FEI 3003961774) was conducted on January 23-31, 2020. The site is responsible for manufacture of DS filgrastim intermediate (FI), and FI release and stability testing. The inspection was system based and covered Quality, Facilities and Equipment, Production, Laboratory Control and Materials. The inspection was classified as no action indicated (NAI). The details of the inspection are covered in the EIR. I concur with these recommendations.

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

Not applicable. Refer to Section 4.1, 6.1, and 6.2.

1.6. Biosimilarity Assessment

Table 1: Summary and Assessment of Biosimilarity

Comparative Analytical Studies	
Summary of Evidence	• PF-06881894 is highly similar to US-Neulasta • The strength of PF-06881894 in prefilled syringes is the same as that of US-Neulasta • The dosage form and route of administration are also the same as those of US-Neulasta .
Residual Uncertainties and Outcomes	• There are no residual uncertainties from the product quality assessment
Nonclinical Studies	

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Summary of Evidence	• One comparative repeat-dose nonclinical study was reviewed in support of the BLA submission, a 28-day toxicology study with a 6-week recovery period in rats (Study 1550-064) that compared the PD, toxicokinetics, and toxicity profiles of PF-06881894 and US-Neulasta. The PD, toxicokinetics and toxicity profiles of PF-06881894 and US-Neulasta appeared similar at all doses examined (≥ 200 ug/kg). • The information in the pharmacology/toxicology assessment support the demonstration of biosimilarity.
Residual Uncertainties and Outcomes	• There were no residual uncertainties from the pharmacology/toxicology assessment.
Clinical Pharmacology Studies	
Summary of Evidence	• The applicant submitted pharmacokinetic (PK) and pharmacodynamic (PD) data (Study C1221001/ZIN-130-1505), and immunogenicity data (C1221005) to support a demonstration of no clinically meaningful differences between PF-06881894 and US- Neulasta. • In Study ZIN-130-1505,PK similarity has been demonstrated between PF-06881894 and US-Neulasta. The 90% CI of the GMR for the primary PK endpoints of C_{max}, and $AUC_{0\text{-}inf}$ fell within the prespecified margin of 80-125%. • In Study ZIN-130-1505, PD (ANC) similarity has been demonstrated between PF-06881894 and US-Neulasta . The 90% CI of the GMR for the primary PD endpoints of ANC_{max} and $AUEC_{last}$ fell within the prespecified margin of 80-125%. • In Study C1221005, a similar incidence of ADA formation was observed for PF-06881894 and US-Neulasta in healthy subjects. The upper bound of the 90% CIs for risk difference was <10%, and met the prespecified limit. • Overall, the results from Study ZIN-130-1505 and Study C1221005 support the demonstration of no clinically meaningful differences between PF-06881894 and US- Neulasta and add to the totality of the evidence to support a demonstration of biosimilarity between PF-06881894 and US-Neulasta.

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Residual Uncertainties and Outcomes	• There are no residual uncertainties from the clinical pharmacology assessment.
Clinical Studies	
Summary of Evidence	• In study C1221005, among subjects with negative anti-drug antibody at baseline, the incidence of post-dose positive anti-drug antibody was similar between the arms (PF-06881894: 6%, US-Neulasta: 7%). The overall incidences of AEs in these subjects with treatment-emergent positive anti-drug antibody were also similar between the two arms (PF-06881894: 92%, US-Neulasta: 100%). • The overall safety profile of PF-06881894 was similar to that of US-Neulasta (and EU-Neulasta). The safety results from Study ZIN-130-1505 and Study C1221005 support a demonstration of no clinically meaningful differences between PF-06881894 and US-Neulasta.
Residual Uncertainties and Outcomes	• There are no residual uncertainties based on the clinical safety evaluation.
Extrapolation of Data to Support Licensure as a Biosimilar	
Summary of Evidence	• The 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 PF-06881894 as a biosimilar, under section 351(k) of the PHS Act, for the following indication for which US-Neupogen 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 were no residual uncertainties regarding the extrapolation of data and information to support licensure of PF-06881894 as a biosimilar to US-Neulasta for the above indication. .

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1.7. Conclusions on Licensure

In considering the totality of the evidence submitted, the data submitted by the Applicant show that Nyvepria is highly similar to U.S.-licensed Neulasta, notwithstanding minor differences in clinically inactive components, and that there are no clinically meaningful differences between Nyvepria and U.S.-licensed Neulasta in terms of the safety, purity, and potency of the product. The Applicant also provided adequate scientific justification for extrapolation of data and information to support licensure of PF-06881894 for the proposed indication, as listed below. The information submitted by the Applicant demonstrates that Nyvepria is biosimilar to U.S.-licensed Neulasta for the following indication for which U.S.-licensed Neulasta is currently licensed and Applicant is seeking licensure of Nyvepria:

- *Decrease the incidence of infection, as manifested by febrile neutropenia, in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a clinically significant incidence of febrile neutropenia.*

Author:
Kathy Robie-Suh, M.D., Ph.D.
CDTL

2. Introduction and Regulatory Background

2.1. Important Safety Issues with Consideration to Neulasta

Important safety issues with US-Neulasta include the following as described in the Warnings and Precautions section of the US-Neulasta prescribing information:

- Splenic rupture (including with fatal outcome)
- Acute respiratory distress syndrome (ARDS)
- Serious allergic reactions (including anaphylaxis)
- Severe and fatal sickle cell crises in patients with sickle cell disorders
- Glomerulonephritis
- Leukocytosis
- Capillary leak syndrome
- Potential for tumor growth stimulatory effects on malignant cells
- Aortitis

Most common adverse reactions (5%) reported in patients who received US-Neulasta in a double-blind, placebo-controlled breast cancer study receiving docetaxel 100 mg/m^2 every 21 days were bone pain and pain in extremity (US-Neulasta Prescribing information).

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2.2. Summary of Presubmission Regulatory Activity Related to Submission

The table below summarizes the relevant regulatory history pertaining to this BLA.

Table 2. Regulatory History

May 1, 2017	Biosimilar Product Development (BPD) Type 2 meeting was held to discuss the transition from the 351(a) to the 351(k) pathway, and to discuss the proposed 351(k) pathway development program. -The FDA stated that for the proposed non-inferiority, parallel-design, comparative immunogenicity study (C1221005) in healthy volunteers, an adaptive study design may be considered which allows for increasing the sample size to demonstrate that the difference in immunogenicity rates between HSP-130 and U.S.-licensed Neulasta is not more than the pre-specified amount. In the adaptive design, the Applicant should consider terminating the study if any neutralizing ADA activity is observed in the HSP-130 arm or if the results from first cohort clearly suggest that HSP-130 has increased ADA responses compared to U.S.-licensed Neulasta.
May 25, 2018	The FDA communicated to the Applicant that with regard to the comprehensive risk analysis, FDA determined that the risks associated with the proposed single-use pre-filled syringe for use in patients weighing 45 kg and greater were adequately considered and agreed that a human factors validation study is not needed.
October 9, 2018	A second BPD Type 2 meeting was held. -The FDA stated that the proposed approach to include data from the non-comparative ascending single- and multiple-dose study in women with non-distantly metastatic breast cancer (C1221002) in the BLA submission as supportive, rather than as integral, data for the biosimilar clinical development package is reasonable. -The FDA stated that BIMO information does not need to be submitted for the “Phase 1-2” dose escalation supportive study (C1221002). The proposal to submit BIMO data from the comparative PK/PD study in heathy subjects (ZIN-130-1505) and comparative immunogenicity study in healthy subjects (C1221005) is acceptable.
November 13, 2018	The FDA issued an “Agreed Initial Pediatric Study Plan (iPSP)” to IND 124793 for the proposed indication “Decrease the incidence of infection, as manifested by febrile neutropenia (FN), 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 or proposed. The Applicant is planning to fulfill PREA requirements based on demonstration of biosimilarity of PF-06881894 to the reference product, and extrapolation of pediatric information from the reference product to the proposed

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	biosimilar PF-06881894 for all pediatric age groups. The Applicant requested deferral of the requirement of a presentation that can be used to administer PF-06881894 to pediatric patients weighing <45 kg.The Applicant intends to submit a pediatric assessment by December 2025.
March 11, 2019	BPD Type 4 meeting was held to discuss the overall content and format of the BLA. Key discussions were as follows: - (b) (4) -The Applicant stated that the PF-06881894 proposed biosimilar clinical program will consist of 2 clinical studies: comparative single-dose, crossover design, PD/PK study in healthy subjects (PF-06881894 vs US-Neulasta and EU-Neulasta, Study ZIN-130-1505 and comparative multiple-dose immunogenicity study in healthy subjects (PF-06881894 vs US-Neulasta, Study C1221005). The CSRs for these 2 studies will be provided in the BLA including discussion and interpretation of the immunogenicity results. The Applicant asked whether the proposed clinical package would be adequate for review. -The FDA commented that the proposed clinical package, including immunogenicity information, appears reasonable to support a BLA submission. However, the decision on the adequacy of the clinical package supporting filing will be made during the review of the BLA Submission.

[Source: FDA compilation]

2.3. Studies and Publicly Available Information Submitted by the Applicant

Table 3. PF-06881894: Comparative Nonclinical Studies*

Study Number	Study Title	Dose Regimen/Route/Duration	Population
1550-064	A 4-Week Subcutaneous Comparative Repeat-Dose Toxicity Study with PF-06881894 and Neulasta in Rats With a 6-Week Recovery Period	200 or 1800 µg/kg/week SC once weekly for 4 weeks (5 doses)	Sprague Dawley Rats

*In addition, the BLA submission contained 12 other noncomparative nonclinical studies. For more information, see Sections 5 and 12.2.

Table 4. Listings of Clinical Studies Relevant to this BLA

Study ID/ country	Study Design	Regimen	Objectives	No. of Subjects/ Status

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PK Similarity Study				
C1221001 (ZIN-130-1505) (non-IND study) Australia	Open-label, randomized, single-dose, comparator-controlled, 3-treatment, 3-period, 6-sequence, crossover, study to assess the PD and PK of PF-06881894, and US-Neulasta and EU-Neulasta in healthy subjects.	A single SC dose of: -Treatment A: PF-06881894 6 mg -Treatment B: US-Neulasta 6 mg -Treatment C: EU-Neulasta 6 mg. There were 3 treatment periods and 6 sequences within the study as follows with a target of at least 56 days of washout between each study drug: - Sequence 1: A/B/C - Sequence 2: B/C/A - Sequence 3: C/A/B - Sequence 4: B/A/C - Sequence 5: A/C/B - Sequence 6: C/B/A	-To assess the PK and PD similarity of PF-06881894 with US-Neulasta and EU-Neulasta administered as a single SC dose. -To assess the PD and PK similarity of US-Neulasta and EU-Neulasta when administered as a single SC dose. -To assess the safety of PF-06881894.	153 subjects. Study completed on 6/3/16
Immunogenicity Study				
C1221005 United States	Randomized, open-label, multiple-dose, and parallel design non-inferiority study to assess the immunogenicity of multiple doses of PF-06881894 and US-Neulasta in healthy subjects.	Each randomized subject received a total of 2 doses of assigned treatment: -PF-06881894, 6 mg, SC injection -Regimen A (Test Product) -US-Neulasta, 6mg, SC injection -Regimen B (Reference Product)	-To assess the non-inferiority of PF-06881894 versus US-Neulasta with respect to immunogenicity (anti-drug antibodies). -To assess the safety of PF-06881894 and US-Neulasta.	422 subjects. Study completed on 7/25/18.
Other Study				
C1221002 (ZIN-130-1504) Hungary and Spain	Open-label, non-comparative, parallel-group, Phase 1-2 study characterizing the PD, PK, and safety (including immunogenicity) of PF-06881894 in patients with non-distantly metastatic (non-Stage IV) breast cancer who had not received chemotherapy prior to	Phase 1 (Cycle 0) -Regimen A: PF-6881894, 3 mg, single SC injection in deltoid region (n=6) - Regimen B: PF-06881894, 6 mg, single SC injection in deltoid region (n=6). Phase 2 (Cycles 1-4) - Regimen B:	-Phase 1: To characterize the safety, PK/PD of PF-06881894 at doses of 3 mg and 6 mg when administered as a single SC dose without chemotherapy to determine whether it would be appropriate to study multiple	25 subjects Study completed on 10/5/17.

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	enrollment in this study.	PF-06881894, 6 mg, single SC injection in the deltoid region, at least 24 hours after administration of chemotherapy (Day 2) in Cycle 1, Cycle 2, Cycle 3, and Cycle 4 (n = 13).	doses of 3 mg in the context of background chemotherapy. -Phase 2: To characterize the PK/PD and safety of PF-06881894 over a range of doses when administered as single and multiple SC doses.	

[Source: Applicant's submission]

Authors:

Hyon-Zu Lee, Pharm.D.
Clinical Reviewer

Kathy Robie-Suh, M.D., Ph.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. The quality control processes were reviewed by the Applicant's own independent quality assurance group or by CRO. This audit was conducted according to applicable standard operating procedures and local regulation.

3.3. Compliance with Good Clinical Practices

All studies were conducted according to Good Clinical Practice (GCP) as described in International Conference on Harmonisation (ICH) Guideline E6 and in accordance with the ethical principles outlined in the Declaration of Helsinki. The studies were conducted in compliance with the protocols. Informed consent, protocol, amendments, and administrative letters for the studies received Institutional Review Board/Independent Ethics Committee approval prior to implementation. Subjects signed informed consent documents. Written informed consent was obtained prior to subjects entering the studies (before initiation of protocol-specified procedures). The investigators explained the nature, purpose, and risks of

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the study to each subject. Each subject was informed that he/she could withdraw from the study at any time and for any reason. Each subject was given sufficient time to consider the implications of the study before deciding whether to participate. The investigators conducted all aspects of these studies in accordance with applicable national, state, and local laws of the pertinent regulatory authority.

3.4. Financial Disclosures

The Applicant has adequately disclosed financial arrangements with clinical investigators. The applicant provided financial certification form 3454 certifying that there were no financial arrangements with investigators involved in the three clinical studies ZIN-130-1505, C1221005 and C1221002. 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 58 of the 59 clinical investigators who participated in the covered studies. There was one investigator, (b) (6) who participated in study ZIN-130-1504 who reported payments of $64,209 for consulting. However, (b) (6). Therefore, it is unlikely that this financial conflict of interest affected the overall study results.

The Applicant reported that no clinical investigators were full-time or part-time employees of the Applicant for the covered studies.

Authors:

Hyon-Zu Lee, Pharm.D.	Kathy Robie-Suh, M.D., Ph.D.
Clinical Reviewer	Clinical Team Leader

4. Summary of Conclusions of Other Review Disciplines

4.1. Chemistry, Manufacturing and Controls (CMC)

The Office of Pharmaceutical (OPQ), CDER, recommends approval of BLA 761111 for Nyvepria (PF-06881894, pegfilgrastim-apgf) manufactured by Hospira, Inc. Refer to the Drug Substance Review (primary reviewer Xu Di, final signature in Panorama 4/16/2020 10:46:35AM)) and the Drug Product Review (primary reviewer Xu Di, final signature in Panorama 4/16/2020 11:07:17AM) for detailed information. The OPQ team determined that the data submitted in this application are adequate to support the following conclusions:

- The manufacture of PF-06881894 is well-controlled and leads to a product that is pure, potent, and safe
- PF-06881894 is highly similar to US-Neulasta notwithstanding minor differences in clinically inactive components
- The strength of PF-06881894 in a prefilled syringe is the same as that of US-Neulasta. PF-06881894 also has the same dosage form and route of administration as that of US-Neulasta.

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- The analytical component of the scientific bridge between PF-06881894, US-Neulasta, and EU-Neulasta was established to support the relevance of the data generated from clinical studies using EU-Neulasta as the comparator to the assessment of biosimilarity.

The analytical component of the scientific bridge between PF-06881994, US-Neulasta, and EU-Neulasta was established; however, data generated using EU-Neulasta were not used to support the assessment of biosimilarity.

4.2. Clinical Microbiology

Not applicable [Insert text here.]

4.3. Devices

PF-06881894 drug product is a sterile liquid solution with the following proposed strength and presentation:

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

4.3.1. Center for Devices and Radiological Health (CDRH)

The Division Of Drug Delivery, General Hospital & Human Factors of CDRH reviewed the application for pre-filled syringes (final Intercenter Consult review primary review by Gang Peng, final signature 4/7/2020). CDRH concluded that the device constituent part of the combination product is approvable with a post marketing commitment for lot release testing for safety activation force of the final finished combination product.

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

Primary risk assessment review of the labeling was performed by the Division of Medication Error Prevention and Analysis (DMEPA)/Office of Medication Error Prevention and Risk Management (OMEPRM) (Stephanie DeGraw, final signature 1/16/2020 and 3/23/2020)). The evaluation of the package insert did not identify unique areas of vulnerability that may lead to medication errors; however, areas of vulnerability were identified for the container and carton labels and proposed Instructions for Use and these were communicated to the Applicant and the Applicant made appropriate revisions.

Also, refer to Section 8.3 of this review for discussion of issues related to pediatric dosing.

4.4. Office of Study Integrity and Surveillance (OSIS)

OSIS and the Office of Regulatory Affairs (ORA) inspected the analytical portion of Studies ZIN-130-1505 and C1221005 (BLA 761111, pegfilgrastim-apgf/HSP-130/PF-06881894) conducted at

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[redacted] (b) (4) During [redacted] (b) (4) (OSIS Memorandum, Yiyue Zhang, 1/24/2020). No objectionable conditions were observed. The final inspection classification is No Action Indicated (NAI). One verbal item noted that [redacted] (b) (4) It was concluded that the immunogenicity data from Studies ZIN-130-1505 and C1221005 are reliable to support a regulatory decision. The method validation reports of further assessment on the [redacted] (b) (4) could be requested to verify if exceeded [redacted] (b) (4) affected the stability of ADA and anti-PEG antibodies. An NAI Letter was issued on 1/29/2020.

Surveillance inspection of analytical facilities for the PK portion of Study ZIN-130-1505 at [redacted] (b) (4) was performed during [redacted] (b) (4) and found no objectional conditions or practices and issued a NAI letter (Seongeun Cho, 2/20/2020).

4.5. Office of Scientific Investigations (OSI)

Not applicable.

Author:
Kathy Robie-Suh, M.D., Ph.D.
CDTL

5. Nonclinical Pharmacology and Toxicology Evaluation and Recommendations

5.1. Nonclinical Executive Summary and Recommendation

PF-06881894 (pegfilgrastim-apgf) has been developed as a biosimilar product to US Neulasta. One comparative nonclinical repeat-dose study was reviewed in support of the BLA submission, a 28-day toxicology study with a 6-week recovery period in rats (Study 1550-064) that compared the PD, toxicokinetics, and toxicity profiles of PF-06881894 (also known as HSP-130),EU-Neulasta andUS-Neulasta Based on the results of the study, the PD, toxicokinetics, and toxicity profiles of PF-06881894 and US-Neulasta appeared similar at the doses examined (200, 1800 µg/kg).

5.1.1. Nonclinical Residual Uncertainties Assessment

There were no residual uncertainties identified in the animal studies regarding the pharmacodynamic activity, safety, or pharmacokinetic parameters intended to support a demonstration of biosimilarity.

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5.2. Product Information

Product Formulation

PF-06881894 (pegfilgrastim-apgf) DP is formulated in 10 mM acetate buffer containing 0.04 mg/mL polysorbate 20 and 50 mg/mL sorbitol at pH 4.0.

Comments on Novel Excipients

There are no novel excipients.

Comments on Impurities/Degradants of Concern

There are no impurities/degradants of concern.

Authors:

Emily J. Place PhD MPH	Brenda J. Gehrke, PhD
Reviewer	Team Leader

6. Clinical Pharmacology Evaluation and Recommendations

6.1. Clinical Pharmacology Executive Summary and Recommendation

The applicant submitted pharmacokinetic (PK), pharmacodynamic (PD), and immunogenicity data to support a demonstration of no clinically meaningful differences between PF-06881894 and US-Neulasta.

Study C1221001/ZIN-130-1505 is a single-dose, randomized, 3-period, 3-treatment, 3-way cross over study in 153 healthy subjects designed to determine the PK and PD (absolute neutrophil count [ANC]) similarity of PF-06881894, US-Neulasta, and EU-Neulasta following a 6 mg subcutaneous (SC) dose. The geometric mean ratio (GMR) of the PK and PD parameters along with the 90% confidence intervals (CI) of all pairwise comparisons were within the prespecified acceptability margin of 80% to 125%. The results of the study established the PK and PD similarity between PF-06881894 and US-Neulasta based on the primary PK endpoints of C_{max} and $AUC_{0\text{-}inf}$ and PD endpoints of ANC_{max} and ANC $AUEC_{last}$. While the clinical pharmacology study ZIN-130-1505 included the use of a non-US-licensed comparator product, EU-Neulasta, the clinical data generated using EU-Neulasta was not used to support the assessment of biosimilarity.

The incidence of anti-drug antibodies (ADAs) was compared in Study C1221005, a comparative clinical study with PF-06881894 and US-Neulasta in 420 healthy subjects. The incidence of immunogenicity for PF-06881894 and US-Neulasta following two 6 mg SC doses. The study

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results indicate a similar incidence and titers of ADA for PF-06881894 and US-Neulasta. The assessment of the impact of ADA on PK, PD, efficacy, and safety are limited due to the limited number of subjects who were ADA-positive. Therefore, the data indicates that there is no increase in immunogenicity risk for PF-06881894 compared to US-Neulasta.

Overall, the results from Study ZIN-130-1505 and Study C1221005 support the demonstration of no clinically meaningful differences between PF-06881894 and US-Neulasta and add to the totality of the evidence to support a demonstration of biosimilarity between PF-06881894 and US-Neulasta (Table 5).

Table 5. Clinical Pharmacology Review Summary

Review Issue	Recommendations and Comments
Pharmacokinetic Similarity	• In Study ZIN-130-1505, PK similarity between PF-06881894 and US-Neulasta was demonstrated. The 90% CI of the GMR for the primary PK endpoints of C_{max}, and $AUC_{0\text{-}inf}$ fell within the margin of 80-125%.
Pharmacodynamic Similarity	• In Study ZIN-130-1505, PD (ANC) similarity between PF-06881894 and US-Neulasta was demonstrated. The 90% CI of the GMR for the primary PD endpoints of ANC_{max} and $AUEC_{last}$ fell within the margin of 80-125%.
Immunogenicity	• In Study C1221005, a similar incidence of ADA formation was observed for PF-06881894 and US-Neulasta in healthy subjects. The upper bound of the 90% CIs 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 PF-06881894 with US-Neulasta and showed no increase in immunogenicity risk for PF-06881894 when compared to 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. While the clinical pharmacology study ZIN-130-1505 included the use of a non-US-licensed comparator product, EU-Neulasta, the clinical data generated using EU-Neulasta was not used to support the assessment of biosimilarity.

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6.3. Human Pharmacokinetics and Pharmacodynamics

Clinical Pharmacology Study Design Features

The applicant conducted one clinical pharmacology PK/PD similarity study (i.e., Study ZIN-130-1505) with PF-06881894, US-Neulasta and EU-Neulasta in healthy subjects, as described in **Table 4** in Section 2.3.The study design of Study ZIN-130-1505 is considered adequate to demonstrate PK/PD similarity for the following reasons:

- A study in healthy subjects is considered safe and an appropriately sensitive study population.
- A single SC dose of 6 mg is the approved dose for both US-Neulasta and EU-Neulasta.
- A cross-over study design was used to assess the PK/PD similarity of PF-06881894, US-Neulasta and EU-Neulasta. Refer to Section 7.2.1 for more detailed description on study design.
- A target washout period of at least 56- 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 has returned to baseline by around Day 13 after each treatment.
- Absolute neutrophil count (ANC), the PD marker of drug efficacy, has been well characterized in patients with chemotherapy-induced myelosuppression in clinical studies.

Clinical Pharmacology Study Endpoints

In Study ZIN-130-1505, the prespecified PK endpoints were C_{max} and $AUC_{0\text{-}inf}$, and the prespecified PD endpoints were ANC_{max}, and $AUEC_{last}$. PK and PD similarities were established if the 90% CI of GMR of each parameter between PF-06881894 with both US-Neulasta and EU-Neulasta were within the prespecified limits of 80-125%.

Sampling points were collected as follows:

- PK: Serum samples for assessment of PK parameters were collected at pre-dose and at 1, 2, 4, 6, 8, 10, 12, 16, 24, 48, 72, 96, 120, 144, 168, 192, 216, 240, 264, and 288 hours post-dose.
- PD (ANC): Peripheral blood samples for assessment of ANC were collected at pre-dose and at 12, 24, 48, 72, 96, 120, 144, 168, 192, 216, 240, 264, and 288 hours post-dose.
- ADA: Serum samples for ADA assessment were collected at pre-dose and at Day 13 post-dose.

Bioanalytical PK Method and Performance

See Appendix 12.3.1 for details.

PK Similarity Assessment

PK similarity between PF-06881894, US-Neulasta and EU-Neulasta was demonstrated in the single-dose crossover Study ZIN-130-1505. The 90% CIs of the GMR for PK (C_{max} and $AUC_{0\text{-}inf}$)

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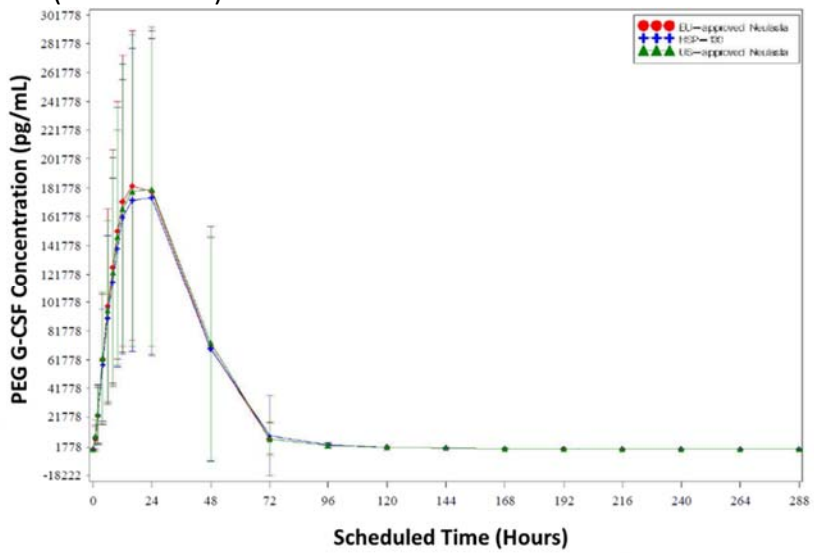
endpoints were within 80-125% (Table 2).

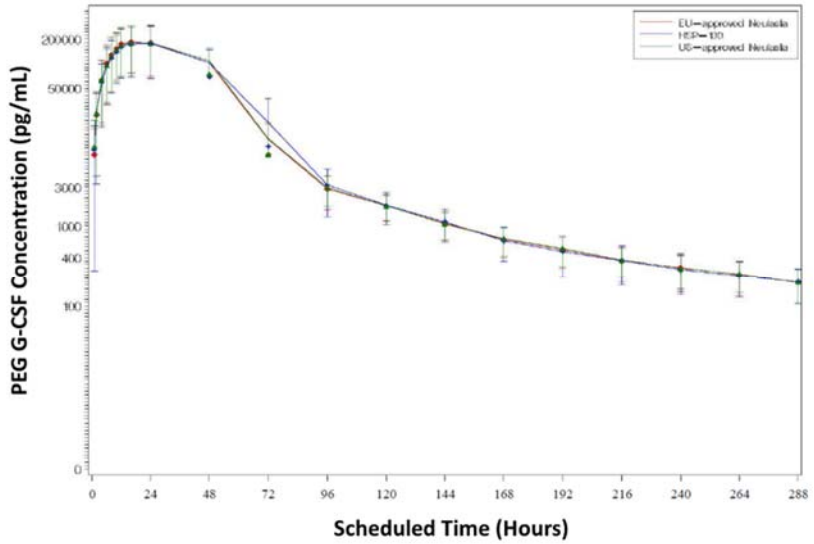
The geometric mean concentration-time profiles and a summary of PK parameters are shown in Figure 1 andTable 6, respectively. Of note, PEG G-CSF is the PK analyte in serum for PF-06881894, US-Neulasta and EU-Neulasta. See Appendix 12.3.1 for details.

Figure 1. Geometric mean serum PEG G-CSF concentration (pg/mL) vs. time (hr) from Study ZIN-130-1505.

A. (Linear scale)



B. (Semi-logarithmic scale)



(Source: Study ZIN-130-1505 CSR)
Symbols represent: PF-06881894 (Blue), US-Neulasta (green) or EU-Neulasta (red)

Table 6. Summary of statistical analyses for assessment of PK similiarity (Study ZIN-130-1505)

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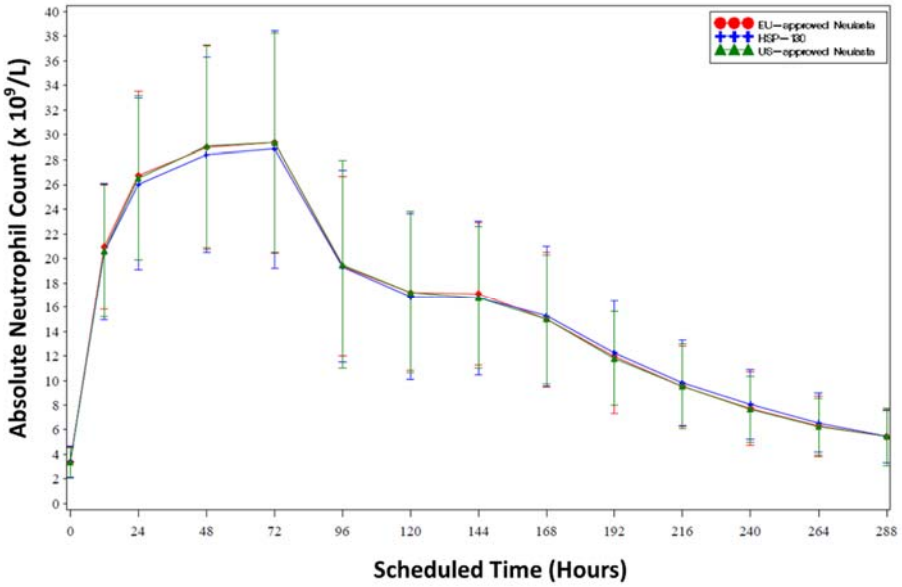
Parameter	Statistic	PF-06881894 (n=136)	US-Neulasta (n=136)	EU-Neulasta (n=138)	Geometric Mean Ratio (90% CI)		
					PF-06881894 vs. US-Neulasta	PF-06881894 vs. EU-Neulasta	EU-Neulasta vs. US-Neulasta*
Primary							
$AUC_{0\text{-inf}}$ (h•pg/mL)	Geometric Mean	5397629	5503224	5547385	0.98 (0.91, 1.06)	0.97 (0.90, 1.05)	0.99 (0.91, 1.07)
C_{max} (pg/mL)	Geometric Mean	154512.2	159688.0	161388.6	0.97 (0.90, 1.04)	0.95 (0.88, 1.03)	0.98 (0.91, 1.06)
Secondary							
$AUC_{0\text{-last}}$ (h•pg/mL)	Geometric Mean	5379269	5482242	5526987	0.98 (0.91, 1.06)	0.97 (0.90, 1.05)	0.99 (0.91, 1.07)

(Source: PF-06881894 SCP)
*Values calculated as US-Neulasta against EU-Neulasta

PD Similarity Assessment

PD (ANC) similarity between between PF-06881894, US-Neulasta and EU-Neulasta was demonstrated in the single-dose crossover Study ZIN-130-1505 (Figure 2). The 90% CIs of the GMR for PD (ANC_{max} and $AUEC_{last}$) endpoints were within 80-125% (Table 7).

Figure 2. Mean ANC concentration (x 10^9/L) vs. time (hr) from Study ZIN-130-1505.



(Source: Study ZIN-130-1505 CSR.)
Symbols represent: PF-06881894 (Blue), US-Neulasta (green) or EU-Neulasta (red)

Table 7. Summary of statistical analyses for assessment of PD similarity (Study ZIN-130-1505)

Parameter	Statistic	PF-06881894 (n=135)	US-Neulasta (n=134)	EU-Neulasta (n=138)	Geometric Mean Ratio (90% CI)		
					PF-06881894	PF-06881894	EU-Neulasta

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					vs. US-Neulasta	vs. EU-Neulasta	vs. US-Neulasta*
Primary							
$AUEC_{ANC0-t}$ (h×10^9/L)c	Geometric Mean	4541.21	4581.48	4588.23	0.99 (0.97, 1.00)	0.98 (0.97, 1.00)	1.00 (0.98, 1.01)
ANC_C_{max} (×10^9/L)	Geometric Mean	30.29	31.30	30.64	0.96 (0.94, 0.98)	0.98 (0.96, 1.00)	1.02 (1.00, 1.04)
Secondary							
$AUEC_{ANC0-inf}$ (h×109/L)	Geometric Mean	5278.19	5328.56	5296.87	0.99 (0.96, 1.01)	0.99 (0.97, 1.02)	1.01 (0.99, 1.03)

(Source: PF-06881894 SCP)
*Values calculated as US-Neulasta against EU-Neulasta

6.4. Clinical Immunogenicity Studies

- **Immunogenicity Assessment in Study C1221005**

Design features of the clinical immunogenicity assessment

The applicant conducted an immunogenicity study (Study C1221005) in healthy subjects, as described in **Table 4** in Section 2.3. The study is a randomized, open-label, multiple dose, parallel study in which approximately 420 subjects were to be enrolled and randomized to one of 2 treatments: PF-06881894 or US-licensed Neulasta. Approximately 210 subjects were planned to be enrolled in each arm.

The primary objective of this study was to demonstrate similarity of PF-06881894 to US-licensed Neulasta with respect to immunogenicity in healthy subjects. The study was designed to exclude an absolute percent difference of no more than 10% in the ADA incidence between PF-06881894 and US-licensed Neulasta. The study design of C1221005 is considered adequate to assess immunogenicity risk.

Secondary objectives of the study were to evaluate the safety profile of PF-06881894 and US-licensed Neulasta as assessed by clinical adverse events (AEs), laboratory variables, vital signs, physical examination, 12-lead ECGs, concomitant medication, and local ISRs (see Section 7 for a discussion of these safety results).

There were 2 treatment periods in the study . Each randomized subject was to receive a total of 2 doses of assigned treatment (PF-06881894 or US-licensed Neulasta), which was administered as 1 SC injection each on Period 1 Day 1 (P1D1) and Period 2 Day 1 (P2D1). In Treatment Period 2, each subject was to receive 1 SC dose of the same regimen received in Treatment Period 1. There was an interval of approximately 1 month between P1D1 and P2D1. The duration of Treatment Period 1 was 30 (± 2) days and the duration of Treatment Period 2 was 60 (± 5) days.

Samples for assessment of immunogenicity (ADA) were collected on Day 1 (predose baseline), 13 and 30 (± 2) during Treatment Period 1; and Day 13, 30 (± 2)/Early Withdrawal and 60 (± 5) during Treatment Period 2.

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Safety assessments were conducted at screening, on Day 1, 3, 5, 13 and 30 (± 2) of Period 1, and on Day 1, 3, 5, 13, 30 (± 2), 45 (± 5) and 60 (± 5) of Period 2.

Immunogenicity endpoints

The primary endpoint is proportion of subjects with a negative baseline anti-drug antibody test result and confirmed postdose positive anti-drug antibody test result at any time during the study. A 90% confidence interval for the test-reference difference were constructed using the exact method of Chan and Zhang. Non-inferiority is demonstrated when the upper bound of the confidence interval is less than or equal to 10%.

Table 8 shows the detailed definition for the Sponsor's and FDA analysis sets and their differences. Note that for a randomized study, the primary analysis is commonly based on all randomized subjects in order to protect the balance of covatiates between arms to avoid potential bias.

Sponsor's Analysis Set: All subjects who are randomized, received at least 1 dose of study medication, and have baseline sample and at least one post-dose ADA sample.

FDA Analysis Set: All subjects who are randomized.

Table 8. Comparison of Immunogenicity Analysis Set defined by Sponsor and the FDA Analysis Set

	Sponsor	FDA
Analysis Set	• Randomized • Received at least 1 dose of study medication • Have baseline sample • Have at least one post-dose ADA sample	All randomized subjects
# No baseline sample	0	
# No post-dose ADA sample	2 in PF-06881894 1 in US-Neulasta	
# Positive baseline sample	4 in PF-06881894 8 in US-Neulasta	
# Subjects	417	420
# Immunogenicity Analysis	204 in PF-06881894 201 in US-Neulasta	210 in PF-06881894 210 in US-Neulasta

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

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The immunogenicity assays were capable of detecting the ADA in the presence of PF-06881894, US-Neulasta and EU-Neulasta in the study samples. The sensitivity of the ADA assay was 9.1 ng/mL for anti- G-CSF antibodies. The drug tolerance was 100 ng/mL tolerates up to 100 ug/mL of pegfilgrastim. The sensitivity of the Nab assay was 4.2 µg/mL for anti- G-CSF neutralizing antibodies. The drug tolerance was 4 µg/mL tolerates up to 10 ng/mL of pegfilgrastim. The sensitivity of the ADA assay was 41.9 ng/mL for anti- PEG antibodies. The drug tolerance was LPC pool 1:4 tolerates up to 100 ug/mL mPEG; 200 ng/mL Mab tolerates up to 100 ug/mL PF-06881894. 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 C1221005 was adequate to capture baseline, early onset, and the dynamic profile (transient or persistent) ADA formation. Samples for ADA assessment were collected as follows:

- Preiod 1: D1 (predose baseline), D13 and D30 (± 2)
- Period 2: D13, D30 (± 2)/Early Withdrawal and P2D60 (± 5)

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

Table 9. Immunogenicity results for binding ADA and nAb in Study C1221005 from Sponsor analysis

	N	Anti- drug antibody			Nab
		Baseline	Treatment-Induced	Risk Difference (90% CI)	
PF-06881894	204	4/210 (1.9%)	12/204 (5.9%)	-1.58% (5.92%, 2.68%)	0
US-Neulasta	201	8/210 (3.8%)	15/201 (7.5%)		0

Source: Sponsor analysis

The risk difference of PF-06881894 – US-Neulasta is -1.58% with a 90% confidence interval of (-5.92%, 2.68%). The upper bound does not exceed 10%, a pre-specified margin for the non-inferiority analysis.

The Sponsor excluded subjects who had no baseline sample, no post-dose ADA sample or had positive baseline sample from the immunogenicity analysis. The FDA statistical reviewer performed re-analyses by including all randomized subjects in the primary analysis to preserve balance of characteristics of the 2 arms. In particular, the FDA statistical reviewer conducted two types of imputations: (1) imputing all subjects who were excluded as no ADA incidences (2) imputing all excluded subjects as ADA incidences for both arms. FDA re-analysis results are

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shown in the following tables 10 and 11. In both of the two imputations, the conclusion was not affected. There is no significant difference in immunogenicity between the biosimilar product and the reference product.

Table 10. Immunogenicity results for binding ADA and nAb in Study C1221005 from FDA analysis. Impute missing post-baseline data or having positive baseline as no ADA incidences

	N	Anti-drug antibody			Nab
		Baseline	Treatment-Induced	Risk Difference (90% CI)	
PF-06881894	210	4/210 (1.9%)	12/210 (5.7%)	-1.43% (-5.60%, 2.65%)	0
US-Neulasta	210	8/210 (3.8%)	15/210 (7.1%)		0

/Source: FDA analysis

The risk difference of PF-06881894 – US-Neulasta is -1.43% with a 90% confidence interval of (-5.60%, 2.65%). The upper bound does not exceed 10%.

Table 11. Immunogenicity results for binding ADA and nAb in Study C1221005 from FDA analysis. Impute missing post-baseline data or having positive baseline as ADA incidences

	N	Anti-drug antibody			Nab
		Baseline	Treatment-Induced	Risk Difference (90% CI)	
PF-06881894	210	4/210 (1.9%)	18/210 (8.6%)	-2.86% (-7.94%, 2.07%)	0
US-Neulasta	210	8/210 (3.8%)	24/210 (11.4%)		0

Source: FDA analysis

The risk difference of PF-06881894 – US-Neulasta is -2.86% with a 90% confidence interval of (-7.94%, 2.07%). The upper bound does not exceed 10%.

Neutralizing antibodies
No subject tested positive for neutralizing antibodies following administration of PF-06881894 or US-Neulasta in this Study C1221005 (refer to Tables 10-11).

Anti-PEG antibodies
The results for anti-PEG antibody is presented in Table 12. The Applicant's analysis suggested that no meaningful differences were observed between the 2 treatment groups

Table 12. Immunogenicity results for anti-PEG in Study C1221005 from Sponsor analysis

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Analysis visit	PF-06881894 (N = 210)		US-Neulasta (N = 210)	
	N	n (%)	N	n (%)
Baseline	210	46 (21.9)	210	48 (22.9)
Day 13, Period 1	207	116 (56.0)	207	124 (59.9)
Day 30, Period 1	203	103 (50.7)	208	113 (54.3)
Day 13, Period 2	188	78 (41.5)	194	82 (42.3)
Day 30, Period 2	189	75 (39.7)	192	87 (45.3)
Day 60, Period 2	186	72 (38.7)	190	81 (42.6)
Last post baseline visit	208	83 (39.9)	209	93 (44.5)

Source: Study C1221005CSR Table 10.

- **Immunogenicity Assessment in Study ZIN-130-1505**

Immunogenicity was also evaluated in Study ZIN-130-1505. However, due to the crossover study design, the immunogenicity data from Study ZIN-130-1505 cannot be used for accurate assessment of immunogenicity difference between PF-06881894 and US-Neulasta. Refer to Section 7.2.1 for more detailed description on study design.

Study ZIN-130-1505 the same immunogenicity assays as Study C1221005. The immunogenicity sampling plan in Study ZIN-130-1505 was adequate to capture baseline, early onset, and the dynamic profile (transient or persistent) ADA formation. Samples for ADA assessment were collected as follows:

- Preiod 1 - 3: D1 (predose baseline), D13 and D30 (± 1)

The results for anti-drug antibody is presented in **Error! Reference source not found.**. Two subjects treated with PF-06881894 were tested positive for Nab. According to the Applicant, the anti-drug responses for these 2 subjects were not specific for the G-CSF protein. Both subjects had high titer anti-PEG responses that remained elevated for the duration of the study which suggests that the NAb was related to the PEG moiety, not the G-CSF protein moiety. No subject treated with US-Neulasta was tested positive for Nab. The results for anti-PEG antibody is presented in Table 14.

Table 13. Immunogenicity results for binding ADA in Study ZIN-130-1505 from Sponsor analysis

Visit of First Occurrence of Positive Result	PF-06881894 N = 148 N(%)	US-Neulasta N = 146 N(%)	EU-Neulasta N = 148 N(%)
Period 1: Day 1	0	0	0
Period 1: Day 13	5 (9.8)	2 (3.9)	1 (2.0)
Period 1: follow-up	1 (2.0)	0	0
Period 2: Day 1	0	0	1 (2.1)
Period 2: Day 13	0	0	0
Period 2: follow-up	0	0	0
Period 3: Day 1	0	0	0

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Period 3: Day 13	0	0	0
Period 3: follow-up	0	0	0
At any visit	6 (4.1)	2 (1.4)	2 (1.4)

Source: Study ZIN-130-1505 CSR Table 20.

Table 14. Immunogenicity results for anti-PEG in Study ZIN-130-1505 from Sponsor analysis

Visit of First Occurrence of Positive Result	PF-06881894 N = 148 N(%)	US-Neulasta N = 146 N(%)	EU-Neulasta N = 148 N(%)
Period 1: Day 1	16 (31.4)	16 (31.4)	12 (23.5)
Period 1: Day 13	19 (37.3)	22 (43.1)	22 (43.1)
Period 1: follow-up	1 (2.0)	0	2 (3.9)
Period 2: Day 1	0	0	0
Period 2: Day 13	0	0	0
Period 2: follow-up	0	0	0
Period 3: Day 1	0	1 (2.2)	0
Period 3: Day 13	0	0	0
Period 3: follow-up	0	0	
At any visit	36 (24.3)	39 (26.7)	

Source: Study ZIN-130-1505 CSR Table 20.

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

The incidence of ADA was low in both Study ZIN-130-1505 or Study C1221005. No apparent impact of ADA on PK, PD, or safety endpoints was observed from Study C1221005. In Study ZIN-130-1505, the ANC results from one subject tested positive for Nab suggested an apparent negative impact of Nab on the ANC result. Refer to Section 7.4 for more detailed information.

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7. Statistical and Clinical Evaluation and Recommendations Statistical and Clinical Executive Summary and Recommendation

The BLA submission contained a clinical PD/PK crossover study (ZIN-130-1505) and a randomized, parallel, non-inferiority, immunogenicity study (C1221005) to support licensure of PF-06881894 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-

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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 PF-06881894 was primarily based on a total of 573 subjects who participated in the comparative studies (ZIN-130-1505 crossover study: 153 subjects [PF-06881894: 148 subjects, US-Neulasta: 146 subjects, EU-Neulasta: 148 subjects], C1221005: 420 subjects [PF-06881894: 210 subjects, US-Neulasta: 210 subjects]).

In study C1221005, among subjects with negative anti-drug antibody at baseline, the incidence of post-dose positive anti-drug antibody was similar between the arms (PF-06881894: 6%, US-Neulasta: 7%). The overall incidences of AEs in these subjects with treatment-emergent positive anti-drug antibody were also similar between the two arms (PF-06881894: 92%, US-Neulasta: 100%).

The overall safety profile of PF-06881894 was similar to that of US-Neulasta (and EU-Neulasta). The safety results from the comparative clinical studies supports demonstration of no clinically meaningful differences between PF-06881894 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. ZIN-130-1505 (C1221001)

Title: A Phase 1 Study Assessing the Pharmacodynamic and Pharmacokinetic Equivalence of HSP-130 With US-Approved Neulasta (Registered) and EU-Approved Neulasta (Registered) Administered as a Single Subcutaneous Dose to Healthy Volunteers.

Study Initiation Date: August 21, 2015
Study Completion Date (Last Subject Last Visit): June 3,2016
Study Site: The study was conducted at 1 site in Australia

Study Design and Endpoints

This study was an open-label, randomized, single-dose, comparator-controlled, 3-treatment, 3-period, 6-sequence, crossover study to assess the PD and PK of PF-06881894, and US-Neulasta and EU-Neulasta. The PD and PK similarity of US-Neulasta and EU-Neulasta was also assessed.

Subjects were randomized to 1 of 6 sequence groups to receive each of the following study drugs over 3 study periods, with a target of at least 56 days of washout between successive study drugs. A total of 150 subjects were to be randomized to the 6 sequences, such that 25

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subjects would be randomized to each of the sequences. The 3 treatments were as follows:

- Treatment A: PF-06881894, 6 mg, single SC injection in the deltoid region;
- Treatment B: US-Neulasta, 6 mg, single SC injection in the deltoid region;
- Treatment C: EU-Neulasta, 6 mg, single SC injection in the deltoid region.

The 6 sequence groups are presented in the table below.

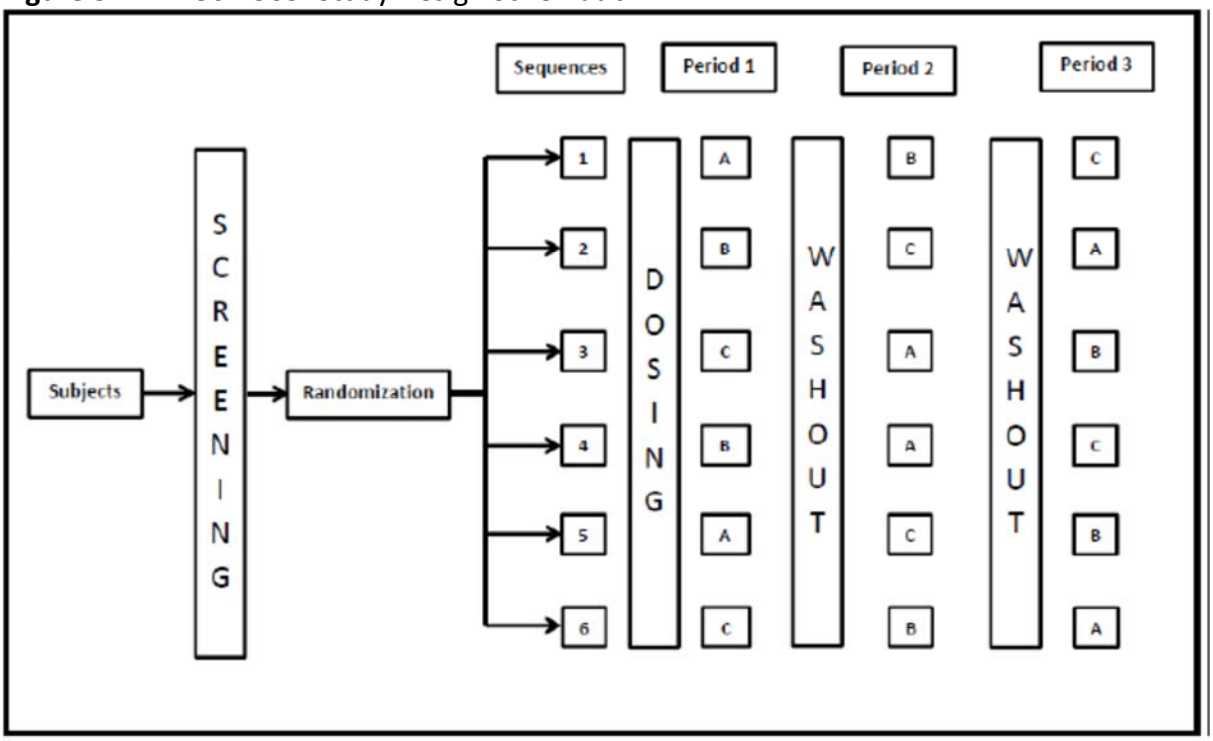
Table 15. ZIN-130-1505: Study Assignment by Sequence Group

Sequence Group	Study Period		
	1	2	3
1	A	B	C
2	B	C	A
3	C	A	B
4	B	A	C
5	A	C	B
6	C	B	A

[Source: CSR]

Study drug was administered in the morning on Day 1 in each period. Subjects were provided with a snack approximately 10 hours before dosing and then fasted until breakfast was given following collection of the 2-hour PK sample. Subjects remained confined until the PD and PK samples were collected and all other Day 5 procedures were completed. Subjects returned to the clinical unit on an outpatient basis for PD and PK sample collection and other scheduled assessments on Day 6 to Day 13. Subjects were discharged from the study after a follow-up visit that occurred 30 days after administration of the study drug in Period 3.

Figure 3. ZIN-130-1505: Study Design Schematic



[Source: CSR]

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Subjects were to receive one of the following study drugs: PF-06881894 (Treatment A) or US-Neulasta (Treatment B) or EU-Neulasta (Treatment C) in each period as a single dose via SC injection on Study Day 1, as per the randomization schedule (Table 15). There were 3 treatment periods and 6 sequences within the study.

Population: Healthy male or female volunteers 18 to 65 years of age (inclusive), with a body mass index (BMI) between 19 and 30 kg/m^2 (inclusive), and body weight that was not <50 kg or >100 kg were enrolled. A subject had to be a non-smoker at screening. 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 assess the PD similarity of PF-06881894 with US-Neulasta and EU-Neulasta administered as a single SC dose.

The secondary objectives were:

- To assess the PK similarity of PF-06881894 with US-Neulasta and EU-Neulasta administered as a single SC dose;
- To assess the PD and PK similarity of US-Neulasta and EU-Neulasta when administered as a single SC dose;
- To assess the safety of PF-06881894.

The PD endpoints were based on the following variables:

- Primary Variables: Area under the effect versus time curve for ANC from the time of dose administration to 288 hours after dose administration ($AUEC_{ANC}$) and maximum observed value for ANC (ANC_Cmax).
- Secondary Variable: The time of maximum value for ANC (ANC_Tmax).

Schedule of Events

Table 16. ZIN-130-1505: Schedule of Assessments

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Evaluation		Treatment Periods 1, 2, and 3														
Study Days	Screening[a]	-1	1	2	3	4	5	6	7	8	9	10	11	12	13	Follow-up[b]
Subject confinement to the Phase 1 Unit[c]		X	X	X	X	X	X									
Informed consent form signed	X															
Inclusion/exclusion criteria assessment	X	X[d]														
Demography	X															
Medical history and current conditions	X	X														
Clinical Assessments																
Physical examination	X														X	X
Directed physical examination (spleen assessment)		X		X	X	X	X			X		X				
Vital signs[e]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Weight	X															X[f]
Height	X															
Chest X-ray	X															
12-lead ECG[g]	X															X
Adverse events	To be captured from consent through to the follow-up visit at Period 3															
Concomitant medications	To be captured from screening through to the follow-up visit at Period 3															
Laboratory Assessments																
HIV, hepatitis B & C screen	X															
Serum pregnancy test[h]	X	X														X
Drugs of abuse and alcohol screen	X															
CBC, platelets, Chemistry Panel, and urinalysis[i,j]	X	X		X		X									X	X
Liver panel only (AST, ALT, LDH, ALP, GGT)			X[k]		X		X			X		X				
ANC for PD assessment			X	X	X	X	X	X	X	X	X	X	X	X	X	
Serum pegylated filgrastim samples			X	X	X	X	X	X	X	X	X	X	X	X	X	
Anti-pegfilgrastim antibodies[m]			X												X	X
Treatments																
Randomization[l] and administration of IMP			X													

a. Screening took place up to 28 days prior to Day 1.
b. Follow-up took place on Day 30 of each period or early termination.
c. Subject was admitted to the Phase 1 Unit on Day -1 and discharged on Day 5.
d. Confirmation of inclusion/exclusion criteria without repeat of screening labs in Period 1 only.
e. Vital signs included assessment of tympanic temperature, pulse, BP, and respiratory rate.
f. At each period.
g. 12-lead ECG was performed at rest.
h. Serum pregnancy test was required for all females except for those who were surgically sterile and without childbearing potential.
i. Chemistry panel comprised: urea, glucose, AST, ALT, ALP, sodium, potassium, chloride, total protein, albumin, creatinine, calcium, phosphate, total bilirubin, GGT, LDH, and uric acid.
j. ANC included differential and absolute values. Urinalysis was conducted only at screening. Urine assessment included PCR at Day -1, Day 2, Day 4, Day 13, and follow-up visit.
k. The liver panel assessment on Day 1 was collected predose (up to 1 hour prior to dosing).
l. Randomization in Period 1 only.
m. Day 1 samples in each period for anti-drug antibody testing (both anti-pegfilgrastim and anti-PEG) were collected predose.

[Source: CSR]

Statistical Methodologies

PD similarity was assessed by constructing the 90% confidence intervals (CIs) for the geometric mean ratio (GMR; test/reference) for $AUEC_{ANC}$ and ANC_Cmax. PD similarity was concluded if the 90% CIs for both $AUEC_{ANC}$ and ANC_Cmax were completely contained within the acceptance limits of 80%-125%. A step down testing in AUECANC and ANC_Cmax was utilized. PF-06881894 was tested against US-Neulasta first. If the test was positive, PF-06881894 was tested against EU-Neulasta . If this test was positive, US-Neulasta was tested against EU-Neulasta.

PK similarity was assessed by constructing the 90% CIs for the GMR(test/reference) for $AUC_{0\text{-inf}}$ and Cmax. PK similarity was concluded if the 90% CIs for both AUC0-inf and Cmax were

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completely contained within the acceptance limits of 80%-125%. The same step down testing as that for PD variables was performed. All subjects who received at least 1 dose of study drug were included in the safety population.

Subject Disposition

Study ZIN-130-1505 enrolled a total of 153 subjects. A total of 142 (93%) subjects completed the study and 11 (7%) subjects discontinued the study prematurely mostly due to "withdrawal by subject" (5%). The subject disposition in the 6 sequences were largely balanced.

Table 17. ZIN-130-1505: Subject Disposition (Enrolled Population)

	PF/US/EU N=26	**US/EU/PF N=25**	**EU/PF/US N=25**	**US/PF/EU N=26**	**PF/EU/US N=25**	**EU/US/PF N=26**	**Total n=153**
Completed study	24 (92%)	23 (92%)	21 (84%)	24 (92%)	25 (100%)	25 (96%)	142 (93%)
Safety population	26 (100%)	25 (100%)	25 (100%)	26 (100%)	25 (100%)	26 (100%)	153 (100%)
PK population	24 (92%)	24 (96%)	24 (96%)	25 (96%)	20 (80%)	26 (100%)	143 (94%)
PK Population plus subjects with positive anti-pegylated filgrastim results	26 (100%)	25 (100%)	25 (100%)	26 (100%)	25 (100%)	26 (100%)	153 (100%)
PD population	24 (92%)	24 (96%)	24 (96%)	25 (96%)	20 (80%)	26 (100%)	143 (94%)
PD population plus subjects with positive anti-pegylated filgrastim results	26 (100%)	25 (100%)	25 (100%)	26 (100%)	25 (100%)	26 (100%)	153 (100%)
Discontinued study prematurely	2 (8%)	2 (8%)	4 (16%)	2 (8%)	0	1 (4%)	11 (7%)
Adverse event	0	1 (4%)	0	1 (4%)	0	0	2 (1%)
Other	0	0	0	1 (4%)	0	0	1 (<1%)
Physician decision	0	1 (4%)	0	0	0	0	1 (<1%)
Withdrawal by subject	2 (8%)	0	4 (16%)	0	0	1 (4%)	7 (5%)

PF = PF-06881894 (also referred to as HSP-130). US = US-Neulasta. EU = EU-Neulasta
[Source: CSR]

Among the subjects who discontinued the study prematurely, a total of 2 subjects experienced AEs (spontaneous abortion, generalized rash); 1 subject had other reasons (moved overseas for personal reasons), and for 1 subject it was deemed appropriate in the best interest of the subject's welfare by the treating physician. Also see section 7.3.3.

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In the 6 sequences, a total of 148, 146, and 148 subjects received at least one dose of PF-06881894, US-Neulasta, and EU-Neulasta, respectively.

Demographics and Baseline Characteristics

See Table 21 in Section 7.3.2.

Efficacy Results

No efficacy evaluations were conducted in this study.

PK/PD results

The primary objective was to assess the PD similarity of PF-06881894 with US-Neulasta and EU-Neulasta administered as a single SC dose using the $AUEC_{ANC}$ and ANC_C_{max} variables. For analysis of the primary analysis, see Section 6.

7.2.2 C1221005

Title: Phase 1, Randomized Open Label, Multiple Dose, Parallel Study to Assess the Immunogenicity of Multiple Subcutaneous (SC) Doses of the Proposed Pegfilgrastim Biosimilar (PF-06881894) and US-Approved Neulasta (Registered) in Healthy Volunteers.

Study Initiation Date: October 27, 2017
Study Completion Date: July 25, 2018
Study Site: The study was conducted at 3 centers in the US.

Study Design and Endpoints

This study was a randomized (1:1), open-label, multiple-dose, and parallel design non-inferiority study to assess the immunogenicity of multiple subcutaneous (SC) doses of PF-06881894 and US-Neulasta in healthy subjects. Approximately 420 healthy subjects were to be enrolled and randomized to one of two treatments: PF-06881894 (Regimen A) or US-Neulasta (Regimen B).

There were two treatment periods in the study. Each subject was to receive a total of 2 doses of assigned treatment (PF-06881894 or US-Neulasta), which was administered as one SC injection each on Period 1 Day 1 (P1D1) and Period 2 Day 1 (P2D1). In Treatment Period 2, each subject was to receive one SC dose of the same regimen received in Treatment Period 1. There was an interval of approximately 1 month between P1D1 and P2D1. The duration of Treatment Period 1 was 30 days and the duration of Treatment Period 2 was 60 days. Samples for immunogenicity assessment were collected on P1D1 (pre-dose baseline), P1D13 and P1D30 during Treatment Period 1; and P2D13, P2D30/Early Withdrawal and P2D60 during Treatment Period 2.

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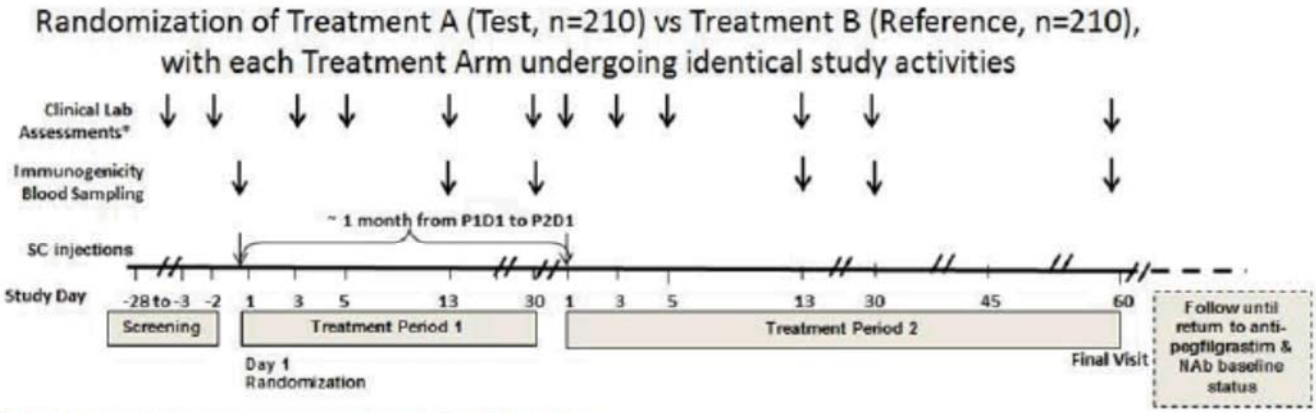
Figure 4. C1221005: Study Design



*Clinical Lab Assessments included the following:
Screening: including chemistry, hematology (included ANC, platelets) and UA with PCR if 1+ to 4+ protein; serum β-hCG; urine drug/alcohol/cotinine screen
Day -2: urine β-hCG; Chemistry Panel; hematology (included ANC, platelets); urine drug/alcohol screen;
P1D3, P1D5, and P1D13: Enzyme Panel; hematology (included ANC, platelets);
P1D30 (±2): Chemistry Panel; hematology (included ANC, platelets);
P2D1: Urine β-hCG; Chemistry Panel; hematology (included ANC, platelets);
P2D3, P2D5, and P2D13: Enzyme Panel; hematology (included ANC, platelets);
P2D30 (±2): Chemistry Panel; hematology (included ANC, platelets); UA with PCR if 1+ to 4+ protein and urine β-hCG;
Early Termination: Chemistry Panel; hematology (included ANC, platelets); UA with PCR if 1+ to 4+ protein and urine β-hCG;
P2D60 (±5): Urine β-hCG; Chemistry Panel; hematology (included ANC, platelets).
Abbreviations: ANC = absolute neutrophil count; β-hCG = beta-human chorionic gonadotropin; n = number of subjects; NAb = neutralizing antibody; P1D1 = Period 1 Day 1; P2D1 = Period 2 Day 1; PCR = protein: creatinine ratio; SC = subcutaneous; UA = urinalysis.

[Source: CSR]

Subjects were administered 6 mg of study drug as a SC bolus injection in the deltoid region. The study drugs were:

- Regimen A (Test Product): PF-06881894
- Regimen B (Reference Product): US-Neulasta

<u>Population:</u> Healthy male or female volunteers between 18 and 65 years of age, with a BMI between 19 and 30 kg/m^2 and body weight of 50 kg to 100 kg.

Subjects with hematologic laboratory abnormalities (including leukocytosis [defined as total leukocytes >11,000/mcL], leukopenia [defined as total leukocytes <4000/mcL], or neutropenia [defined as ANC <1500/mcL] or thrombocytopenia (defined as platelet count of <150,000/mcL), or other clinically significant abnormal laboratory abnormalities, lack of adequate hepatic or renal reserve, any active systemic or immunologic disease or condition, and/or a history of biological growth factor exposure were excluded from the study. Subjects who had received live vaccination or exposure to communicable viral diseases within 4 weeks prior to Screening

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were also excluded.

Objectives:

The primary objective was:

- To assess the non-inferiority of the proposed biosimilar PF-06881894 versus US-Neulasta with respect to immunogenicity.

The secondary objective of the study was:

- To assess the safety of the proposed biosimilar PF-06881894 and US-Neulasta by AEs, including AEs of Special Interest (AESIs), laboratory variables, vital signs, physical examination, 12-lead electrocardiograms (ECGs), concomitant medication, and local injection site reactions (ISRs).

Endpoints:

- The primary endpoint was the proportion of subjects with a negative anti-drug antibody test result at baseline and confirmed post-dose positive anti-drug antibody test result at any time during the study. A 90% CI for the test-reference difference between the two treatment groups was to be constructed. When the upper bound of the 90% CI was less than or equal to 0.10, non-inferiority was demonstrated.
- The immunogenicity-related secondary endpoint was the proportion of subjects with a negative baseline anti-drug antibody test result and post-dose positive NAb result at any time during the study.

Schedule of Events

Table 18. C1221005: Schedule of Assessment

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	Screening[a]		Treatment Period 1[b]					Treatment Period 2[b]						
Visit Identifier/Study Day (Visit Window)	**-28 to -3**	**-2**	**1**	**3**	**5**	**13**	**30 (±2)**	**1**	**3**	**5**	**13**	**30 (±2) or Early Withdrawal[c]**	**45 (±5)**	**60 (±5) Final Visit**
Informed consent	X													
Review inclusion/exclusion criteria	X	X												
Randomization			X[d]											
Outpatient visit	X	X	X	X	X	X	X	X	X	X	X	X		X
Phone contact													X	
Collect medical history	X	X[e]												
Physical examination, including spleen assessment[f]	X											X		X
Directed physical examination (spleen)		X		X	X	X	X	X[d]	X	X	X			
Demography, height and weight assessments	X													
Contraception check[g]	X	X	X[d]	X	X	X	X	X[d]	X	X	X	X	X	X
Pregnancy test[h]	X	X						X[d]				X		X
FSH[i]	X													
Serology testing	X													
Safety laboratory tests[j]	X	X		X	X	X	X	X[d]	X	X	X	X		X
Urine drug and alcohol screening[k]	X	X												
Urine cotinine testing	X													
Chest X-ray[l]	X													
Single 12-lead ECG	X											X		X
Vital signs[m]	X	X	X[d]	X	X	X	X	X[d]	X	X	X	X		X
Study treatment administration			X					X						
Injection site reaction assessment[n]			X	X	X			X	X	X				
ADA blood sampling			X[d]			X	X				X	X		X
Prior/concomitant treatment assessment	X	→	→	→	→	→	→	→	→	→	→	→	→	X
Serious and non-serious AE monitoring	X	→	→	→	→	→	→	→	→	→	→	→	→	X
Visit Identifier/Study Day (Visit Window)	**-28 to -3**	**-2**	**1**	**3**	**5**	**13**	**30 (±2)**	**1**	**3**	**5**	**13**	**30 (±2) or Early Withdrawal[c]**	**45 (±5)**	**60 (±5) Final Visit**

Abbreviations: → = ongoing/continuous event; β-hCG = beta-human chorionic gonadotropin; ADA = anti-drug antibody; AE = adverse event; ANC = absolute neutrophil count; BP = blood pressure; ECG = electrocardiogram; FSH = follicle-stimulating hormone; P1D1 = Period 1 Day 1; P2D1 = Period 2 Day 1; PCR = protein:creatinine ratio; UA = urinalysis.

a. Screening visit occurred within 28 days prior to administration of the investigational product in Treatment Period 1.
b. There were 2 treatment periods in the study. Each subject received 2 subcutaneous injections of the investigational product to which they had been randomized (PF-06881894 or pegfilgrastim-US), once in each treatment period. The time interval between P1D1 and P2D1 was approximately 1 month.
c. In the event of early withdrawal, the subject was to return for an Early Withdrawal visit (P2D30 procedures) at least 28 days after the last dose of investigational product.
d. Prior to dosing.
e. Updated medical, illicit drug, tobacco, and alcohol history, as well as blood donation within the 60 days prior to the first dose, and record of prior medications to determine any change from screening evaluation.
f. Full physical examination at Screening, P2D30 (±2) Visit/Early Withdrawal, and P2D60 (±5).
g. The investigator or his/her designee was to discuss with the subject the need to use highly effective contraception consistently and correctly according to contraception guidelines, and confirm and document that proper contraception was being used for the subject and their partner as appropriate.
h. β-hCG test for women of childbearing potential (serum at screening and urine at all other times); serum pregnancy was to be performed during Day -28 to -3 Screening visit, and urine pregnancy tests were to be performed at all other times, including the screening reverification visit on Day -2.
i. Serum FSH concentration for all females who were amenorrheic for at least 12 consecutive months.
j. Screening: including chemistry, hematology and urinalysis (UA) with protein:creatinine ratio (PCR) if 1+ to 4+ protein; serum β-hCG. Day -2: urine β-hCG; Chemistry Panel; hematology (including ANC, platelets). P1D3, P1D5 and P1D13: Enzyme Panel; hematology (including ANC, platelets). P1D30 (±2): Chemistry Panel; hematology (including ANC, platelets). P2D1: urine β-hCG; Chemistry Panel; hematology (including ANC, platelets). P2D3, P2D5 and P2D13: Enzyme Panel; hematology (including ANC, platelets). P2D30 (±2): Chemistry Panel; hematology (including ANC, platelets); UA with PCR if 1+ to 4+ protein and urine β-hCG. Early Termination: Chemistry Panel; hematology (including ANC, platelets); UA with PCR if 1+ to 4+ protein and urine β-hCG. P2D60 (±5): urine β-hCG; Chemistry Panel; hematology (including ANC, platelets).
k. At Screening and Day -2 and the discretion of the investigator.
l. The result for chest x-rays previously obtained for this study may have been used in the event of subject re-screening.
m. Sitting BP, pulse rate, respiratory rate and tympanic temperature.
n. On Day 1 (both Treatment Periods), subjects were to remain in the research outpatient unit for at least 90 minutes after dosing.

[Source: CSR]

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Statistical Methodologies

Analysis Populations:

- Full analysis set (FAS): All subjects who were randomized and received at least 1 dose of study drug. Anti-PEG antibody data were analyzed using FAS and by the treatment to which subjects were randomized.
- Immunogenicity analysis set: All subjects who were randomized, received at least 1 dose of study drug, and had at least 1 post-dose anti-drug antibody sample. Anti-drug antibody data and NAb data were analyzed using immunogenicity analysis set and by the treatment to which subjects were randomized.
- Safety analysis set: all subjects who received at least 1 dose of study drug.

Subject Disposition

In study C1221005, a total of 422 subjects were randomized (PF-06881894: 212 subjects, US-Neulasta: 210 subjects) and 420 subjects received treatment with the study drug.

Table 19. C1221005: Analysis Populations

	PF-06881894 (n=212)	**US-Neulasta (n=210)**	**Total (n=422)**
Full analysis set	210 (99.1%)	210 (100.0%)	420 (99.5%)
Immunogenicity set	208 (98.1%)	209 (99.5%)	417 (98.8%)
Safety analysis set	210 (99.1%)	210 (100.0%)	420 (99.5%)

[Source: ADSL.xpt]

Of the 422 randomized subjects 375 subjects (89%) completed the study. A total of 46 subjects (11%) (PF-06881894: 26 subjects, US-Neulasta: 20 subjects) discontinued the study mostly due to lost to follow up (4%) and withdrawal by subject (3%). In study C1221005, in the event of an early withdrawal, the subject was to return for a Final Visit at least 28 days after the last dose of study drug. If a subject did not return for a scheduled visit, every effort was made to contact the subject. After two attempts, a staff member sent a registered letter. If no response was received from the subject, the subject was considered lost to follow-up.

A total of 2 subjects discontinued the study due to AEs (serious urinary tract infection, non-serious angioedema). See section 7.3.3 for more details.

Table 20. C1221005: Subject Disposition

	PF-06881894 (n=212)	**US-Neulasta (n=210)**	**Total (n=422)**
Randomized	212 (100%)	210 (100%)	422 (100%)
Treated	210 (99%)	210 (100%)	420 (99%)
Not treated	2 (<1%)	0	2 (<1%)
Completed	186 (88%)	190 (91%)	376(89%)

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Discontinued	26 (12%)	20 (10%)	46 (11%)
Reasons for study discontinuation			
Adverse event	1 (<1%)	1 (<1%)	2 (<1%)
Lost to follow up	11 (5%)	7 (3%)	18 (4%)
Protocol deviation	2 (<1%)	0	2 (<1%)
Withdrawal by subject	7 (3%)	7 (3%)	14 (3%)
No longer met eligibility criteria	0	1 (<1%)	1(<1%)
Other[a]	5 (2%)	4 (2%)	9 (2%)

a. Not provided by the Applicant.
[Source: CSR]

Demographics and Baseline Characteristics

See Table 22 in Section 7.3.2.

Efficacy Results

Efficacy evaluations were not conducted in this study.

Immunogenicity Results

The primary endpoint was the proportion of subjects with a negative anti-drug antibody test result at baseline and confirmed post-dose positive anti-drug antibody test result during the study. For the analysis of primary endpoints, see Section 6.4.

7.2.3 C1221002 (ZIN-130-1504)

Title: A Phase 1-2 Ascending Dose Study to Assess the Pharmacodynamics, Pharmacokinetics, and Safety of PF-06881894 (HSP-130) in Subjects with Non-Metastatic Breast Cancer Following Single-Dose and Multiple-Dose Administration by Subcutaneous Injection.

Study Initiation Date: December 21, 2015
Study Completion Date: October 5, 2017
Study Site: The study was conducted at 10 sites in Hungary and Spain.

Study C1221002 was originally designed as a dose-finding study supporting 351(a) submission. However, as the Applicant transitioned the development program for PF-06881894 from 351(a) pathway to 351(k) (biosimilar) pathway, the purpose of the study changed from dose-finding to provision of supportive data only in patients with breast cancer for biosimilar submission.

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Study Design and Endpoints

This was an open-label, non-comparative, parallel-group study of ascending single-and multiple-dose of PF-06881894 to evaluate PD, PK, and safety in patients with non-distantly metastatic (non-Stage 4) breast cancer who have not previously received prior chemotherapy. The study consisted of 2 phases:

- Phase 1 (Cycle 0): Single dose of PF-06881984 [3 mg (regimen A) or 6 mg (regimen B)] administered by SC injection in patients prior to definitive breast surgery and without chemotherapy;
- Phase 2 (Cycles 1-4): Multiple-dose administration of PF-06881984 as a 6 mg SC dose (once per cycle on Day 2 for 4 cycles) in patients after definitive breast surgery, treated with docetaxel, doxorubicin and cyclophosphamide (TAC) chemotherapy.

Population: Females ≥18 years with chemotherapy-naïve, histologically confirmed and documented invasive breast cancer, and without distant metastases (non-Stage 4) were enrolled in this study. Female subjects of childbearing potential, and their partners, who agreed to pregnancy prevention throughout the duration of the study (through the follow-up visit) were included. The subjects were required to have adequate bone marrow, hepatic, and renal function reserves and ECOG performance status ≤2.

Subject Disposition and Demographics

Study C1221002 enrolled a total of 25 female subjects [Cycle 0 (3 mg: 6 subjects, 6 mg: 6 subjects), Cycles 1-4 (6 mg: 13 subjects)]. All 25 subjects completed the study. For baseline demographics, see section 7.3.2.

Efficacy Results

Not applicable.

7.3. Review of Safety Data

7.3.1. Methods

The safety database of PF-06881894 consisted of a total of 383 subjects who received PF-06881894 in the three studies (ZIN-130-1515: 148 healthy volunteers, C1221005: 210 healthy volunteers, C1221002: 25 female subjects with non-metastatic breast cancer). However, since study C1221002 was a non-comparative study, the safety analysis was primarily conducted on the 358 subjects who received at least one dose of PF-06881894 in studies ZIN-130-1515 and C1221005. The dose of PF-6881894 administered in these two studies were 6 mg, consistent with the approved dose of the US-Neulasta and EU-Neulasta. The safety review included the following:

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- 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

The safety database was adequate for a biosimilar application (to US-Neulasta). There were no major concerns regarding data integrity. The overall quality of data was acceptable for safety evaluation.

Categorization of Adverse Events

AEs 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 were categorized as mild, moderate or severe. The laboratory results were graded according to the Common Technology Criteria for Adverse Events (CTCAE) version 4.03 coding system.

Treatment-emergent AEs (TEAEs) was defined if the event started or worsened in severity after the first dose of the study drug until 30 days after the last dose of study drug.

7.3.2. Relevant Characteristics of the Population Evaluated for Safety

ZIN-130-1505:
In study ZIN-130-1505 , 53% of subjects were males and 86% were White. The median age for all subjects was 26 years (range, 18 to 65). The baseline demographics and characteristics were generally balanced in the 6 sequences.

Table 21. ZIN-130-1505: Demographics and Baseline Characteristics (Safety Population)

	PF/US/EU N=26	**US/EU/PF N=25**	**EU/PF/US N=25**	**US/PF/EU N=26**	**PF/EU/US N=25**	**EU/US/PF N=26**	**Total n=153**
Age (years)							
Median	29	25	26	23	26	26	26
Range	19, 64	19, 64	19, 63	19, 64	21, 51	18, 65	18, 65
Sex							
Female	14 (54%)	14 (56%)	9 (36%)	12 (46%)	10 (40%)	13 (50%)	72 (47%)
Male	12 (46%)	11 (44%)	16 (64%)	14 (54%)	15 (60%)	13 (50%)	81 (53%)
Race							
White	21 (81%)	21 (84%)	21 (84%)	24 (92%)	21 (84%)	24 (92%)	132 (86%)
Black or African American	1 (4%)	0	0	0	2 (8%)	1 (4%)	4 (3%)
Asian	2 (8%)	2 (8%)	1 (4%)	0	2 (8%)	1 (4%)	8 (5%)
Other	2 (8%)	2 (8%)	3 (12%)	2 (8%)	0	0	9 (6%)
Weight (kg)							
Median	73	68	77	68	75	72	71
Range	50, 96	54, 100	54, 98	49, 98	55, 96	49, 98	49, 100

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Height (cm)							
Median	169	168	171	174	174	174	171
Range	156, 193	153, 186	159, 187	157, 195	154, 187	156, 190	153, 195
Body mass index (kg/m^2)							
Median	24	25	25	24	25	24	24
Range	20, 29	21, 30	19, 29	19, 29	22, 30	19, 30	19, 30

[Source: ADSL.xpt]

C1221005:

In study C1221005, 56% of subjects were females and 69% were White. The median age for all subjects were 35 (range, 18 to 65). The baseline demographics and characteristics were balanced between the two treatment arms.

Table 22. C1221005: Demographics and Baseline Characteristics (Safety Analysis Set)

	PF-06881894 (n=210)	**US-Neulasta (n=210)**	**Total (n=420)**
Age (years)			
Median	35	35	35
Range	18, 65	18, 64	18, 65
Sex			
Female	126 (60%)	111 (53%)	237 (56%)
Male	84 (40%)	99 (47%)	183 (44%)
Race			
White	150 (71%)	141 (67%)	291 (69%)
Black or African American	54 (26%)	62 (30%)	116 (28%)
Asian	2 (1%)	5 (2%)	7 (2%)
Other	4 (2%)	2 (<1%)	6 (1%)
Weight (kg)			
Median	72	72	72
Range	50, 100	51, 100	50, 100
Height (cm)			
Median	168	166	167
Range	150, 195	147, 192	147, 195
Body mass index			
(kg/m^2)			
Median	26	26	26
Range	19, 30	19, 30	19, 30

[Source: ADSL.xpt and ADVS.xpt]

C1221002:

In study C1221002, the median age was 61 years (range, 39 to 78) and most of the subjects were White (96%).

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7.3.3 Safety Results

The table below summarizes the overall safety results of studies ZIN-130-1505 and C1221005. The overall safety profile was generally similar between the arms in both studies.

Table 23. ZIN-130-1505 and C1221005: Overall Summary of Safety (Safety Population)

	Study ZIN-130-1505			**Study C1221005**	
	PF 6 mg N=148	**US 6 mg N=146**	**EU 6 mg N=148**	**PF 6 mg N=210**	**US 6 mg N=210**
All AEs	147 (99%)	139 (95%)	141 (95%)	194 (92%)	202 (96%)
Treatment related	143 (97%)	134 (92%)	138 (93%)	191 (91%)	198 (94%)
Severe AEs	2 (1%)	0	1 (<1%)	0	0
All deaths	0	0	0	0	0
SAEs	1 (<1%)	1 (<1%)	1 (<1%)	1 (<1%)	3 (1%)
AEs leading to treatment discontinuation	1 (<1%)	3 (2%)	0	1 (<1%)	1 (<1%)
AEs of special interests	8 (5%)	12 (8%)	10 (7%)	11 (5%)	9 (4%)

PF = PF-06881894 (also referred to as HSP-130). US = US-Neulasta. EU = EU-Neulasta.
[Source: ADAE.xpt]

Exposure

In the comparative studies (ZIN-130-1505 and C1221005), the dose of PF-06881894 was 6 mg.

In study ZIN-130-1505, a total of 148, 146, and 148 subjects received at least one dose of PF-06881894, US-Neulasta, and EU-Neulasta, respectively, across the 6 sequence groups. The median doses of the 3 study drugs in the 3 treatment period were all 6 mg.

Table 24. ZIN-130-1505: Dose of Study Treatment (Safety Population)

	Study ZIN-130-1505		
	PF 6 mg N=148	**US 6 mg N=146**	**EU 6 mg N=148**
Study period 1 (n)	51	51	51
Median (mg)	6.0	6.0	6.0
Range (mg)	6.0-6.0	6.0-6.0	6.0-6.0
Study period 2 (n)	49	49	48
Median (mg)	6.0	6.0	6.0
Range (mg)	6.0-6.0	6.0-6.0	6.0-6.0
Study period 3 (n)	48	46	49
Median (mg)	6.0	6.0	6.0
Range (mg)	6.0-6.0	6.0-6.0	6.0-6.0

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Overall (n)	148	146	148
Median (mg)	6.0	6.0	6.0
Range (mg)	6.0-6.0	6.0-6.0	6.0-6.0

PF = PF-06881894 (also referred to as HSP-130). US = US-Neulasta. EU = EU-Neulasta.
[Source: EX.xpt]

In study C1221005, a total of 420 subjects (PF-06881894: 210 subjects, US-Neulasta: 210 subjects) received at least one dose of the study drug. The majority of subjects (PF-06881894: 93%, US-Neulasta: 94%) received the planned 2 doses of the study drug.

Table 25. C1221005: Exposure of Study Treatment (Safety Population)

	Study C1221005	
	PF 6 mg N=210	**US 6 mg N=210**
Number of treatment (day)		
Median	2.0	2.0
Range	1.0-2.0	1.0-2.0
Subjects treated		
1 day	15 (7%)	13 (6.2%)
2 days	195 (93%)	197 (94%)

PF = PF-06881894 (also referred to as HSP-130). US = US-Neulasta.
[Source: ADEX.xpt]

Deaths

There were no deaths among subjects who participated in studies ZIN-130-1505, C1221005 and C1221002.

Serious Adverse Events

Study ZIN-130-1505
A total of 3 subjects had SAEs (1 subject in each of the PF-06881894, US-Neulasta, and EU-Neulasta treatment arms) in study ZIN-130-1505. A total of two subjects (1 subject each in the PF-06881894, US-Neulasta arms) had spontaneous abortion (both assessed as not related to study treatment) and one subject (ID: (b) (6), a 62 year-old male) in the EU-Neulasta arm experienced renal colic in Period 1 (35 days after receiving EU-Neulasta). The renal colic was assessed as unrelated to the study drug and the subject continued the study without any interruptions in study drug administration.

Study C1221005
A total of 4 subjects [PF-06881894: 1 subject (0.5%), US-Neulasta: 3 subjects (1.4%)]. reported SAEs. Only one SAE of urinary tract infection that occurred in the PF-06881894 arm was considered treatment-emergent. The urinary tract infection was assessed as not related to the

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study treatment, however, resulted in treatment discontinuation.

Table 26. C1221005: Serious Adverse Event (Safety Population)

	PF-06881894 (n=210)	**US-Neulasta (n=210)**
All	1 (<1%)	3 (1%)
Urinary tract infection	1 (<1%)	0
Multiple injuries	0	1 (<1%)
Abortion spontaneous	0	2 (1%)
Physical assault	0	1 (<1%)

Incidences are based on the number of subjects, not the number of events. The same subject may appear in different categories.
[Source: ADAE.xpt]

Treatment Emergent Adverse Events

Study ZIN-130-1505
Similar proportion of subjects experienced AEs in study ZIN-130-1505 (PF-06881894: 99%, US-Neulasta: 95%, EU-Neulasta: 95%). Most of the AEs were mild or moderate in severity. Severe AEs were reported in a total of 3 subjects (see below under Significant Adverse Events section).

Study C1221005
In study C1221005, the proportion of subjects who reported at least one AE were also comparable between the two arm (PF-06881894: 92%, US-Neulasta: 96%). All AEs were mild or moderate in severity.

In study ZIN-130-1505, the most frequently reported AEs (≥10%) in the PF-06881894 arm were musculoskeletal pain, headache, nausea, injection site pain, dizziness, catheter site pain and vessel puncture site bruise while in study C1221005, they were back pain, headache, musculoskeletal pain, pain in extremity and myalgia.

Table 27. ZIN-130-1505 and C1221005: Summary of AEs (All Causality) in ≥ 5% of Subjects in Any Treatment Arm (Safety Population)

	Study ZIN-130-1505			**Study C1221005**	
	PF 6 mg N=148	**US 6 mg N=146**	**EU 6 mg N=148**	**PF 6 mg N=210**	**US 6 mg N=210**
All subjects	147 (99%)	139 (95%)	141 (95%)	194 (92%)	202 (96%)
Musculoskeletal pain	118 (80%)	116 (80%)	111 (75%)	47 (22%)	37 (18%)
Headache	101 (68%)	99 (68%)	105 (71%)	111 (53%)	107 (51%)
Nausea	28 (19%)	25 (17%)	25 (17%)	9 (4%)	14 (7%)
Injection site pain	22 (15%)	22 (15%)	18 (12%)	8 (4%)	3 (1%)
Dizziness	16 (11%)	3 (2%)	8 (5%)	8 (4%)	4 (2%)
Catheter site pain	15 (10%)	13 (9%)	14 (10%)	0	0

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Vessel puncture site bruise	15 (10%)	11 (8%)	9 (6%)	0	0
Contusion	13 (9%)	11 (8%)	15 (10%)	0	2 (1%)
Abdominal pain	13 (9%)	11 (8%)	13 (9%)	9 (4%)	11 (5%)
Pharyngitis	12 (8%)	8 (6%)	9 (6%)	3 (1%)	0
Back pain	10 (7%)	7 (5%)	9 (6%)	123 (59%)	126 (60%)
Laceration	11 (7%)	2 (1%)	2 (1%)	0	0
Injection site erythema	9 (6%)	9 (6%)	8 (5%)	1 (<1%)	0
Injection site bruising	7 (5%)	12 (8%)	10 (7%)	0	0
Lethargy	8 (5%)	4 (3%)	7 (5%)	0	1 (<1%)
Cough	8 (5%)	5 (3%)	6 (4%)	5 (2%)	3 (1%)
Upper respiratory tract infection	5 (3%)	6 (4%)	5 (3%)	13 (6%)	8 (4%)
Fatigue	5 (3%)	7 (5%)	11 (7%)	8 (4%)	5 (2%)
Rhinitis	5 (3%)	4 (3%)	8 (5%)	0	0
Sunburn	5 (3%)	8 (6%)	9 (6%)	0	0
Arthralgia	4 (3%)	3 (2%)	1 (<1%)	15 (7%)	9 (4%)
Vomiting	4 (3%)	6 (4%)	9 (6%)	5 (2%)	9 (4%)
Oropharyngeal pain	3 (2%)	5 (3%)	5 (3%)	12 (6%)	4 (2%)
Pain in extremity	2 (1%)	10 (7%)	4 (3%)	37 (18%)	31 (15%)
Myalgia	2 (1%)	1 (<1%)	5 (3%)	24 (11%)	35 (17%)
Neck pain	1 (<1%)	2 (1%)	2 (1%)	8 (4%)	14 (7%)
Epistaxis	1 (<1%)	2 (1%)	8 (5%)	3 (1%)	1 (<1%)
Non-cardiac chest pain	0	0	0	11 (5%)	7 (3%)

PF = PF-06881894 (also referred to as HSP-130). US = US-Neulasta. EU = EU-Neulasta.
US-Neulasta referred to as US-approved Neulasta, and EU-Neulasta referred to as EU-approved Neulasta.
[Source: ADAE.xpt]

Dropouts and/or Discontinuations

Study ZIN-130-1505
A total of 4 subjects [PF-06881894: 1 subject (0.7%; spontaneous abortion), US-Neulasta: 3 subjects (2%; Grade 2 ALT increased, generalized rash, injection site pain)] discontinued treatment with the study drug due to AEs.

Study C1221005
In study C1221005, a total of 2 subjects [PF-06881894: 1 subject (0.5%; serious urinary tract infection), US-Neulasta: 1 subject (0.5%; non-serious angioedema) discontinued treatment with the study drug due to AEs.

Significant Adverse Events

ZIN-130-1505
Severe AEs were reported in a total of 3 subjects [PF-06881894 arm: 2 subjects (1.4%; one

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subject had skin abrasion/skin laceration considered non-treatment-related, and the other subject had arthralgia in left hip considered possibly related to study treatment), EU-Neulasta arm: 1 subject (0.7%; one case of renal colic considered unrelated to study treatment)].

In study C1221005, no severe AEs were reported.

Laboratory Findings

Study ZIN-130-1505

Hematology:
No meaningful differences in hematology parameters were observed across the three arms. The median values of neutrophils and leukocytes increased after the administration of each study drug with a peak at Day 4, and returning to baseline by the follow-up visit (Day 30). No subjects had elevated leukocyte count of ≥ 100 x10^9/L or leukocytosis as a TEAE during the study.

In all three arms, the median platelet count generally decreased with a nadir at Day 13, returning to baseline at follow-up on Day 30.

Table 28. ZIN-130-1505: Summary of Hematology Laboratory Tests* (Safety Population)

		PF 6 mg N=148	**US 6 mg N=146**	**EU 6 mg N=148**
Neutrophils (x10^9/L)	Baseline	3.2	3.0	3.2
	Day 4	28.1	29.2	28.5
	Day 13	5.1	4.7	5.5
	Follow-up	3.0	3.0	2.9
Leukocytes (x10^9/L)	Baseline	6.1	5.9	6.0
	Day 4	34.9	35.7	35.3
	Day 13	7.9	7.7	8.4
	Follow-up	5.6	5.5	5.7
Hemoglobin (g/L)	Baseline	138.5	139.0	138.5
	Day 4	138.0	139.0	138.0
	Day 13	137.0	135.5	134.0
	Follow-up	132.0	132.0	131.0
Platelets (x10^9/L)	Baseline	253.0	254.0	251.5
	Day 4	230.0	232.5	229.5
	Day 13	183.0	180.0	182.0
	Follow-up	265.0	266.0	267.0

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

Biochemistry:
No meaningful differences in chemistry laboratory values were observed across the three arms in study ZIN-130-1505. Most of the abnormalities were grade 1 or 2. The only grade 3 or 4

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laboratory abnormalities that occurred in at least 2% of subjects in any arm was hypoglycemia. However, the incidence of grade 3/4 hypoglycemia was balanced across the three arms with no corresponding reported adverse events.

Study C1221005

In study C1221005, the changes in hematology and chemistry laboratory values from baseline were generally similar between the PF-06881894 and US-Neulasta arms. No meaningful differences in laboratory abnormalities were reported between the two arms.

The median values for neutrophils and leukocytes increased following administration of each study drug, with a peak on Day 3 of each period and returning to baseline on Day 13 of each period.

The applicant conducted an analysis for ANC on subjects with with positive anti-drug antibody results at any visit including baseline. Similar trends in ANC were observed in these subjects when compared to the overall population of the study, indicating no effect on ANC by the presence of anti-drug antibody.

Table 29. C1221005: Summary of Hematology Laboratory Tests – Changes from Baseline to Last Observation* (Safety Analysis Set)

	PF 6 mg N=210		**US 6 mg N=210**	
	Baseline	**Change from baseline**	**Baseline**	**Change from baseline**
Neutrophils ($x10^9$/L)	3.4	-0.2	3.4	-0.4
Leukocytes ($x10^9$/L)	6.4	-0.4	6.7	-0.6
Hemoglobin (g/dL)	15.8	-0.2	15.9	-0.1
Platelets ($x10^9$/L)	252	2	250	1

*The median values are listed in the table. Last observation was defined as the last observation while on study drug or during the lag time.
[Source: Adapted from CSR]

Vital Signs

In studies ZIN-130-1505 and C1221005, the values for vital sign parameters were similar across treatment arms and no meaningful safety findings were reported related to vital signs.

Product Specific Safety Concerns

Based on the safety profile of the reference product, the protocol-defined AEs of special interests (AESIs) included allergic reactions, splenomegaly, splenic rupture, acute respiratory distress syndrome (ARDS), alveolar hemorrhage, hemoptysis, leukocytosis, thrombocytopenia, capillary leak syndrome, cutaneous vasculitis, cytokine release syndrome and glomerulonephritis. In addition, based on the AE profile of G-CSFs, preferred terms under the

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Musculoskeletal and Connective Tissue Disorders SOC (considered as the AESI of Musculoskeletal disorders) and injection site reactions were also analyzed.

In studies ZIN-130-1505 and C1221005, no cases of ARDS, alveolar hemorrhage, capillary leak syndrome, cutaneous vasculitis, cytokine release syndrome, glomerulonephritis, hemoptysis, leukocytosis and splenic rupture were reported.

In the ZIN-130-1505, the overall incidences of AESIs were similar across the three arms (PF-6881894: 5%, US-Neulasta: 8%, EU-Neulasta: 7%). All events were mild or moderate in severity, and none were severe.

The incidences of AESIs in study C1221005 were also comparable between the two arms (PF-06881894: 5%, US-Neulasta: 4%). All AESIs were of mild or moderate in severity.

The table below summarizes the incidence of AESIs that occurred in studies ZIN-130-1505 and C1221005.

Table 30. ZIN-130-1505 and C1221005: Summary of AEs of Special Interest (Safety Population)

	Study ZIN-130-1505			**Study C1221005**	
	PF 6 mg N=148	**US 6 mg N=146**	**EU 6 mg N=148**	**PF 6 mg N=210**	**US 6 mg N=210**
All	8 (5%)	12 (8%)	10 (7%)	11 (5%)	9 (4%)
Potential allergic reactions	8 (5%)	11 (8%)	10 (7%)	6 (3%)	5 (2%)
Allergic respiratory disease	0	1 (<1%)	0	0	0
Angioedema	0	0	0	0	1 (<1%)
Dermatitis[a]	3 (2%)	2 (1%)	3 (2%)	2 (1%)	1 (<1%)
Eczema	0	1 (<1%)	0	0	0
Periorbital swelling	0	0	0	1 (<1%)	0
Hypersensitivity	0	0	0	0	3 (1%)
Injection site rash	2 (1%)	2 (1%)	1 (<1%)	1 (<1%)	0
Rash[b]	1 (<1%)	4 (3%)	4 (3%)	2 (1%)	0
Rhinitis allergic	1 (<1%)	2 (1%)	0	0	0
Skin reaction	0	0	1 (<1%)	0	0
Swelling face	0	0	1 (<1%)	1 (<1%)	0
Vessel puncture site rash	1 (<1%)	0	0	0	0
Splenomegaly	1 (<1%)	1 (<1%)	0	0	0
Thrombocytopenia	0	0	0	5 (2%)	4 (2%)

PF = PF-06881894 (also referred to as HSP-130). US = US-Neulasta. EU = EU-Neulasta.
US-Neulasta referred to as US-approved Neulasta, and EU-Neulasta referred to as EU-approved Neulasta.
a. Includes dermatitis allergic and dermatitis contact.
b. Includes rash generalized and rash macular.
The same subject may appear in different categories.
[Source: ADAE.xpt]

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Musculoskeletal Disorders:

The overall incidences of musculoskeletal disorders were comparable between the treatment arms in study ZIN-130-1505 (PF-6881894: 86%, US-Neulasta: 86%, EU-Neulasta: 82%). and study C1221005 (PF-06881894: 83%, US-Neulasta: 85%).

All cases were either mild or moderate in severity, except one subject in the PF-06881894 arm in study ZIN-130-1505 who experienced severe arthralgia. In study ZIN-130-1505, the most frequently reported AEs (≥10%) under the musculoskeletal and connective tissue disorders SOC were musculoskeletal pain (PF-6881894: 80%, US-Neulasta: 80%, EU-Neulasta: 75%) while in study C1221005, those were back pain (PF-06881894: 59%, US-Neulasta: 60%), musculoskeletal pain (PF-06881894: 22%, US-Neulasta: 18%), pain in extremity (PF-06881894: 18%, US-Neulasta: 15%) and myalgia (PF-06881894: 11%, US-Neulasta: 17%).

Table 31. ZIN-130-1505 and C1221005: Summary of Musculoskeletal Connective Tissue Disorders that Occurred ≥ 2% in Any Arm (Safety Population)

System Organ Class Preferred Term	**Study ZIN-130-1505**			**Study C1221005**	
	PF 6 mg N=148	**US 6 mg N=146**	**EU 6 mg N=148**	**PF 6 mg N=210**	**US 6 mg N=210**
Musculoskeletal and Connective Tissue Disorders	127 (86%)	125 (86%)	121 (82%)	175 (83%)	178 (85%)
Arthralgia	4 (3%)	3 (2%)	1 (<1%)	15 (7%)	9 (4%)
Back pain	10 (7%)	7 (5%)	9 (6%)	123 (59%)	126 (60%)
Muscle spasms	3 (2%)	7 (5%)	6 (4%)	6 (3%)	4 (2%)
Musculoskeletal chest pain	3 (2%)	0	3 (2%)	3 (1%)	3 (1%)
Musculoskeletal pain	118 (80%)	116 (80%)	111 (75%)	47 (22%)	37 (18%)
Myalgia	2 (1%)	1 (<1%)	5 (3%)	24 (11%)	35 (17%)
Neck pain	1 (<1%)	2 (1%)	2 (1%)	8 (4%)	14 (7%)
Pain in extremity	2 (1%)	10 (7%)	4 (3%)	37 (18%)	31 (15%)

PF = PF-06881894 (also referred to as HSP-130). US = US-Neulasta. EU = EU-Neulasta.
US-Neulasta referred to as US-approved Neulasta, and EU-Neulasta referred to as EU-approved Neulasta.
[Source: CSR and confirmed by FDA]

Injection Site Reactions (ISRs):

In study ZIN-130-1505, the overall incidences of injection site reactions were higher in the PF-06881894 and US-Neulasta arms compared to the EU-Neulasta arm (PF-06881894: 27%, US-Neulasta: 27%, EU-Neulasta: 22%). In study C1221005, the incidences were similar between the PF-06881894 and US-Neulasta arms (PF-06881894: 7%, US-Neulasta: 4%). The most frequently reported injection site reaction in the PF-06881894 arm in both studies was injection site pain [ZIN-130-1505 (PF-06881894: 15%, US-Neulasta: 15%, EU-Neulasta: 12%), C1221005 (PF-06881894: 4%, US-Neulasta: 1%)].

All injection site reactions were mild in intensity except one subject in the PF-06881894 arm in study ZIN-130-1505 experienced moderate injection site rash.

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Among the subjects who reported injection site reactions in the PF-06881894 arm in studies ZIN-130-1505 and C1221005, 2 subjects and 1 subject, respectively, had confirmed positive anti-drug antibody results (See under Section 7.4).

Table 32. ZIN-130-1505 and C1221005: Summary of Injection Site Reactions that Occurred ≥2% in Any Arm (Safety Population)

	Study ZIN-130-1505			**Study C1221005**	
	PF 6 mg N=148	**US 6 mg N=146**	**EU 6 mg N=148**	**PF 6 mg N=210**	**US 6 mg N=210**
All injection site reactions	40 (27%)	40 (27%)	32 (22%)	14 (7%)	9 (4%)
Injection site bruising	7 (5%)	12 (8%)	10 (7%)	0	0
Injection site erythema	9 (6%)	9 (6%)	8 (5%)	1 (<1%)	0
Injection site hemorrhage	1 (<1%)	0	0	5 (2%)	6 (3%)
Injection site pain	22 (15%)	22 (15%)	18 (12%)	8 (4%)	3 (1%)

PF = PF-06881894 (also referred to as HSP-130). US = US-Neulasta. EU = EU-Neulasta.
US-Neulasta referred to as US-approved Neulasta, and EU-Neulasta referred to as EU-approved Neulasta.
[Source: CSR and confirmed by FDA]

7.3.3. Additional Safety Evaluations

C1221002 (ZIN-130-1504):
An overall assessment of safety was conducted for study C1221002. The safety profile of PF-06881894 was generally consistent with the safety results from the comparative studies.

All subjects experienced at least one AE during the study. Serious AEs were observed in a total of 2 subjects during Cycles 1-4 (both subjects had serious febrile neutropenia assessed as not related to the study drug). No deaths were reported during the study. No subject discontinued the study drug due to an AE.

A total of 4 subjects (Cycle 0, 6 mg: 2 subjects, Cycles 1-4, 6 mg: 2 subjects) experienced AEs of special interest. During Cycle 0, one subject had contact dermatitis considered mild and not related to PF-06881894 (with no ADA response), and the other subject had leukocytosis (considered mild) and related to PF-06881894. During Cycles 1-4, mild face edema was observed in one subject assessed as not related to PF-06881894 (with no ADA response), and the second subject had two events of platelet count decreased.

Table 33. C1221002: Overall Summary of Safety (Safety Population)

	Cycle 0		**Cycles 1 to 4**
	PF 3 mg N=6	**PF 6 mg N=6**	**PF 6 mg N=13**
All AEs	6 (100%)	6 (100%)	13 (100%)
Treatment related	5 (83%)	6 (100%)	5 (39%)
Severe AEs	0	0	5 (39%)
All deaths	0	0	0

Reference ID: 4622626

SAEs	0	0	2 (15%)
AEs leading to treatment discontinuation	0	0	0
AEs of special interests	0	2 (33%)	2 (15%)

PF = PF-06881894 (also referred to as HSP-130).
[Source: ADAE.xpt]

7.4. Clinical Conclusions on Immunogenicity

The impact of immunogenicity on safety was assessed by reviewing the AEs reported in study C1221005 in subjects with confirmed positive anti-drug antibody results.

Study C1221005
Among the subjects with negative anti-drug antibody at baseline (PF-06881894: 208 subjects, US-Neulasta: 209 subjects), a total of 27 subjects (PF-06881894: 12 subjects [6%], US-Neulasta: 15 subjects [7%]) had at least 1 post-dose positive anti-drug antibody sample. All 27 subjects, except 1 subject in the PF-06881894 arm experienced at least 1 AE during the study. The overall incidences of AEs were similar between the two arms (PF-06881894: 92%, US-Neulasta: 100%). However, the incidence of AEs in the gastrointestinal disorders SOC was higher in the PF-06881894 arm (PF-06881894: 25%, US-Neulasta: 13%) while the incidence of AEs in the immune system disorders (PF-06881894: 0%, US-Neulasta: 13%) and nervous system disorders (PF-06881894: 42%, US-Neulasta: 67%) SOCs was higher in the US-Neulasta arm.

Table 34. C1221005: Incidence of AEs in Subjects with Treatment-Emergent Positive Anti-drug Antibody Results

System Organ Class	**PF-06881894 (n=12)**	**US-Neulasta (n=15)**
All	11 (92%)	15 (100%)
Ear and labyrinth disorders	0	1 (7%)
Gastrointestinal disorders	3 (25%)	2 (13%)
General disorders and administration site conditions	3 (25%)	4 (27%)
Immune system disorders	0	2 (13%)
Infections and infestations	2 (17%)	3 (20%)
Injury, poisoning and procedural complications	0	1 (7%)
Musculoskeletal and connective tissue disorders	10 (83%)	12 (80%)
Nervous system disorders	5 (42%)	10 (67%)
Renal and urinary disorders	1 (8%)	0
Respiratory, thoracic and mediastinal disorders	2 (17%)	3 (20%)

Reference ID: 4622626

Skin and subcutaneous tissue disorders	1 (8%)	1 (7%)

Includes data up to 30 days after the last dose of study drug.
Subjects with treatment-emergent positive anti-drug antibody results refer to subjects with negative baseline and confirmed positive post-dose anti-drug antibody results.
The same subject may appear in different categories.
[Source: CSR]

A total of 11 subjects had potential allergic reactions in study C1221005 (PF-06881894: 6 subjects, US-Neulasta: 5 subjects) (see Table 30). Of these 11 subjects, a total of 3 subjects in the PF-06881894 arm were confirmed positive for anti-drug antibody at least once during the study:

- Two subjects in the US-Neulasta arm ([redacted] (b) (6)) reported hypersensitivity, not related to the study drug, but due to perfume and cleaning agents, respectively. Both subjects were negative for anti-drug antibody at baseline (P1D1) and positive at the P1D13 visit. The G-CSF-specificity tests were negative for both the subjects.
- One subject in the PF-06881894 arm ([redacted] (b) (6)) reported an event of injection site rash, related to the study drug. The subject was positive for anti-drug antibody at baseline (P1D1) and remained positive through the P1D30 visit. The subject discontinued from the study (withdrawal by subject) after the P2D5 visit; therefore, no additional immunogenicity samples were collected. This subject was also confirmed NAb positive. Of note, the subject had a confirmed positive baseline anti-drug antibody result. The G-CSF-specificity tests were negative for this subject.

<u>Study ZIN-130-1505</u>
In study ZIN-130-1505 , anti-drug (anti-drug and anti-PEG) antibodies were assessed.

A total of 111 subjects (72.5%) were positive for anti-PEG antibody at least once during study ZIN-130-1505. The incidence was similar across the three arms [PF-06881894: 36 subjects (24.3%), US-Neulasta: 39 subjects (26.7%), EU-Neulasta: 36 subjects (24.3%)]. According to the Applicant, there was no evidence of boosting of the anti-PEG antibody response upon administration of the second or third study drug in Period 2 and Period 3, respectively. The overall percentage of subjects with anti-PEG antibodies decreased over the duration of the study to 29.1% by the Final Visit (P3D30).

At baseline, no subjects were positive for anti-drug antibody. Of the 153 enrolled subjects, a total of 10 subjects (6.5%) [PF-06881894: 6 subjects (4.1%), US-Neulasta: 2 subjects (1.4%), EU-Neulasta: 2 subjects (1.4%)] were confirmed positive for anti-drug antibody at least once during the study. Eight of the 10 subjects were negative for anti-drug antibody by the final visit. Two subjects (subject IDs [redacted] (b) (6)) were positive for anti-drug antibody at their final visit (Period 3 Follow-up visit).

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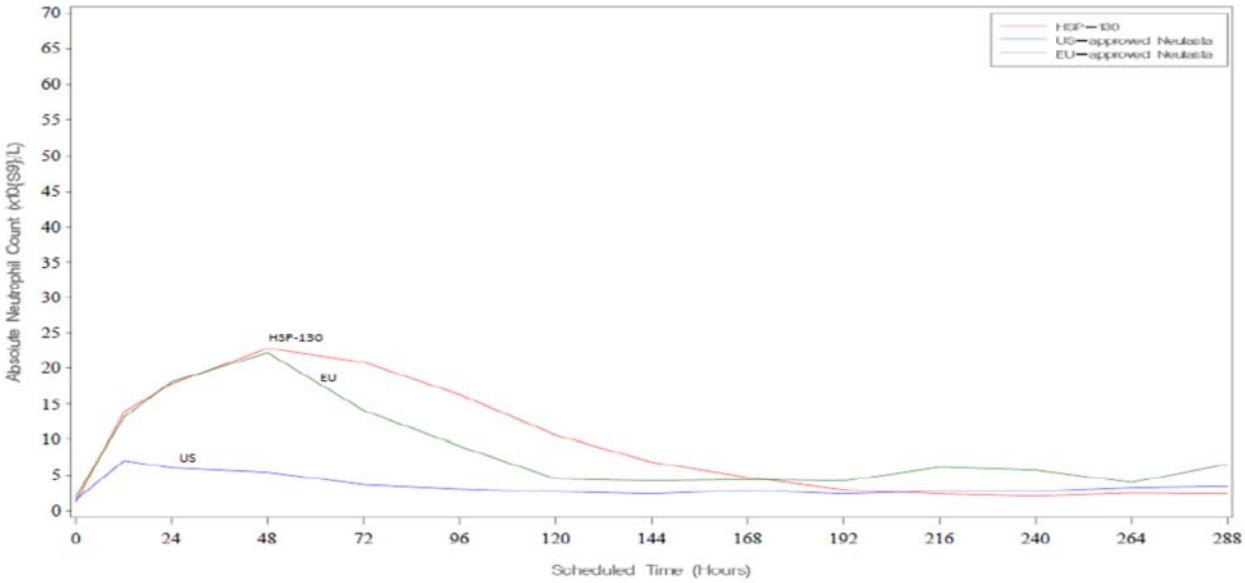
Of the 10 subjects with positive anti-drug antibody, a total of 5 subjects had more than one anti-drug antibody positive sample indicative of a true antibody positive response; and the incidence of anti-drug antibody response was similar between the arms [PF-06881894: 2 subjects (1.4%), US-Neulasta: 1 subject (0.7%), EU-Neulasta: 2 subjects (1.4%)].

Of the 10 subjects with anti-drug antibody positive results, a total of 2 subjects who received PF-06881894, had a single sample positive for Nab that occurred on P1D13. According to the Applicant, the anti-drug responses for these 2 subjects were not specific for the G-CSF protein. Both subjects had high titer anti-PEG responses that remained elevated for the duration of the study which suggests that the NAb was related to the PEG moiety, not the G-CSF protein moiety. In one (ID: (b) (6) in arm HSP/US/EU) of the two subjects, there was an effect of Nab on PD, PK and safety. The ANC results in this subject ((b) (6)) with an apparent negative impact suggest an effect of NAbs noted at P1D13 was greater in Period 2 and a lesser effect in Period 3 as shown in the figures below.

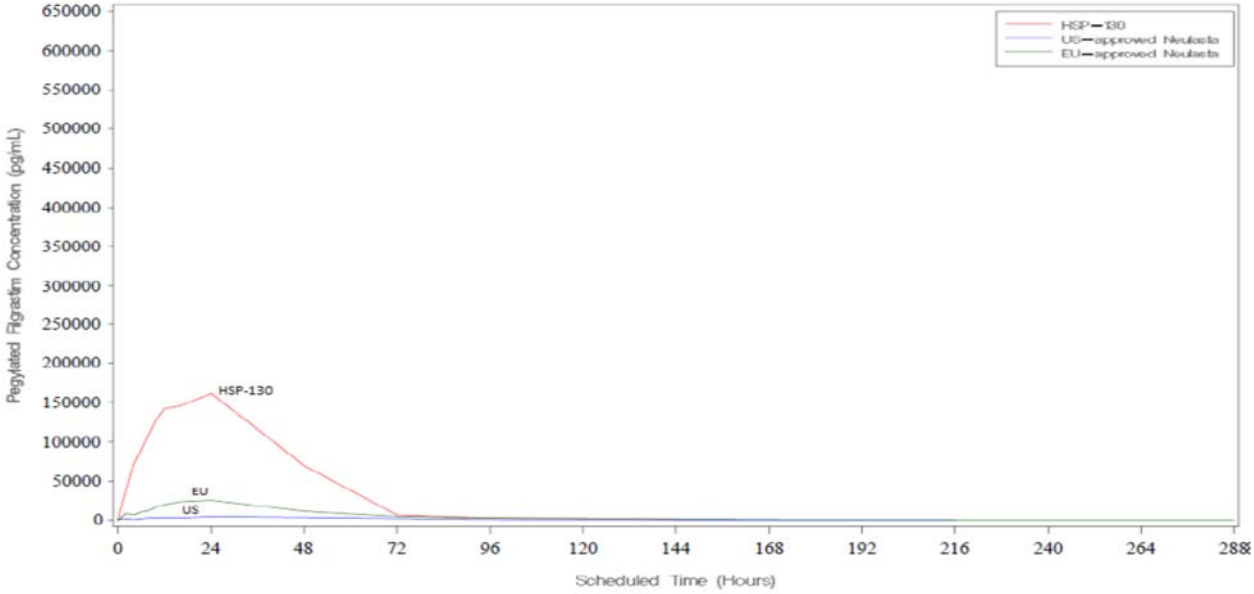
Figure 5. Absolute Neutrophil Count Over Time for the Subject (b) (6) (HSP/US/EU)



[Source: ZIN-130-1505 CSR]

Figure 6. PD, PK Results in NAb Positive Subject (b) (6) (HSP/US/EU)

Reference ID: 4622626



[Source: ZIN-130-1505 CSR]

In study ZIN-130-1505, AEs occurred in all 10 subjects who had at least 1 positive anti-drug antibody sample. In subjects who had confirmed positive anti-drug antibody result at post-dose, the most common AEs were musculoskeletal pain (10 subjects) and headache (9 subjects) across the 3 study drugs.

Three subjects who had potential allergic reactions had confirmed positive treatment-emergent anti-drug antibody at least once during the study:

- One subject [redacted] (b) (6)) in the PF-06881894 arm experienced injection site rash in Period 1. The subject also experienced an additional treatment related Injection site rash with US-Neulasta in Period 2. This subject was confirmed positive for anti-drug antibody during the P1D13 and Period 1 Follow-up visits, and the specificity testing was negative for G-CSF; the subject was positive for NAb at the P1D13 visit.
- One subject ([redacted] (b) (6)) in the PF-06881894 arm experienced non-treatment related TEAEs of vessel puncture site rash in Period 1. This subject was confirmed positive for anti-drug antibody beginning at the P1D13 visit through P3D13, and the specificity testing was negative for G-CSF; the subject was positive for NAb at the P1D13 visit.
- One subject [redacted] (b) (6)) in the US-Neulasta arm experienced non-treatment related TEAEs of rhinitis allergic (due to concurrent illness) in Period 1. This subject was confirmed positive for anti-drug antibody at the P1D13 visit, and specificity testing was positive for G-CSF.

Of the 111 subjects who reported injection site reactions (ISRs) in Study ZIN-130-1505, 7 subjects (6%) were confirmed positive anti-drug antibody at least once during the study. Of these, a total of 2 subjects reported potential hypersensitivity-related ISRs (the remaining ISRs were injection site pain and injection site bruising):

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- Subject (b) (6) (PF/EU/US) experienced treatment related Injection site erythema with EU-Neulasta group in Period 2. This subject was confirmed positive for anti-drug antibody at the P1D13 visit, and specificity testing was positive for G-CSF.
- Subject (b) (6) (PF/US/EU) experienced treatment related Injection site rash with PF-06881894 in Period 1 (verbatim: urticarial rash left deltoid at injection site).

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 can be concluded that PF-06881894 was similar to US-Neulasta and/or EU-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.	Kathy Robie-Suh, M.D., Ph.D.
Clinical Reviewer	Clinical Team Leader

7.5. Extrapolation to Support Licensure of Non-Studied Indications

The Applicant is seeking licensure of PF-06881894 as a biosimilar product to US-Neulasta for the following indication which has been previously approved for US-Neulasta and for which PF-06881894 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 for extrapolation of data and information to support licensure of PF-06881894 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 Non-Malignant Hematology (DNH)

Overall, the collective evidence from the comparative clinical studies supports demonstration of no clinically meaningful differences between PF-06881894 and US-Neulasta in terms of safety, purity and potency based on similar PK, PD, safety and immunogenicity to support licensure of PF-06881894 for the proposed indication (refer to Section 7.5).

- The Applicant provided data to support that PF-06881894 has the same mechanism of action as US-Neulasta, which support extrapolation for the sought indication. PF-06881894 is highly similar to US-Neulasta notwithstanding minor differences in clinically inactive components.
- Similar PK and bio-distribution of PF-06881894 was demonstrated with US-Neulasta in the comparative PD/PK Study (ZIN-130-1505) as concluded in section 6.1. The

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comparative PK data indicate that PF-06881894 will have a PK profile similar to US-Neulasta for the sought indication for licensure.

- The immunogenicity profile of PF-06881894 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 Applicant showed that the overall safety profile of PF-06881894 was similar to that of US-Neulasta. The safety results from the comparative clinical studies supports demonstration of no clinically meaningful differences between PF-06881894 and US-Neulasta.

DNH concludes that the Applicant has provided sufficient scientific justification (based on the mechanism of action, PK, immunogenicity and toxicity profile), and sufficient data and information, including clinical data, to support licensure of PF-06881894 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.
Clinical Reviewer

Kathy Robie-Suh, M.D., Ph.D.
Clinical Team Leader

I concur.

Ann T. Farrell, M.D.
Division Director

8. Labeling Recommendations

8.1. Non-proprietary Name

The Applicant's proposed nonproprietary name, pegfilgrastim-apgf, was found conditionally acceptable by the Division of Medication Error Prevention and Analysis (DMEPA). Refer to DMEPA's memorandum dated January 24, 2020.

8.2. Proprietary Name

The proposed proprietary name, Nyvepria, was found conditionally acceptable. Refer to review and letter issued by DMEPA on August 14 and 19, 2019, respectively.

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8.3. Other Labeling Recommendations

PF-06881894 is a proposed biosimilar to US-Neulasta. The Applicant is proposing the following dosage forms and strengths:

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

The proposed PF-06881894 labeling (USPI, IFU, and PPI) were reviewed by the primary multi-disciplinary team and consultants [including DMEPA, DMPP, OPDP, and OTBB] and incorporated relevant data and information from the US-Neulasta prescribing information, with appropriate modifications.

The Applicant is seeking licensure for the following indication, for which US-Neulasta has been previously approved: Decrease the incidence of infection, as manifested by febrile neutropenia, in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a clinically significant incidence of febrile neutropenia.

It was determined that the proposed labeling is compliant with Physician Labeling Rule (PLR) and Pregnancy and Lactation Labeling Rule (PLLR), and is consistent with labeling guidance recommendations and CDER/OND best labeling practices and policies, is clinically meaningful and scientifically accurate, and conveys the essential scientific information needed for safe and effective use of the product.

We made the following revisions to the submitted draft labeling:

USPI

- Throughout the document, inserted the conditionally approved biosimilar suffix (-apgf) in place of -xxxx.
- Throughout the document, inserted the conditionally approved proprietary name, NYVEPRIA.
- Throughout the document, revised the word “pegfilgrastim” to “NYVEPRIA”, in directive statements or recommendations (per the Biosimilar Labeling Guidance).
- At the end of Highlights, revised the word “Issued” to “Revised”, per the PLR Template.
- In the FPI, Section 2, revised text to be consistent with labeling regulations and for clarity.
- In the FPI, Section 3, revised text to remove the term “sterile” (which should appear in Section 11) and text describing the needle guard (which should appear in section 16).
- In the FPI, Section 6, revised the word “serious” to “clinically significant” per the Adverse Reactions guidance and the Neulasta USPI.
- In the FPI, throughout labeling, added the word “products” after the word “pegfilgrastim” where the text was referring to all pegfilgrastim products.
- In the FPI, Section 11, removed the description of the needle guard, as this text is more relevant to Section 16.
- In the FPI, Section 16, removed the attributes “sterile” and “preservative-free” as they are not required in this section and are already presented in Section 11***IFU***

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- Recommended that the spring in the Guide to Parts image be renamed "needle safety spring" or "needle safety guard unactivated".
- Commented that the text "Throw away…for more than 15 days." Remained under FDA review.
- Revised text for clarity in Step 1: Prepare
- Recommended adding a figure to Step 1 to show how to remove the pre-filled syringe (PFS) from the inner carton.
- Recommended removing the biohazard symbol from the "sharps disposal container" because the FDA-cleared sharps disposal information at the end of the IFU provides alternative disposal containers in case a biohazard container is not available.
- Revised text for clarity in Step 4: Finish.
- Relocated the "Examine the injection site" instructions to beneath Step J (Slowly release the plunger…), as patients should attend to bleeding and application of a bandage before they discard the syringe.

PPI

- Throughout the document, inserted the conditionally approved biosimilar suffix (-apgf) in place of -xxxx.
- Throughout the document, inserted the conditionally approved proprietary name, NYVEPRIA.
- Throughout the document, added the word "products" after the word "pegfilgrastim" where the text was referring to all pegfilgrastim products.
- In the section "What are the possible side effects…", revised the text to be consistent with the Neulasta PPI. Revised "pegfilgrastim" to "Nyvepria" for consistency with the Biosimilar Labeling guidance regarding directive statements and recommendations.
- Commented that the text "Throw away…for more than 15 days." Remained under FDA review.

Authors:
Virginia Kwitkowski
Associate Director For Labeling, DHP

Additional Labeling Comments:
DMEPA conducted a search in FAERS related to pediatric dosing error for US-Neulasta and biosimilars to US-Neulasta. A total of 19 U.S. pediatric dosing error cases were identified from the initial marketing of US-Neulasta in 2002 until August 12, 2019 (see review in DARRTS signed off on October 4, 2019). Based on the identified FAERS error report, it was determined that the following relevant sections of the prescribing information of US-Neulasta and biosimilars to US-Neulasta were to be revised.

"Section 2.2:

Pediatric Patients Weighing Less than 45 kg

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The DRUG prefilled syringe is not designed to allow for direct administration of doses less than 0.6 mL (6 mg). The syringe does not bear graduation marks, which are necessary to accurately measure doses of DRUG less than 0.6 mL (6 mg) for direct administration to patients. Thus, the direct administration to patients requiring dosing of less than 0.6 mL (6 mg) is not recommended due to the potential for dosing errors. Refer to Table 1.

Table 1. Dosing of DRUG for Pediatric Patients Weighing Less than 45 kg

Body Weight	NYVEPRIA Dose	Volume to Administer
Less than 10 kg*	See below*	See below*
10 - 20 kg	1.5 mg	0.15 mL
21-30 kg	2.5 mg	0.25 mL
31-44 kg	4 mg	0.4 mL

* For pediatric patients weighing less than 10 kg, administer 0.1 mg/kg (0.01 mL/kg) of DRUG.

Section 16:

DRUG prefilled syringe does not bear graduation marks and is intended only to deliver the entire contents of the syringe (6 mg/0.6 mL) for direct administration. Use of the prefilled syringe is not recommended for direct administration for pediatric patients weighing less than 45 kg who require doses that are less than the full contents of the syringe."

To address pediatric dosing error, a PMR was issued to the Applicant of US-Neulasta and the sponsors of biosimilars to US-Neulasta (see Section 10). A PMR will be issued to the Nyvepria application. Sections 2.2 and 16 of the Nyvepria prescribing information will be revised after the Applicant fullfils the PMR.

The CMC Labeling Review was completed by Scott Dallas (final signature in Panorama 4/28/2020). Recommendations generated during the review were communicated to the sponsor and applicant provided revisions. The CMC Labeling Review concluded that the prescribing information, patient labeling, instructions for use, submitted on April 27, 2020 container labels and carton labeling submitted on March 13, 2020 were assessed and found to be acceptable from an OBP labeling perspective.

The final wording of the review was developed in discussions with the entire review team and negotiation with the Applicant.

Authors:

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Kathy Robie-Suh, M.D., Ph.D.
Clinical Team Leader

Reference ID: 4622626

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:
Kathy Robie-Suh, M.D. Ph.D.
CDTL

10. Pediatrics

Nyvepria (pegfilgrastim-apgf) is a proposed biosimilar to US-Neulasta. The Nyvepria product labeling is, in relevant part, substantially the same as US-Neulasta's product labeling, including pediatric use information. The proposed dosage form and strength of Nyvepria is 6 mg/0.6 mL solution in a single-dose prefilled syringe with no gradation markings.

Neulasta is currently manufactured as a 6 mg/0.6 mL solution in a single-dose pre-filled syringe. Nyvepria is supplied as injection for subcutaneous use as a 6 mg/0.6 mL solution in a single-dose prefilled syringe. The recommended dose of US-Neulasta for pediatric patients weighing less than 45 kg is a fraction of the 6 mg dose based on patient weight – however, none of the pre-filled syringes for US-Neulasta are labeled with gradation markings, so an accurate dose for patients weighing less than 45 kg can not be assured. Possible dosing errors associated with pegfilgrastim products could result in: infection manifesting as neutropenic fever (if underdosed); leukocytosis, bone pain, edema, dyspnea, pleural effusion, and potential for delay of chemotherapy (if overdosed).

The Agency identified 19 U.S. pediatric dosing error cases in FAERS from the initial marketing of Neulasta in 2002 until August 12, 2019. The reported root causes of the dosing errors included inability to directly administer pediatric doses from the commercially available prefilled syringe, absence of graduation markings on the prefilled syringe to measure doses less than 0.6 mL (6 mg), and confusion regarding how to prepare a dose of less than 6 mg.

CDER determined that, for licensed pegfilgrastim products, this absence of adequate pediatric labeling explaining how to directly dose pediatric patients weighing under 45 kg could pose a risk to pediatric patients. Therefore, pursuant to section 505B(b) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), the sponsor of US-Neulasta and the sponsors of biosimilars to US-Neulasta are subject to a PMR that includes the development of an "appropriate formulation" (presentation)that can be dosed directly and accurately to pediatric patients weighing less than 45 kg and requiring doses less than 0.6 mL, and conductof any necessary human factors studies to evaluate the ability of healthcare providers and/or caregivers to measure the appropriate doses.

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This PMR listed above will be issued for the Nyvepria BLA application; refer to section 11.2 below.

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11. REMS and Postmarketing Requirements and Commitments

11.1. Recommendations for Risk Evaluation and Mitigation Strategies

None.

11.2. Recommendations for Postmarket Requirements and Commitments

The following postmarketing requirement (PMR) and commitments (PMCs) will be requested:

PMR 3825-1:
Submit pediatric assessments for Nyvepria (pegfilgrastim-apgf) as described in section 505B(a)(2)(A) of the FD&C Act, including development of an "appropriate formulation" (presentation) that can be used to directly and accurately administer NYVEPRIA (pegfilgrastim-apgf) to pediatric patients who weigh less than 45 kg and require doses that are less than 0.6 mL (6 mg), and conducting any necessary human factors studies to evaluate the ability of healthcare providers and/or caregivers to measure the appropriate doses.

Final Report Submission: 10/2025

PMC 3825-2:
To perform a simulated shipping validation study representing real world shipping conditions, such as temperature, mode of transport, shipping duration, and packaging configuration using PF-06881894 drug product representative of commercial drug product to confirm that product quality is maintained. The simulated shipping validation data will be submitted in accordance with 21 CFR 601.12.

Final Report Submission: 08/2020

PMC 3825-3:
To update the control strategy to include lot release testing for the safety activation force (also referred to as safety device trigger force) of the final finished combination product in order to demonstrate that the product is not more than (NMT (b) (4) N trigger force.

Reference ID: 4622626

Authors:
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Clinical Reviewer

Kathy -Robie-Suh, M.D., Ph.D.
Clinical Team Leader

12.Appendices

12.1. Financial Disclosure

Covered Clinical Study (Name and/or Number): ZIN-130-1505

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 8		
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

Reference ID: 4622626

		from Applicant)

Covered Clinical Study (Name and/or Number): C1221005

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

Covered Clinical Study (Name and/or Number): ZIN-130-1504

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 36		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		

Reference ID: 4622626

Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 1		
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: 0 Significant payments of other sorts: 1 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator: 0 Sponsor of covered study: 0		
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)

12.2. Nonclinical Appendices

12.2.1. General Toxicology

A comparative nonclinical toxicology study (Study 1550-064) in rats of 4-week duration with a 6-week recovery period that compared the PD, toxicokinetics, and toxicity profile of PF-06881894 (also known as HSP-130) with EU-Neulasta and US-Neulasta was reviewed in support of the BLA submission. Rats were administered vehicle or PF-06881894, US-Neulasta or EU-Neulasta at 200 or 1800 µg/kg/weekly. No mortalities occurred during the study. Major histopathology findings at dose levels of 200 µg/kg and higher included myeloid hyperplasia and hyperstosis in bone marrow (femur and sternum) and increased extramedullary hematopoiesis in the spleen and liver, which were absent following the recovery period. Based on the results of the study, the PD, toxicokinetics, and toxicity profiles of PF-06881894 and US-Neulasta appeared similar at the doses examined (200, 1800 µg/kg).

Study title: HSP-130: A 4-week subcutaneous comparative repeat-dose toxicity study with HSP-130 and Neulasta in rats with a 6-week recovery period

Reference ID: 4622626

Study no.:	1550-064
Study report location:	eCTD 4.2.3.2
Conducting laboratory and location:	(b) (4)
Date of study initiation:	November 4, 2015
GLP compliance:	Signed and Included
QA statement:	Signed and Included
Drug, lot #:	HSP-130; PFS01P-14 US-Neulasta; 1057373 EU-Neulasta; 1058436B

Key Study Findings

- There were no drug related mortalities.
- Histopathology findings present in both males and females at doses of 200 µg/kg and higher in all treatment groups included granulocytic hyperplasia in the bone marrow, increased hematopoiesis in the spleen and liver, increased incidence of hypocellularity and vacuolated/tangible body macrophages in the spleen, and sinusoidal leukocytosis in the liver.
- Trabecular hyperostosis observed in the femur of males in all treatment groups at 1800 µg/kg was associated with increased ALP and related to increased osteoblast activity.
- Toxicokinetics indicated exposures (based on Cmax and AUC) increased in a greater than dose-proportional manner in both males and females throughout the study in all treatment groups.

Methods

Doses:	200, 1800 µg/kg: HSP-130 (PF-06881894), EU-Neulasta, US-Neulasta
Frequency of dosing:	Once weekly (Days 1, 8, 15, 22, and 29)
Route of administration:	Subcutaneous bolus injection
Dose volume:	1.0 mL/kg
Formulation/Vehicle:	10 mM Sodium Acetate pH 4.0, 5% Sorbitol, and 0.004% Polysorbate 20
Species/Strain:	CD rats (Sprague Dawley)
Number/Sex/Group:	15/sex/group in vehicle and high dose and 10/sex/group in intermediate doses with 5/sex/group in vehicle and high dose for recovery
Age:	Approximately 8 weeks old
Weight:	Males: 268 to 309 g; Females: 195 to 225 g
Satellite groups:	N/A

Study Design in Rat Repeat-Dose Toxicology Study

Reference ID: 4622626

Group Number	Treatment	Dose Level (µg/kg)	Dose Volume (mL/kg)	Dose Concentration (µg/mL)	Number of Animals	
					Male	Female
			Main Study			
1	Vehicle	0	1	0	15[a]	15[a]
2	TA1	200	1	200	10	10
3	TA1	1800	1	1800	15[a]	15[a]
4	TA2	200	1	200	10	10
5	TA2	1800	1	1800	15[a]	15[a]
6	TA3	200	1	200	10	10
7	TA3	1800	1	1800	15[a]	15[a]
			Toxicokinetic and Immunogenicity			
8	Vehicle	0	1	0	6	6
9	TA1	200	1	200	12	12
10	TA1	1800	1	1800	12	12
11	TA2	200	1	200	12	12
12	TA2	1800	1	1800	12	12
13	TA3	200	1	200	12	12
14	TA3	1800	1	1800	12	12

TA1 = HSP-130; TA2 = US-licensed Neulasta®; TA3 = EU-licensed Neulasta®
[a]Five animals were maintained for a 6-week recovery period

(Excerpted from the submission)

Observations and Results

Mortality

Unremarkable

Body Weights

Unremarkable

Feed Consumption

Unremarkable

Ophthalmoscopy

Unremarkable

ECG

Unremarkable

Hematology

Hematology findings from the 4-week toxicity study in rats show a dose-dependent response in the absolute neutrophil count (ANC) and total leukocytes based on % change relative to control, prior to terminal necropsy.

Absolute Neutrophil Count (ANC) and Total Leukocytes from 4-week toxicity study in Rats

Reference ID: 4622626

	Group:	2		4		6	
	Dose Level:	200 µg/kg HSP-130		200 µg/kg US-licensed Neulasta®		200 µg/kg EU-licensed Neulasta®	
	Sex:	M	F	M	F	M	F
Endpoint	**Interval**						
Total Leukocytes	Day 3	+3.1x	+3.0x	+3.2x	+3.0x	+3.3x	+3.5x
	Day 10	+4.2x	+3.8x	+4.6x	+4.1x	+4.7x	+4.3x
	Day 17	+4.9x	+4.2x	+5.1x	+3.8x	+5.3x	+4.1x
	Day 24	+4.6x	+5.0x	+4.8x	+4.5x	+4.6x	+4.4x
	Terminal	+4.5x	+4.0x	+4.3x	+4.0x	+4.5x	+4.5x
	Day 45	-	-	-	-	-	-
	Recovery	-	-	-	-	-	-
Neutrophils	Day 3	+12.1x	+10.7x	+13.1x	+10.8x	+13.3x	+11.6x
	Day 10	+18.9x	+12.8x	+21.4x	+15.0x	+23.9x	+14.0x
	Day 17	+25.6x	+15.8x	+26.1x	+17.7x	+25.7x	+16.5x
	Day 24	+23.1x	+22.0x	+27.1x	+21.3x	+24.2x	+19.0x
	Terminal	+24.9x	+20.6x	+23.0x	+20.5x	+24.7x	+22.8x
	Day 45	-	-	-	-	-	-
	Recovery	-	-	-	-	-	-

[a]: Change relative to controls; M: Males; F: Females; x: Fold-change relative to controls; -: No meaningful changes relative to controls

	Group:	3		5		7	
	Dose Level:	1800 µg/kg HSP-130		1800 µg/kg US-licensed Neulasta®		1800 µg/kg EU-licensed Neulasta®	
	Sex:	M	F	M	F	M	F
Endpoint	**Interval**						
Total Leukocytes	Day 3	+3.0x	+3.2x	+3.2x	+3.4x	+3.1x	+3.2x
	Day 10	+7.4x	+7.1x	+8.2x	+7.8x	+7.6x	+7.2x
	Day 17	+9.2x	+8.5x	+9.2x	+7.8x	+9.8x	+8.4x
	Day 24	+9.3x	+9.4x	+9.2x	+9.0x	+9.5x	+9.6x
	Terminal	+9.6x	+9.3x	+9.6x	+9.3x	+9.8x	+8.7x
	Day 45	-	-	-	-	-	-
	Recovery	-	-	-	-	-	-
Neutrophils	Day 3	+11.5x	+10.9x	+13.1x	+11.9x	+12.4x	+10.9x
	Day 10	+41.3x	+30.2x	+44.3x	+33.8x	+44.0x	+30.9x
	Day 17	+56.4x	+42.0x	+54.6x	+39.4x	+61.4x	+42.4x
	Day 24	+59.3x	+49.8x	+57.5x	+46.5x	+63.4x	+53.4x
	Terminal	+62.8x	+57.8x	+63.2x	+57.0x	+66.4x	+54.2x
	Day 45	-	-	-	-	-	-
	Recovery	-	-	-	-	-	-

[a]: Change relative to controls; M: Males; F: Females; x: Fold-change relative to controls; -: No meaningful changes relative to controls

Reference ID: 4622626

(Excerpted from the submission)

Clinical Chemistry

There were mild to moderate, dose-dependent increases in alkaline phosphatase (ALP) at values up to (+8.7x +9.8x and +9.1x) and gamma-glutamyltransferase (GGT) (+5.6x ,+4.4x ,and +4.4x) for HSP-130, US-Neulasta, and EU-Neulasta, respectively.

Bone marrow

Both males and females showed increases in myeloid/erythroid ratio (M:E) for all test articles. There were increased granulocytic cells and decreased erythroid cells.

Urinalysis

Unremarkable

Gross Pathology

Gross pathology findings from 4 week toxicity study in rats

Test Article	HSP-130				US-licensed Neulasta®				EU-licensed Neulasta®			
Dose Level: µg/kg	200		1800		200		1800		200		1800	
Sex	M	F	M	F	M	F	M	F	M	F	M	F
Number Examined	10	10	10	10	10	10	10	10	10	10	10	10
Spleen												
enlarged	0	1	9	3	0	0	9	4	1	0	10	2
- mild	0	1	4	3	0	0	5	3	1	0	5	1
- moderate	0	0	5	0	0	0	4	1	0	0	5	1
M – Male; F – Female												

(Excerpted from the submission)

Organ Weights

Organ weight changes from 4 week toxicity study in rats (main study)

Reference ID: 4622626

Males (Percent change relative to control)

Test Article	HSP-130		US-licensed Neulasta®		EU-licensed Neulasta®	
Dose Level: µg/kg	200	1800	200	1800	200	1800
Number Examined	10	10	10	10	10	10
Mean Terminal BWt	↓0.23	↓4.45	↓0.70	↓1.64	↓0.70	↓4.68
Spleen (g)	↑80.69[b]	↑300.00[b]	↑86.15[b]	↑287.48[b]	↑89.88[b]	↑286.82[b]
Spleen/BWt%	↑81.73[b]	↑321.23[b]	↑86.68[b]	↑298.06[b]	↑91.58[b]	↑306.77[b]
Spleen/BrWt ratio	↑86.54[b]	↑293.28[b]	↑82.03[b]	↑282.30[b]	↑88.83[b]	↑286.09[b]

[b]Significantly different from control; ($p<0.01$) ↑ - Increased
BWt - Body Weight ↓ - Decreased
BrWt - Brain Weight

Females (Percent change relative to control)

Test Article	HSP-130		US-licensed Neulasta®		EU-licensed Neulasta®	
Dose Level: µg/kg	200	1800	200	1800	200	1800
Number Examined	10	10	10	10	10	10
Mean Terminal BWt	↑6.84	↑4.70	↑3.85	↑4.70	↑6.41	↑4.70
Spleen (g)	↑59.92[b]	↑227.86[b]	↑64.89[b]	↑223.09[b]	↑76.15[b]	↑209.16[b]
Spleen/BWt%	↑49.93[b]	↑214.45[b]	↑59.35[b]	↑210.27[b]	↑67.12[b]	↑197.08[b]
Spleen/BrWt ratio	↑54.58[b]	↑218.09[b]	↑62.04[b]	↑221.26[b]	↑74.49[b]	↑195.97[b]
Liver (g)	↑5.52	↑13.43[a]	↑5.08	↑6.43	↑6.13	↑14.65[b]
Liver/BWt%	↓1.03	↑8.33	↑1.00	↑1.89	↓0.04	↑9.74[a]
Liver/BrWt ratio	↑1.84	↑9.49	↑2.80	↑5.53	↑4.48	↑9.40
Lung (g)	↑5.76	↑13.91[a]	↑10.55	↑9.03	↑3.12	↑12.55[b]
Lung/BWt%	↓0.54	↑9.25	↑6.42	↑4.62	↓2.96	↑7.96
Lung/BrWt ratio	↑1.74	↑9.75	↑8.06	↑7.84	↑1.44	↑7.16

[a]Significantly different from control; ($p<0.05$) ↑ - Increased
[b]Significantly different from control; ($p<0.01$) ↓ - Decreased
BWt - Body Weight
BrWt - Brain Weight

(Excerpted from the submission)

Reference ID: 4622626

Organ weight changes from 4 week toxicity study in rats (recovery)

Male and Female (Percent change relative to control)						
Test Article	HSP-130		US-licensed Neulasta®		EU-licensed Neulasta®	
Dose level: µg/kg	1800		1800		1800	
Sex	M	F	M	F	M	F
Number Examined	5	5	5	5	5	5
Mean Terminal BWt	↑6.90	↓4.68	↑9.94	↓2.16	↑8.11	↓3.96
Spleen (g)	↑46.42[a]	↓2.23	↑45.07	↑21.19	↑41.16[a]	↑8.92
Spleen/BWt%	↑36.04	↑2.17	↑30.29	↑23.69	↑30.89	↑12.21
Spleen/BrWt ratio	↑48.37[a]	↓0.78	↑49.84	↑25.50	↑40.47[a]	↑14.33

[a]Significantly different from control; ($p<0.05$)
BWt - Body Weight
BrWt - Brain Weight
↑ - Increased
↓ - Decreased
M - Male; F - Female

(Excerpted from the submission)

Histopathology
Adequate Battery: Yes
Peer Review: Yes

Histological Findings
Histopathology findings from 4 week toxicity study in rats (males, main study)

Reference ID: 4622626

Test Article	None	HSP-130		US-licensed Neulasta®		EU-licensed Neulasta®	
Dose Level: µg/kg	0	200	1800	200	1800	200	1800
Number Examined	10	10	10	10	10	10	10
Bone marrow, femur							
Hyperplasia, granulocytic	0	10	10	10	10	10	10
-mild	0	10	5	10	6	10	5
-moderate	0	0	5	0	4	0	5
Bone marrow, sternum							
Hyperplasia, granulocytic	0	10	10	10	10	10	10
-mild	0	10	3	10	4	10	3
-moderate	0	0	7	0	6	0	7
Bone, femur							
Hyperostosis, trabecular	1	1	8	0	8	0	7
-minimal	1	0	4	0	3	0	2
-mild	0	0	1	0	1	0	1
-moderate	0	1	3	0	4	0	4
Bone, tibia							
Hyperostosis	0	1	0	1	0	0	0
-minimal	0	0	0	1	0	0	0
-moderate	0	1	0	0	0	0	0
Spleen							
Cellularity increased, hematopoiesis	1	10	10	10	10	10	10
-minimal	1	4	0	5	0	4	0
-mild	0	6	0	5	2	5	0
-moderate	0	0	10	0	8	1	10
Cellularity decreased, marginal zone	0	3	10	1	8	3	9
-minimal	0	3	2	1	2	3	4
-mild	0	0	8	0	6	0	5
Increased macrophages, vacuolated/tingible body	0	10	10	10	9	10	9
-minimal	0	2	0	4	1	1	2
-mild	0	7	10	6	7	9	7
-moderate	0	1	0	0	1	0	0
Liver							
Hematopoiesis, extramedullary, increased	0	4	10	3	10	3	10
-minimal	0	4	3	3	5	3	4
-mild	0	0	7	0	5	0	6
Leukocytosis, sinusoidal							
-minimal	0	7	9	7	9	7	10

(Excerpted from the submission)

Histopathology findings from 4 week toxicity study in rats (females, main study)

Reference ID: 4622626

Test Article:	None	HSP-130		US-licensed Neulasta®		EU-licensed Neulasta®	
Dose Level: µg/kg	0	200	1800	200	1800	200	1800
Number Examined	10	10	10	10	10	10	10
Bone marrow, femur							
Hyperplasia, granulocytic	0	10	10	10	10	10	10
-minimal	0	1	0	0	0	0	0
-mild	0	9	1	10	1	10	0
-moderate	0	0	9	0	9	0	10
Bone marrow, sternum							
Hyperplasia, granulocytic	0	10	10	10	10	10	10
-minimal	0	2	0	1	0	3	0
-mild	0	8	2	9	1	7	4
-moderate	0	0	8	0	9	0	6
Spleen							
Cellularity increased, hematopoiesis	0	9	10	9	10	7	10
-minimal	0	4	0	5	0	3	0
-mild	0	5	0	4	1	4	1
-moderate	0	0	10	0	9	0	9
Cellularity decreased, marginal zone	0	0	8	0	6	1	5
-minimal	0	0	5	0	3	1	2
-mild	0	0	3	0	3	0	3
Increased macrophages, vacuolated/tingible body	0	7	10	9	10	9	10
-minimal	0	5	3	5	4	5	3
-mild	0	2	7	3	6	4	7
-moderate	0	0	0	1	0	0	0
Liver							
Hematopoiesis, extramedullary, increased	0	0	10	0	10	1	10
-minimal	0	0	6	0	3	1	4
-mild	0	0	4	0	7	0	6
Liver							
Leukocytosis, sinusoidal							
-minimal	0	0	8	3	8	2	10

(Excerpted from the submission)

Special Evaluation- Immunogenicity

Anti-drug antibodies for HSP-130, US-Neulasta and EU-Neulasta were detected in rats at 200 µg/kg/dose and 1800 µg/kg/dose.

Summary of anti-drug antibody response in 4 week toxicity study in rats

Reference ID: 4622626

Group	8		9		10		11		12		13		14	
Test Article	Vehicle		TA1[b]		TA1[b]		TA2[c]		TA2[c]		TA3[d]		TA3[d]	
Dose	0 µg/kg		200 µg/kg		1800 µg/kg		200 µg/kg		1800 µg/kg		200 µg/kg		1800 µg/kg	
Sex	M	F	M	F	M	F	M	F	M	F	M	F	M	F
Predose	0/6	0/6	0/6	0/6	0/6	0/6	0/6	0/6	0/6	0/6	0/6	0/6	0/6	1/6
Day 8	0/6	0/6	0/6	0/6	0/6	1/6	0/6	0/6	0/6	0/6	0/6	0/6	0/6	0/6
Day 15	0/6	0/6	0/6	0/6	1/6	0/6	0/6	0/6	1/6	1/6	0/6	1/6	0/6	0/6
Day 22	0/6	0/6	1/6	0/6	1/6	0/6	0/6	0/6	2/6	2/6	1/6	2/6	0/6	1/6
Day 29	0/6	0/6	2/6	1/6	1/6	0/6	1/6	0/6	2/6	2/6	1/6	2/6	0/6	2/6
Day 43	0/6	0/6	2/6	1/6	1/6	1/6	1/6	0/6	2/6	1/6	1/6	2/6	0/6	2/6
Day 57	0/6	0/6	1/6	1/6	1/6	0/6	1/6	0/6	2/6	1/6	1/6	2/6	0/6	2/6
Day 71	0/6	0/6	1/6	1/6	1/6	0/6	1/6	0/6	2/6	1/6	1/6	2/6	0/6	0/6

M = male; F = female
[a] Number of animals with positive ADA response/number of animals assessed
[b] TA1 = Test Article 1 = HSP-130
[c] TA2 = Test Article 2 = US-licensed Neulasta®
[d] TA3 = Test Article 3 = EU-Licensed Neulasta®

(Excerpted from the submission)

Toxicokinetics

- Overall, exposures based on Cmax and AUC increased greater than dose-proportional in both males and females throughout the study for all test articles.
- Tmax ranged from 16-24 hours and the $T_{1/2}$ showed no consistent trend.
- The test articles did not appear to accumulate following the weekly dosing schedule in rats.

Summary toxicokinetic data from 4 week toxicity study in rats

Reference ID: 4622626

HSP-130 (Groups 9 and 10), US-Licensed Neulasta® (Groups 11 and 12), or EU-Licensed Neulasta® (Groups 13 and 14) to Rats (Males and Females Combined)

Group	Dose (µg/kg)	Treatment	Day	Cmax (ng/mL)	Tmax (hr)	$AUC_{0\text{-}120hr}$ (hr*ng/mL)	AUC_{INF} (hr*ng/mL)	$T_{1/2}$ (hr)	Biosimilar Ratio[b]
9[c]	200	200 µg/kg TA1	1	369	16	9500	NA[a]	NA[a]	NA
9	200	200 µg/kg TA1	29	249	24	6460	NA	NA[a]	NA
10[d]	1800	1800 µg/kg TA1	1	5480	16	252000	251000	15.0	NA
10	1800	1800 µg/kg TA1	29	6200	16	245000	NA	6.26	NA
11	200	200 µg/kg TA2	1	423	24	11100	NA[a]	NA[a]	1.17
11	200	200 µg/kg TA2	29	373	16	7580	NA	NA[a]	1.17
12	1800	1800 µg/kg TA2	1	5710	24	259000	258000	15.8	1.03
12	1800	1800 µg/kg TA2	29	4910	24	213000	NA	9.31	0.869
13	200	200 µg/kg TA3	1	395	16	10400	NA[a]	NA[a]	1.09
13	200	200 µg/kg TA3	29	334	16	7940	NA	NA[a]	1.23
14	1800	1800 µg/kg TA3	1	5360	24	232000	NA[a]	NA[a]	0.921
14	1800	1800 µg/kg TA3	29	6230	16	219000	NA	11.5	0.894

NA - Not applicable
a: Secondary parameters (AUC_{INF} and $T_{1/2}$) not determined/reported due to insufficient plasma concentration time data
b: Biosimilar Ratio = $AUC_{0\text{-}120hr\ TA2\ or\ TA3}/AUC_{0\text{-}120hr\ TA1}$, excluding Animal Numbers 9503 and 10501 on Day 1 at 36 hours postdo
c: Excluding Animal Number 9503 on Day 1 at 36 hours postdose
d: Excluding Animal Number 10501 on Day 1 at 36 hours postdose
TA1= HSP-130; TA2 = US-licensed Neulasta®; TA3 = EU-licensed Neulasta®

(Excerpted from the submission)

Dosing Solution Analysis

Dosing solution analysis from 4 week toxicity study in rats

Dose Level (µg/kg)	Nominal Concentration (µg/mL)	Average Calculated Concentration (µg/mL)	Average %Recovery[a,b]	%Relative Standard Deviation
0	0	BLQ	NA	NA
200 HSP-130	200	189.5980 – 206.1904	94.8 – 103.1	2.643 – 3.093
200 US-licensed Neulasta®	200	198.4141 – 216.0227	99.2 – 108.0	0.335 – 1.155
200 EU-licensed Neulasta®	200	197.0188 – 212.3712	98.5 – 106.2	0.075 – 0.177
1800 HSP-130	1800	1792.2646 – 1863.8488	99.6 – 103.5	0.383 – 0.399
1800 US-licensed Neulasta®	1800	1793.2852 – 1880.4376	99.6 – 104.5	0.267 – 1.113
1800 EU-licensed Neulasta®	1800	1802.8871 – 1879.0212	100.2 – 104.4	0.597 – 0.726

BLQ – Below the limit of quantitation (<20.2 µg/mL)
NA – Not applicable/Not available
[a]Average %recovery was calculated from the nominal concentration.
[b]The averaged result from homogeneity analysis served as concentration verification.

Reference ID: 4622626

12.3. Office of Clinical Pharmacology Appendices

12.3.1. Summary of Bioanalytical Method Validation and Performance

12.3.1.1. Pharmacokinetics

For the PK/PD similarity study ZIN-130-1505, serum PF-06881894, serum US-Neulasta and serum EU-Neulasta concentrations measured using a validated ELISA method (TM.1581) were suitable for assessment of PK similarity. Both the method validation and sample analysis for the study were performed at [redacted] (b) (4)). In this method, mouse anti-human G-CSF [redacted] (b) (4) coated in 96-well plate was used to capture serum pegylated granulocyte-colony stimulating factor (PEG G-CSF), biotinylated goat anti-human G-CSF [redacted] (b) (4) and MSD Sulfo-Tag labeled Streptavidin (Meso Scale Discovery, Rockville, MD) were used to detect the bound analytes (Validation report 10135.021116). Table 35 shows the summary of ELISA method performance in quantification of serum PF-06881894, serum US-Neulasta and serum EU-Neulasta during the method validation and during the study.

Table 35. Summary of the bioanalytical method validation and in-study performance for measurement of serum PF-06881894, serum US-licensed Neulasta and serum EU-approved Neulasta

Bioanalytical method review summary	Validation of an Immunoassay for the Quantitation of Hospira Pegfilgrastim, US-Approved Neulasta®, and EU-Approved Neulasta® in Human Serum
Method description	Detection and Quantitation of Pegylated Granulocyte-Colony Stimulating Factor (PEG G-CSF) in Human Serum by Electrochemiluminescence (ECL), describes in detail the analytical methodology used in this validation. Briefly, the assay consists of an Electrochemiluminescence (ECL) Immunoassay where mouse anti-human G-CSF was captured onto an MSD Plate (ECL capable). When standards, controls and samples were pipetted into the pre-coated wells, any PEG G-CSF present in the samples bound to the immobilized antibody. After washing away any unbound substances, a biotin conjugated polyclonal antibody specific to human (mouse anti-human) G-CSF was added to the wells which was followed by and detected with biotinylated goat anti-human G-CSF and MSD Sulfo-Tag labeled Streptavidin. The assay plate was then read using a MSD Sector Imager and the electrochemical signal generated as a result was relative to the amount of PEG G-CSF present in the samples tested.
Materials used for calibration curve & concentration	Pegylated G-CSF (HSP-130, PF-06881894) Lot: ASN107 Retest: February 2018
Validated assay range	100 – 5000 pg/mL

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Material used for QCs & concentration	Pegylated G-CSF (HSP-130, PF-06881894) Lot: ASN107 Retest: 28 Feb 2018 EU-Neulasta(Pre-filled Syringe, 6 mg/0.6 mL) Lot: 1057625 NDC: 55513-190-01 Expiration Date: 31 Oct 2017 US-Neulasta(pegfilgrastim, Pre-filled Syringe, 6 mg/0.6 mL) Lot: 1054726 NDC: 55513-190-01 Expiration Date: 30 Sep 2017 LLOQ QC: 100 pg/mL QCL: 300 pg/mL QCM: 1000 pg/mL QCH: 3750 pg/mL ULOQ QC: 5000 pg/mL		
Minimum required dilutions (MRDs)	1:5		
Source & lot of reagents (LBA)	Human G-CSF Duo set kit (b) (4): • Capture Antibody (mouse anti-human G-CSF; 240 µg/mL) • Detection Antibody (biotinylated goat anti-human G-CSF; 36 µg/mL) MSD SULFO-TAG labeled Streptavidin (500 µg/mL), Lot: R32AD-5 or R32AD-1 Source: Meso Scale Discovery		
Regression model & weighting	Regression Model: 4-parameter logistic Weighting: 1/[concentration]^2		
Validation parameters	**Method validation summary**		**Acceptability**
Calibration curve performance during accuracy & precision[Error! Reference source not found.]	Number of standard calibrators from LLOQ to ULOQ	8	Yes
	Cumulative accuracy (%bias) from LLOQ to ULOQ PF-06881894	-1.6% to 1.2%	Yes
	Cumulative precision (%CV) from LLOQ to ULOQ PF-06881894	≤3.48%	Yes
QCs performance during accuracy & precision	**Cumulative accuracy (%bias) in 5 QCs:** QCs PF-06881894 US-Neulasta EU-Neulasta	 -14.4 to -6.12% -12.7 to -2.51% -18.0 to -5.75%	Yes
	Inter-batch %CV QCs: PF-06881894 US-Neulasta EU-Neulasta	 ≤7.03% ≤7.49% ≤9.64%	Yes
	Total Error QCs: PF-06881894 US-Neulasta EU-Neulasta	 ≤20.9% ≤18.4% ≤25.3%	Yes

Reference ID: 4622626

Selectivity & matrix effect	Ten total lots tested. Range of observed bias at LLOQ: PF-06881894: -24.8 to 26.0% (9/10 lots within -25.0 to 25.0%) US-Neulasta: -14.7 to 46.0% (9/10 lots within -25.0 to 25.0%) EU-Neulasta: -15.7 to 24.0% (10/10 lots within -25.0 to 25.0%)	Yes
Interference & specificity	Not Evaluated	N/A
Hemolysis effect	Five total lots tested. Range of observed bias at LLOQ: PF-06881894: -12.0 to 21.0% (5/5 lots within -25.0 to 25.0%) USNeulasta: -24.4 to 29.0% (4/5 lots within -25.0 to 25.0%) EU-Neulasta: -35.6 to 18.0% (3/5 lots within -25.0 to 25.0%)* Range of observed bias at QCH: PF-06881894: -12.3 to 8.00% (5/5 lots within -20.0 to 20.0%) US-Neulasta: -30.1 to -1.07% (4/5 lots within -20.0 to 20.0%) EU-Neulasta: -24.0 to 0.267% (4/5 lots within -20.0 to 20.0%) * The experiment was repeated and confirmed at the LLOQ for the failed lots of EU-Neulasta as shown in Table 8d of report #10135.021116. The repeated and confirmatory experiment passed for both lots.	Yes
Lipemic effect	Five total lots tested. Range of observed bias at LLOQ: PF-06881894: -22.2 to 13.0% (5/5 lots within -25.0 to 25.0%) US-Neulasta: -11.7 to 18.0% (5/5 lots within -25.0 to 25.0%) EU-Neulasta: -17.1 to 18.0% (5/5 lots within -25.0 to 25.0%) Range of observed bias at QCH: PF-06881894: -25.1 to -14.7% (3/5 lots within -20.0 to 20.0%)* US-Neulasta: -17.3 to -7.47% (5/5 lots within -20.0 to 20.0%) EU-Neulasta: -20.0 to -9.07% (5/5 lots within -20.0 to 20.0%) * The failed lots were repeated yielding results within the acceptance criteria, followed by a confirmatory experiment, in which they were slightly outside the acceptance criteria. The experiment was repeated a second time and confirmed, with all results well within the acceptance criteria.	Yes
Dilution linearity & hook effect	Range of %bias for dilution linearity samples within the range of quantitation (up to 250-fold dilution): PF-06881894: -12.6 to -9.00% US-Neulasta: -13.4 to -9.80% EU-Neulasta: -23.0 to -12.8% * *The experiment failed for the EU-Neulasta at the 250-fold dilution and was successfully repeated and confirmed; this data is presented in Table 7d of the validation report. Hook Effect: All hook effect samples tested produced values above the ULOQ for PF-06881894, US-Neulasta, and EU-Neulasta.	Yes

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Bench-top/ process stability	26 hours PF-06881894: Low:-12.3%; Hight: -7.73% US-Neulasta: Low:-17.7%; Hight: -7.20% EU-Neulasta: Low:-13.0%; Hight: -6.67%	Yes
Freeze-Thaw stability	6 cycles PF-06881894: Low:-6.67%; Hight: -6.93% US-Neulasta: Low:-11.0%; Hight: -9.60% EU-Neulasta: Low:-11.0%; Hight: -9.60%	Yes
Long-term storage	-20°C 54 days PF-06881894: Low:-9.67%; Hight: -12.3% US-Neulasta: Low:-16.0%; Hight: -14.1% EU-Neulasta: Low:-15.7%; Hight: -21.9% to -15.5% -80°C 54 to 839 days PF-06881894: Low:-16.3% to -7.33%; Hight: -17.1% to 0.267% US-Neulasta: Low:-20.0% to 0.00%; Hight: -14.1% to 0.800% EU-Neulasta: Low:-24.0% to -4.67%; Hight: -15.5% to -2.67%	Yes
Parallelism	Not Evaluated	N/A
Carry over	Not Evaluated	N/A
Method performance in Study ZIN-130-1505 Determination of Pegfilgrastim in Human Serum Samples From Protocol ZIN-130-1505		
Materials used for calibration curve & QC	Pegylated G-CSF (HSP-130, PF-06881894) Lot: ASN107	Yes
Assay passing rate	Passed Runs: 365 (95%) Failed Runs: 18 (5%) Total No. of Runs: 383	Yes
Standard curve performance	• Standard Curve Range: 100 – 5000 pg/mL • $R^2 \geq 0.98$ • Cumulative bias range: -2.4 to 1.0% • Cumulative precision: ≤ 5.27% CV	Yes
QC performance	• Cumulative bias range: -0.267 to 2.00% • Cumulative precision: ≤ 12.1% CV • Including values outside acceptance range criteria: ± 20.0% bias for all QC samples	Yes
Method reproducibility	Incurred sample reanalysis was performed in 5.6% of study samples (515 samples tested for ISR out of 9265 total samples tested) and 97.9 % of samples met the pre-specified criteria	Yes
Study sample analysis/ stability	The interval from first sample draw date to last analysis date was 257 days. Adequate long-term stability (839 days) has been established to cover the storage period	

Abbreviations: CV = coefficient of variation; ECL = electrochemiluminescent; EU = European Union; G-CSF = granulocyte colony-stimulating factor; ISR = incurred samples reanalysis; LBA = ligand binding assay; LLOQ = lower limit of quantification; MSD = meso scale discovery; NDC = national drug code; PEG = polyethylene glycol; QC = quality control; QCH = QC high; QCL = QC low; QCM = QC mid; TE = total error; ULOQ = upper limit of quantification; US = United States.

Reference ID: 4622626

12.3.1.2. Pharmacodynamics

For the PK/PD similarity study ZIN-130-1505, ANC in whole blood determined with a validated method using the SYSMEX XN-3000 Haematology Analyser was suitable for assessment of PD similarity between PF-06881894, US-Neulasta and EU-Neulasta. The method validation and sample analysis for the study were performed at (b) (4) The SYSMEX XN-3000 Haematology Analyser consists of a cytochemical reaction of the cells with a reagent set, followed by fluorescence flow cytometric analysis. Table 36 shows the summary of the SYSMEX XN-3000 Haematology Analyser method performance in quantification of ANC in whole blood during the method validation and during the study.

Table 36. Summary Method Performance of a Bioanalytical Method to Measure ANC in K2EDTA Whole Blood

Bioanalytical method review summary	Validation Report Absolute Neutrophil Count (ANC) in Human EDTA Whole Blood (Module 5.3.1.4 Report C1228001)
Method description	The measurement of WBC differential in K_2EDTA whole blood using the SYSMEX XN-3000 Haematology Analyser consists of a cytochemical reaction of the cells with a reagent set, followed by fluorescence flow cytometric analysis. The specially developed lysis reagent initially perforates the cell membranes while leaving the cells largely intact. The fluorescence marker labels the intracellular nucleic acids (mostly RNA) in the second step. The composition of these two reagents effects a mild reaction with the blood cells, so that almost all of the blood cells' structure remains intact. Thus, optimal separation is achieved, particularly of lymphocytes and monocytes. The prepared sample is then analysed using fluorescence flow cytometry. The measurement signals related to side scatter (SSC) and side fluorescence (SFL) are analysed and depicted in a scattergram. Cells with similar cytochemical properties fall within the same area in the scattergram and can be separated using an advanced software algorithm. The WBC differential channel provides counts of different white blood cell subpopulations including immature granulocytes (IG), and flags information in cases of abnormalities. The ANC is measured directly (ie, not calculated).
Materials used for calibration curve & concentration	Per applicant, a calibration is not necessary. No QC sample preparation is required. Quality control samples (XN-CHECK Level 1, XN-CHECK Level 2 and XN-CHECK Level 3), are commercially available
Validated assay range	0.05 to 440 × 10^3 cells/µL (=×10^9cells/L)
Material used for QCs & concentration	XN-Check Level 1: XN-sampler #1 1.18 × 10^9 cells/L Lot #51661101 XN-sampler #2 1.19 × 10^9 cells/L Lot #51661101 XN-sampler #1 1.11 × 10^9 cells/L Lot #52221101 XN-sampler #2 1.12 × 10^9 cells/L Lot #52221101 XN-sampler #1 1.17 × 10^9 cells/L Lot #52781101 XN-sampler #2 1.77 × 10^9 cells/L Lot #52781101 XN-sampler #1 1.15 × 10^9 cells/L Lot #53341101 XN-sampler #2 1.14 × 10^9 cells/L Lot #53341101 XN-sampler #1 1.23 × 10^9 cells/L Lot #60251101 XN-sampler #2 1.23 × 10^9 cells/L Lot #60251101 XN-sampler #1 1.22 × 10^9 cells/L Lot #60811101 XN-sampler #2 1.23 × 10^9 cells/L Lot #60811101 XN-sampler #1 1.11 × 10^9 cells/L Lot #61371101

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	XN-sampler #2 1.11 × 10^9 cells/L Lot #61371101 XN-Check Level 2: XN-sampler #1 3.05 × 10^9 cells/L Lot #51661102 XN-sampler #2 3.05 × 10^9 cells/L Lot #51661102 XN-sampler #1 2.91 × 10^9 cells/L Lot #52221102 XN-sampler #2 2.92 × 10^9 cells/L Lot #52221102 XN-sampler #1 2.85 × 10^9 cells/L Lot #52781102 XN-sampler #2 2.89 × 10^9 cells/L Lot #52781102 XN-sampler #1 2.86 × 10^9 cells/L Lot #53341102 XN-sampler #2 2.88 × 10^9 cells/L Lot #53341102 XN-sampler #1 3.01 × 10^9 cells/L Lot #60251102 XN-sampler #2 3.06 × 10^9 cells/L Lot #60251102 XN-sampler #1 3.00 × 10^9 cells/L Lot #60811102 XN-sampler #2 3.03 × 10^9 cells/L Lot #60811102 XN-sampler #1 2.86 × 10^9 cells/L Lot #61371102 XN-sampler #2 2.85 × 10^9 cells/L Lot #61371102 XN-Check Level 3: XN-sampler #1 7.83 × 10^9 cells/L Lot #51661102 XN-sampler #2 7.90 × 10^9 cells/L Lot #51661102 XN-sampler #1 7.56 × 10^9 cells/L Lot #52221102 XN-sampler #2 7.55 × 10^9 cells/L Lot #52221102 XN-sampler #1 7.64 × 10^9 cells/L Lot #52781102 XN-sampler #2 7.70 × 10^9 cells/L Lot #52781102 XN-sampler #1 7.68 × 10^9 cells/L Lot #53341102 XN-sampler #2 7.65 × 10^9 cells/L Lot #53341102 XN-sampler #1 7.52 × 10^9 cells/L Lot #60251102 XN-sampler #2 7.61 × 10^9 cells/L Lot #60251102 XN-sampler #1 7.84 × 10^9 cells/L Lot #60811102 XN-sampler #2 7.90 × 10^9 cells/L Lot #60811102 XN-sampler #1 7.47× 10^9 cells/L Lot #61371102 XN-sampler #2 7.45 × 10^9 cells/L Lot #61371102.
Minimum required dilutions (MRDs)	NA
Source & lot of reagents (LBA)	

Reagent	Lot Number	Expiration Date (DD/MM/YYYY)	Storage Temp
Cellpack DCL (diluent)	AM4019	19/12/2015	23°C ± 5°C
(b) (4)	AM5023	16/10/2016	23°C ± 5°C
	AM5027	29/12/2016	23°C ± 5°C
	AM5028	02/01/2017	23°C ± 5°C
	AM5033	31/01/2017	23°C ± 5°C
	AM5036	17/02/2017	23°C ± 5°C
	AM5045	08/04/2017	23°C ± 5°C
	AM5050	05/05/2017	23°C ± 5°C
	AM5055	17/05/2017	23°C ± 5°C
	AM5056	17/05/2017	23°C ± 5°C
	AM5060	16/06/2017	23°C ± 5°C
Cellpack DFL (diluent)	A5005	23/03/2016	23°C ± 5°C
(b) (4)	A5008	24/04/2016	23°C ± 5°C
	A5010	19/05/2016	23°C ± 5°C
	A5011	17/06/2016	23°C ± 5°C
	A5021	19/11/2016	23°C ± 5°C
Sulfolyser	A5008	27/04/2016	23°C ± 5°C

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	(b) (4)	A5009	16/06/2016	23°C ± 5°C
		A5011	25/06/2016	23°C ± 5°C
		A5012	30/06/2016	23°C ± 5°C
		A5020	20/11/2016	23°C ± 5°C
		A5021	30/11/2016	23°C ± 5°C
	Flurocell WDF	A5023	11/06/2016	23°C ± 5°C
	(b) (4)	A5027	09/07/2016	23°C ± 5°C
		A5030	27/07/2016	23°C ± 5°C
		A5037	07/09/2016	23°C ± 5°C
		A5041	01/10/2016	23°C ± 5°C
		A5050	30/11/2016	23°C ± 5°C
		A5052	15/12/2016	23°C ± 5°C
	Flurocell WNR	A5048	29/05/2016	23°C ± 5°C
	(b) (4)	A5051	22/06/2016	23°C ± 5°C
		A5055	29/07/2016	23°C ± 5°C
		A5059	01/09/2016	23°C ± 5°C
		A5065	27/10/2016	23°C ± 5°C
		A5068	01/12/2016	23°C ± 5°C
	Lysercell WDF	A5013	12/05/2016	23°C ± 5°C
	(b) (4)	A5006	09/03/2016	23°C ± 5°C
		A5013	12/05/2016	23°C ± 5°C
		A5016	03/06/2016	23°C ± 5°C
		A5018	09/06/2016	23°C ± 5°C
		A5021	07/07/2016	23°C ± 5°C
		A5022	10/07/2016	23°C ± 5°C
		A5027	03/09/2016	23°C ± 5°C
		A5036	12/11/2016	23°C ± 5°C
	Lysercell WNR	A5016	25/05/2016	23°C ± 5°C
	Cat No: 6510213001	A5021	10/06/2016	23°C ± 5°C
		A5021	10/06/2016	23°C ± 5°C
		A5024	06/07/2016	23°C ± 5°C
		A5025	08/07/2016	23°C ± 5°C
		A5033	08/09/2016	23°C ± 5°C
		A5036	16/10/2016	23°C ± 5°C
		A5040	05/11/2016	23°C ± 5°C
		A5043	08/12/2016	23°C ± 5°C
	Qualification Data Reference	ACL CM2115 electronic study file	ACL CM2115 electronic study file	ACL CM2115 electronic study file
Regression model & weighting	SYSMEX XN-3000 instrument installation correlation data (vs previous instrument in use at ACL - SYSMEX XE series) acceptable criteria for correlation study is Slope 0.95 – 1.05 and R2 >0.95. Overall CV for validation – 2.0% (for full details refer to the table below) and for graphs refer to Figure 1 of the validation report.			

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	XN sampler 1 vs XE		XN sampler 2 vs XE		XN sampler 1 vs XN sampler 2	
	WBC	Neut%	WBC	Neut%	WBC	Neut%
Slope	0.9788	0.9604	0.9704	0.9693	1.0074	1.0005
R^2	0.9976	0.9946	0.9979	0.9933	0.9992	0.9963

Validation parameters	Method validation summary		Acceptability
Calibration curve performance during accuracy & precision[Error! Reference source not found.]	Number of standard calibrators from LLOQ to ULOQ	NA	N/A
	Cumulative accuracy (%bias) from LLOQ to ULOQ Product A	NA	N/A
	Cumulative precision (%CV) from LLOQ to ULOQ Product A	NA	N/A
QCs performance during accuracy & precision	***Cumulative accuracy (%bias) in 3 QCs*** *QCs:* **XN-Check Level 1** ***XN*-Check Level 2** ***XN*-Check Level 3**	 L-1(-0.78 to 1.60%) L-2 (-0.71 to 1.68%) L-3 (-0.89 to 0.89%)	Yes
	Inter-batch %CV *QCs:XN-I* *XN-II*	 ≤ 4.8% ≤ 7.6%	Yes
	Total Error (TE) *QCs:* Not Evaluated	 Not Evaluated	N/A
Selectivity & matrix effect	NA		N/A
Interference & specificity	Not Evaluated		N/A
Hemolysis effect	Not Evaluated		N/A
Lipemic effect	Not Evaluated		N/A
Dilution linearity & hook effect	NA		N/A
Bench-top/ process stability	Stability study was performed 15 May 2018 to 18 May 2018– Analysis of 15 patient samples stored for 72 hours post original analysis at room temperature and re-analyzed at 24-hour intervals. Conclusion: Samples were stable up to 72 hours post original analysis with a CV ≤3.75%.		Yes
Freeze-Thaw stability	NA		N/A
Long-term storage	NA		N/A
Parallelism	NA		N/A
Carry over	Analyzed one high concentration sample three times followed by three replicates of one low concentration sample in five runs, per SYSMEX XN-3000 IFU August 2012. Result was ≤1.0 %		Yes
Method performance in study			
The Determination of Absolute Neutrophil Count in Human K_2EDTA Whole Blood Samples By Flow Cytometry From Pfizer Clinical Protocol ZIN-130-1505			

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Assay passing rate	100% samples passed	Yes
Standard curve performance	• NA	N/A
QC performance	• Cumulative bias range: -0.89 to 1.68% • Cumulative precision: ≤2.0% CV • TE: Not Evaluated	Yes
Method reproducibility	ISR: NA	N/A
Study sample analysis/ stability	All TATs within the 72-hour period of stability confirmed in validation report The applicant stated that TAT was approximated as time elapsed between sample collection and time samples were received in the laboratory. Analysis times were not available, so Receipt date and time was utilized as samples are analyzed within 1 hour of receipt. Where receipt date and time were not available, data entry date and time were utilized.	

Note: NA has been marked for instances where the item or assessment is not applicable to either the matrix, format, or methodology of the assay.

Abbreviations: ANC = absolute neutrophil count; CV = coefficient of variation; EDTA = ethylenediaminetetraacetic acid; IG = immature granulocytes; ISR = incurred samples reanalysis; K_2EDTA = dipotassium ethylenediaminetetraacetic acid; LBA = ligand binding assay; LLOQ = lower limit of quantification; MRD = minimum required dilution; NA = not applicable; QC = quality control; RNA = ribonucleic acid; SFL = side fluorescence; SSC = signals related to side scatter; TAT = thrombin-antithrombin complex; TE = total error; ULOQ = upper limit of quantification; WBC = white blood cells

Reference ID: 4622626

BLA 761111 Nyvepria (pegfilgrastim-apgf)				

Signatures

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Nonclinical Reviewer	Emily Place, PhD	OOD/DHOT	Sections: 1.6, 5, and 12.2	**Select one:** ☑ Authored ☐ Approved
	Signature: Emily J. Place -S	Digitally signed by Emily J. Place -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Emily J. Place -S, 0.9.2342.19200300.100.1.1=2001028525 Date: 2020.06.09 17:20:52 -04'00'		
Nonclinical Team Leader	Brenda Gehrke, PhD	OOD/DHOT	Sections: 1.6, 5, and 12.2	**Select one:** ☑ Authored ☑ Approved
	Signature: Brenda Gehrke -S	Digitally signed by Brenda Gehrke -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Brenda Gehrke -S, 0.9.2342.19200300.100.1.1=0012062023 Date: 2020.06.09 17:04:10 -04'00'		
Clinical Pharmacology Reviewer	Xiling Jiang, PhD	OCP/DCPI	Sections: 6 and 12.3	**Select one:** ☑ Authored ☐ Approved
	Signature: Xiling Jiang -S	Digitally signed by Xiling Jiang -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Xiling Jiang -S, 0.9.2342.19200300.100.1.1=2001167656 Date: 2020.06.10 09:30:27 -04'00'		
Clinical Pharmacology Team Leader	Salaheldin Hamed, PhD	OCP/DCPI	Sections: 6 and 12.3	**Select one:** ☐ Authored ☑ Approved
	Signature: Salaheldin S. Hamed -S	Digitally signed by Salaheldin S. Hamed -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2000952138, cn=Salaheldin S. Hamed -S Date: 2020.06.10 09:25:18 -04'00'		
Product Quality Reviewer	Xu (Michael) Di, PhD	OBP/DBRRIII	Sections: 1.4, 1.6, 4.1, 8.3 and 11.2	**Select one:** ☑ Authored ☐ Approved
	Signature: Xu Di -S	Digitally signed by Xu Di -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Xu Di -S, 0.9.2342.19200300.100.1.1=2000630133 Date: 2020.06.09 16:14:31 -04'00'		
Product Quality Team Leader/ATL	Ram Sihag, PhD	OBP/DBRRIII	Sections: 1.4,1.6, 4.1,8.3, 11.2	**Select one:** ☐ Authored ☑ Approved
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Associate Director for Labeling	Virginia Kwitkowski, MS, ACNP-BC	OCHEN/DNH	Sections: 8	**Select one:** ☑ Authored ☐ Approved
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Statistical Reviewer	Wenjuan Gu, PhD	OB/DBIX	Sections: 6.4	**Select one:** ☑ Authored ☐ Approved
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Statistical Team Leader	Yeh-Fong Chen, PhD	OB/DBIX	Sections: 6.4	**Select one:** ☑ Authored ☑ Approved
	Signature: Yeh Fong Chen -S Digitally s gned by Yeh Fong Chen S DN: c=US o=U S Government ou=HHS ou=FDA ou=People cn=Yeh Fong Chen S 0 9 2342 19200300 100 1 1=1300157970 Date: 2020 06 10 08 11 50 04 00			
Clinical Reviewer	Hyon-Zu Lee, PharmD	OCHEN/DNH	Sections: 2, 3, 7, 8, 10, 11 and 12.1	**Select one:** ☑ Authored ☐ Approved
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Clinical Team Leader/Cross Disciplinary Team Leader	Kathy Robie Suh, MD, PhD	OCHEN/DNH	Sections: 1, 2, 3, 4, 7, 8, 9, 10, 11 and 12.1	**Select one:** ☑ Authored ☑ Approved
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Division Director (Clinical)	Ann Farrell, MD	OCHEN/DNH	Sections:	**Select one:** ☑ Authored ☑ Approved
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US Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

Biometrics Division: VI

NDA No.:	761111
Date Received By the Center:	6/10/2019
Drug Name:	PF-06881894
Sponsor:	Hospira, Inc., a Pfizer Company
Indication:	Decrease the incidence of infection, as manifested by febrile neutropenia, in patients with nonmyeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a clinically significant incidence of febrile neutropenia
Dosage Form:	Injection, Solution
Strengths:	6 mg/ 0.6 mL
Review Finished Date:	3/24/2020
Statistical Reviewer:	Xiaoyu Cai, Ph.D
Secondary Reviewer:	Meiyu Shen, Ph.D
Project Manager:	Michael Gwathmey

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Reference ID: 4680682

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1. Executive summary and recommendation

In this review, I analyzed the Applicant's data for one Tier 1 quality attribute (QA), In Vitro Potency. Tier 1 statistical equivalence testing was performed pair-wise between the proposed biosimilar product PF-06881894 and US-licensed Neulasta, between EU-approved Neulasta and US-licensed Neulasta, and between PF-06881894 and EU-approved Neulasta. The statistical equivalence testing was conducted using two methods: TOST method and MWCMLE method.

Ten independent DP lots of PF-06881894, 14 DP lots of US-licensed Neulasta and 14 DP lots of EU-approved Neulasta were used for equivalence test of the Tier 1 QA. My independent analysis shows that the In Vitro Potency passes the equivalence test using both TOST method and MWCMLE method, and support a demonstration that the proposed biosimilar PF-06881894 is highly similar to US-licensed Neulasta and also support the analytical bridge between US-licensed Neulasta and EU-approved Neulasta.

2. Introduction

On June 10, 2019, Hospira, Inc., a Pfizer Company (the Applicant) submitted a 351(k) BLA to the US Food and Drug Administration (the Agency), which included an analytical similarity assessment of comparing the proposed biosimilar product PF-06881894, US-licensed Neulasta and EU-approved Neulasta.

In the Applicant's data analysis for the Tier 1 quality QA, In Vitro Potency, 10 independent PF-06881894 DP lots were used to compare with 14 DP lots of US-licensed Neulasta and 14 DP lots of EU-approved Neulasta.

My independent analysis on the Applicant's provided data shows that the Tier 1 QA, In Vitro Potency, passes the equivalence test and support a demonstration that the proposed biosimilar PF-06881894 is highly similar to US-licensed Neulasta and also support the analytical bridge between US-licensed Neulasta and EU-approved Neulasta.

3. The FDA statistical reviewer's analysis

A tiered approach was used by the Applicant and was agreed by the Agency during previous discussion with the Applicant. That is, product QAs amenable to statistical evaluation are assigned to three tiers based on their criticality. The QAs with potential highest risk in product quality, efficiency, safety, and PK/PD are generally assigned to Tier 1, in which analytical similarity is assessed by statistical equivalence test. QAs with lower impact are generally assigned to Tier 2 and their analytical similarity is evaluated by Quality Range approach. That is, a high percentage of the biosimilar data should be covered by $(\hat{\mu}_R - X\hat{\sigma}_R\ ,\ \hat{\mu}_R + X\hat{\sigma}_R)$, where $\hat{\mu}_R$ is the sample mean, $\hat{\sigma}_R$ is the sample standard deviation based on the reference product lots, and the multiplier X typically ranges from 2 to 4. The QAs with the lowest risk are generally assigned to Tier 3 and their analytical similarity is evaluated by side-by-side comparison using graphic display. This review focuses on the equivalence test for Tier 1 QAs.

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3.1 Data analyzed

The analytical data for the Tier 1 quality attribute (QA), In Vitro Potency, was submitted by the Applicant in the original submission on June 10, 2019. The analytical data include 10 independent DP lots of PF-06881894, 14 DP lots of US-licensed Neulasta and 14 DP lots of EU-approved Neulasta. The summary of the applicant's submitted data of PF-06881894, US-licensed Neulasta and EU-approved Neulasta DP lots used in my independent analysis are provided in **Table 1, 2 and 3**.

Table 1. Summary of Biosimilar Product (PF-06881894) DP lots

Lot Number	Age at Time of Test (Months)	Date of Test	Relative Potency (%)
2056034	27	Jun 2016	99.9
2078064	24	Jun 2016	95.1
2082094	20	Jun 2016	91.3
2051124	18	Jun 2016	102
2573125	6	Jun 2016	103
2459066	4	Oct 2016	103
213047	14	Jun 2018	95
3058V	6	Nov 2018	92
4058V	6	Dec 2018	98
2068V	5	Nov 2018	88

Table 2. Summary of US Reference Product (US-licensed Neulasta) DP lots

Lot Number	Age at Time of Test (Months)	Date of Test	Relative Potency (%)
1057097	20	Oct 2016	101
1057133	20	Jun 2016	91.6
1057373	17	Jun 2016	98.4
1057416	19	Oct 2016	99.8
1060058	12	Jun 2016	106
1064191	13	Oct 2016	99.2
1071087	29	Jun 2018	105
1072044	23	Jun 2018	93
1078875	25	Jun 2018	93
1083446	20	Dec 2018	100
1084476	19	Jun 2018	100
1085896	14	Jun 2018	115
1089511	24	Nov 2018	90
1094104	18	Dec 2018	92

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Table 3. Summary of EU Reference Product (EU-approved Neulasta) DP lots

Lot Number	Age at Time of Test (Months)	Date of Test	Relative Potency (%)
1058436B	25	Sep 2016	99.0
1060064C	20	Jun 2016	91.7
1061466C	20	Jun 2016	92.3
1065041B	17	Sep 2016	103
1066011C	33	Jun 2018	99
1069490C	9	Sep 2016	102
1079877A	20	Jun 2018	110
1085288A	23	Dec 2018	97
1087927A	18	Dec 2018	99
1088493A	18	Dec 2018	102
1088500D	13	Dec 2018	92
1090139B	13	Dec 2018	89
1093686K	12	Dec 2018	94
1094582	10	Dec 2018	97

3.2 The statistical equivalence testing methods

In this review, I used the two equivalence testing methods which are also agreed and used by the Applicant, TOST method and MWCMLE method.

TOST method

Let μ_T and μ_R be the population mean of the QA for the test product and the population mean of the QA for the reference product, respectively. Let σ_R be the standard deviation of the QA of interest for the reference product. To conclude the equivalence in the QA of interest between the test product and the reference product, we aim to reject the null hypothesis of the following null and alternative hypotheses (Tsong et al., 2017) :

$$\begin{aligned} H_0 &: \mu_T - \mu_R \le \theta_1 \text{ or } \mu_T - \mu_R \ge \theta_2 \\ H_1 &: \theta_1 < \mu_T - \mu_R < \theta_2 \end{aligned} \tag{1}$$

where $\theta_1 = -1.5\sigma_R$, $\theta_2 = 1.5\sigma_R$, θ_1 and θ_2 are equivalence margins.

In the current practice for TOST method, we reject H_0 if 90% CI for the mean difference in the QA of interest falls within $(-1.5\sigma_R, 1.5\sigma_R)$. In other words, we conclude that the equivalence in the QA of interest between the test product and the reference product if 90% CI for the mean difference in the QA of interest falls within $(-1.5\sigma_R, 1.5\sigma_R)$. This specific equivalence margin was set as 1.5 times the standard deviation of the QA for the reference product to ensure an adequate power for the case in which a small but sufficient number of lots are available for testing. For example, the probability of rejecting H_0 in the above two one-sided tests procedure with the

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equivalence margin being $\pm 1.5\sigma_R$ is 87% if the true mean difference is $0.125\sigma_R$ for a sample size of 10 test product lots and 10 reference product lots.

First, we estimate σ_R by the sample variability of the reference product, and then θ_1 and θ_2 are treated as a constant, but not a random variable in the statistical analysis.

Let X_{Tj} be the observed value of the QA of interest for Lot *j* of the test product (the proposed biosimilar product) and X_{Rj} be the observed value of the QA of interest for Lot *j* of the reference product. Since the two products are manufactured by two manufacturers, two products are independent. $\bar{X}_i = \sum_{j=1}^{n_i} X_{ij} \Big/ n_i$, and $S_i^2 = \sum_{j=1}^{n_i} \left(X_{ij} - \bar{X}_i\right) \Big/ \left(n_i - 1\right)$, where n_i is the number of lots in the ith product, $i = T, R$.

Under the unequal variance of the test product and the reference product, the (1-2α)*100% CI of the mean difference in the QA of interest using the TOST method can be calculated as:

$$\left(\bar{X}_T - \bar{X}_R - t_\alpha(\nu)\sqrt{\frac{S_T^2}{n_T} + \frac{S_R^2}{n_R}},\ \bar{X}_T - \bar{X}_R + t_\alpha(\nu)\sqrt{\frac{S_T^2}{n_T} + \frac{S_R^2}{n_R}}\right).$$

where $t_\alpha(\nu)$ is the 1-α quantile and ν is the degrees of freedom calculated by Satterthwaite's approximation.

If $n_R > 1.5n_T$, the (1-2α)*100% sample size imbalanced adjusted CI of the mean difference in the QA of interest using the TOST method can be calculated as (Dong et. al., 2017):

$$\left(\bar{X}_T - \bar{X}_R - t_\alpha(\nu^*)\sqrt{\frac{S_T^2}{n_T} + \frac{S_R^2}{n_R^*}},\ \bar{X}_T - \bar{X}_R + t_\alpha(\nu^*)\sqrt{\frac{S_T^2}{n_T} + \frac{S_R^2}{n_R^*}}\right).$$

where $n_R^* = \min\left(n_R, 1.5n_T\right)$ and $\nu^* = \dfrac{\left(\dfrac{S_T^2}{n_T} + \dfrac{S_R^2}{n_R^*}\right)^2}{\dfrac{1}{n_T - 1}\left(\dfrac{S_T^2}{n_T}\right)^2 + \dfrac{1}{n_R - 1}\left(\dfrac{S_R^2}{n_R^*}\right)^2}$.

If $n_T > 1.5n_R$, we can apply a similar approach as above with $n_T^* = \min(1.5\times n_R, n_T)$ for the CI calculation.

MWCMLE Method

The TOST method can result in inflating type I error rate and reducing power when sample size is not sufficiently large, as pointed out by Dong et. al. (2017). Hence, one needs to consider σ_R as a parameter to be estimated with the study data. We recommend the MWCMLE method for reducing the type I error rate to the significance level (5%) and increasing the power to 86% for the true mean difference is $0.125\sigma_R$ for a sample size of 10 test product lots and 10 reference product lots.

The null and alternative hypotheses in equation (1) for reference scaled equivalence can be rewritten as the two-one-sided hypothesis testing as follows.

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$$H_{0U}: \mu_T - \mu_R \geq f\sigma_R \text{ vs. } H_{aU}: \mu_T - \mu_R < f\sigma_R$$

$$H_{0L}: \mu_T - \mu_R \leq -f\sigma_R \text{ vs. } H_{aL}: \mu_T - \mu_R > -f\sigma_R$$

where μ_T and μ_R are the population means of the test product and the reference product, respectively; σ_R is the Standard Deviation (SD) of the reference product; and f is 1.7.

The test statistics of the MWCMLE method to test H_{0U} and H_{0L} in (1) are as follows:

$$W_L = \frac{\hat{\mu}_T - \hat{\mu}_R + f\tilde{\sigma}_R}{\sqrt{\frac{\breve{\sigma}^2_{T_L}}{n_T} + \left(\frac{1}{n_R} + \frac{f^2 V_{n_R}}{n_R - 1}\right)\breve{\sigma}^2_{R_L}}} \text{ and } W_U = \frac{\hat{\mu}_T - \hat{\mu}_R - f\tilde{\sigma}_R}{\sqrt{\frac{\breve{\sigma}^2_{T_U}}{n_T} + \left(\frac{1}{n_R} + \frac{f^2 V_{n_R}}{n_R - 1}\right)\breve{\sigma}^2_{R_U}}},$$

where $\hat{\mu}_T$, $\hat{\mu}_R$, and $\tilde{\sigma}_R$ denote the MLE for the mean of the test product, the MLE for the mean of the reference product, and the sample estimator for the SD of the reference product, respectively. When X_T follows $N(\mu_T, \sigma_T^2)$ distribution and X_R follows $N(\mu_R, \sigma_R^2)$ distribution, $\hat{\mu}_T = \frac{\sum_{i=1}^{n_T} X_{T_i}}{n_T} = \bar{X}_T$, $\hat{\mu}_R = \frac{\sum_{i=1}^{n_R} X_{R_i}}{n_R} = \bar{X}_R$, $\tilde{\sigma}_R = \sqrt{\frac{\sum_{i=1}^{n_R}\left(X_{R_i} - \hat{\mu}_R\right)^2}{n_R - 1}}$ where n_T and n_R denote the sample sizes of test product lots and reference lots, respectively. σ_T^2 is the variance of the test product. Under the null hypothesis, each test follows an asymptotically standard normal distribution. The overall null hypothesis is rejected by either of the following two criteria: first, $W_L > Z_{1-\alpha}$ and $W_U < -Z_{1-\alpha}$ at significance level α, where Z_p is the 100pth percentile of the standard normal distribution; or second, the intersection (L, U) of two one-sided (1- α)*100% confidence intervals falls within the equivalence margin $(-f\tilde{\sigma}_R, f\tilde{\sigma}_R)$ and is listed as follows.

$$(L, U) =$$

$$\left(\hat{\mu}_T - \hat{\mu}_R - Z_{1-\alpha}\sqrt{\frac{\breve{\sigma}^2_{T_L}}{n_T} + \left(\frac{1}{n_R} + \frac{f^2 V_{n_R}}{n_R - 1}\right)\breve{\sigma}^2_{R_L}}, \hat{\mu}_T - \hat{\mu}_R + Z_{1-\alpha}\sqrt{\frac{\breve{\sigma}^2_{T_U}}{n_T} + \left(\frac{1}{n_R} + \frac{f^2 V_{n_R}}{n_R - 1}\right)\breve{\sigma}^2_{R_U}}\right)$$

Following the above same logic of the sample size imbalanced adjustment, the Adjusted MWCMLE statistics for imbalanced sample (AMWCMLE) can be written as follows:

$$W_{L'} = \frac{\hat{\mu}_T - \hat{\mu}_R + f\tilde{\sigma}_R}{\sqrt{\frac{\breve{\sigma}^2_{T_L}}{n_T} + \left(\frac{1}{n_R^*} + \frac{f^2 V_{n_R}}{n_R - 1}\right)\breve{\sigma}^2_{R_L}}} \text{ and } W_{U'} = \frac{\hat{\mu}_T - \hat{\mu}_R - f\tilde{\sigma}_R}{\sqrt{\frac{\breve{\sigma}^2_{T_U}}{n_T} + \left(\frac{1}{n_R^*} + \frac{f^2 V_{n_R}}{n_R - 1}\right)\breve{\sigma}^2_{R_U}}},$$

where the sample sizes of adjusted reference lots, n_R^* , is equal to $\min(1.5 \times n_T, n_R)$. n_T and n_R denote the sample sizes of test product lots and the sample sizes of reference product lots, respectively. More details are described in Weng et al. (2018).

In the following analysis, the nominal size is set as $\alpha = 0.05$.

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3.3 Equivalence test for In Vitro Potency

For In Vitro Potency, the data are summarized in **Table 4 and** illustrated in **Figure 1**. The equivalence test results using TOST method are summarized in **Table 5** and graphically displayed in **Figure 2**. The equivalence test results using MWCMLE method are summarized in **Table 6** and graphically displayed in **Figure 3**. The equivalence test results using both methods show that In Vitro Potency passes the equivalence test and support a demonstration that the proposed biosimilar PF-06881894 is highly similar to US-licensed Neulasta and also support the analytical bridge between US-licensed Neulasta and EU-approved Neulasta.

Table 4. Summary of Data for In Vitro Potency

Product	Number of DP lots	Min, %	Max, %	Sample Mean, %	Sample SD, %	CV, %
PF-06881894	10	88	103	96.73	5.29	5.47
US-licensed Neulasta	14	90	115	98.86	6.82	6.90
EU-approved Neulasta	14	89	110	97.64	5.61	5.75

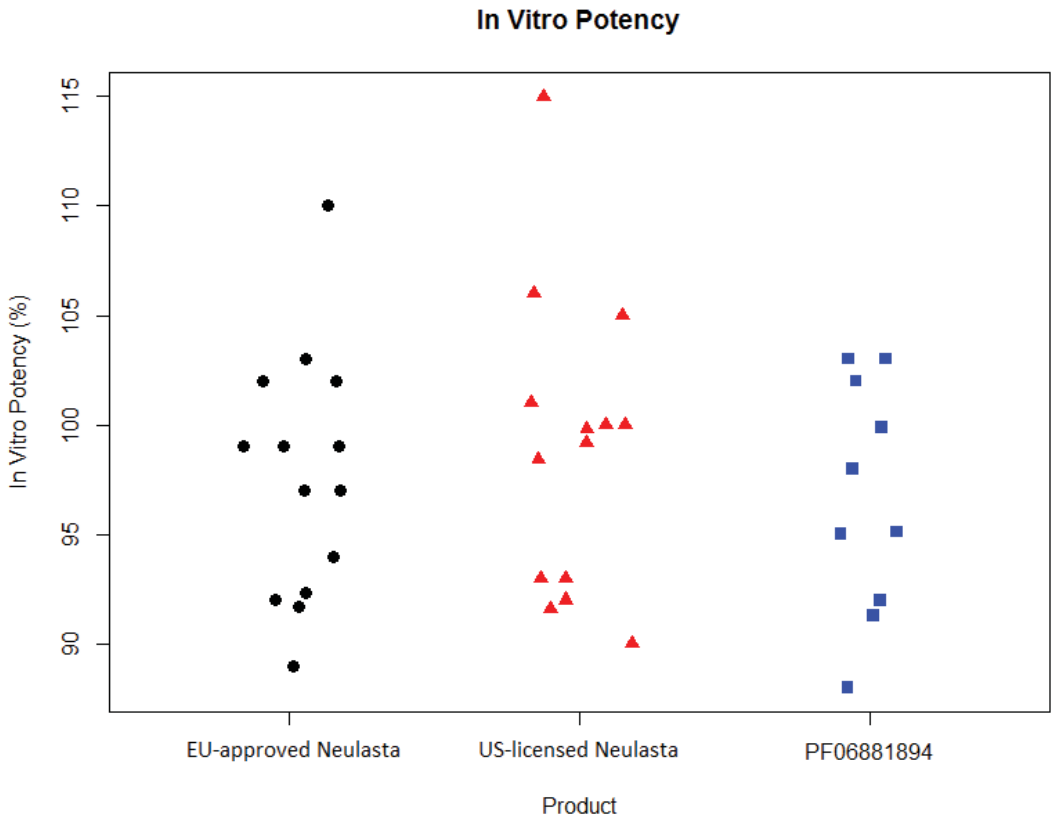

Figure 1. Illustration of In Vitro Potency Data

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Table 5. Equivalence Test Results for In Vitro Potency Data Using TOST Method

Comparison	Number of DP lots	Mean Difference, %	90% CI for Mean Difference, %	Equivalence Margin, %	Statistical Equivalence
PF-06881894 vs. US-licensed Neulasta	(10,14)	-2.13	(-6.38, 2.12)	(-10.23, 10.23)	**Yes**
PF-06881894 vs. EU-approved Neulasta	(10,14)	-0.91	(-4.79, 2.96)	(-8.42,8.42)	**Yes**
EU-approved Neulasta vs. US-licensed Neulasta	(14,14)	-1.21	(-5.25, 2.82)	(-10.23,10.23)	**Yes**

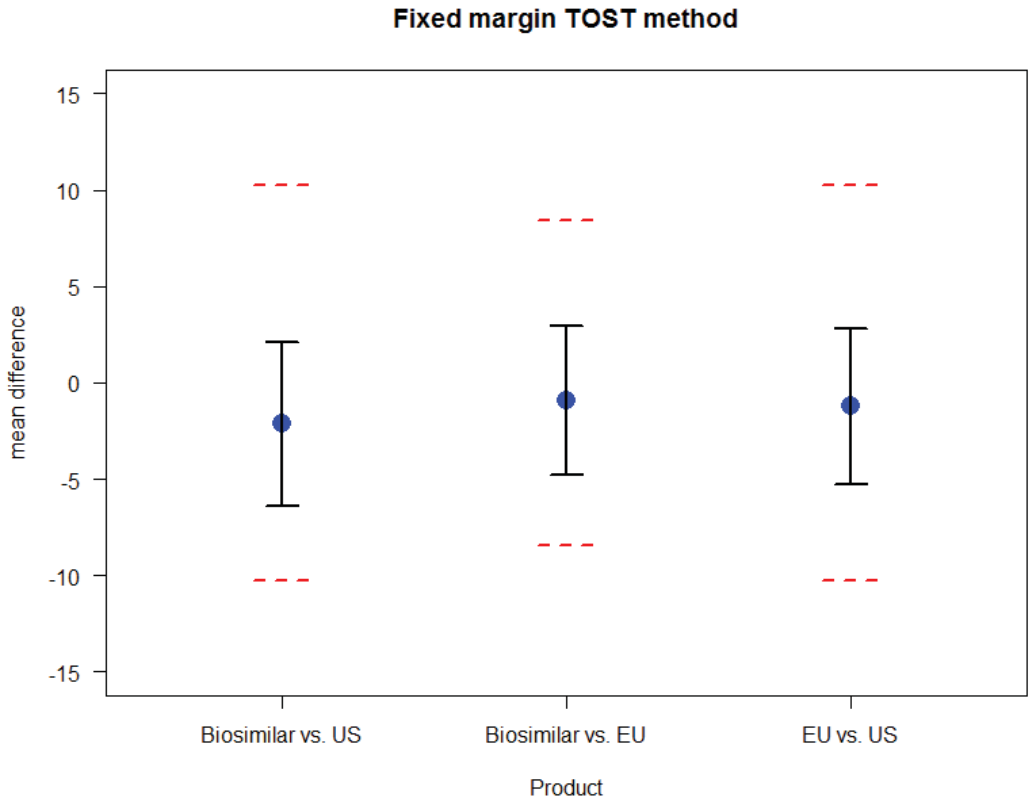

Figure 2. Equivalence Test Results for In Vitro Potency Data Using TOST Method
Black solid line: 90% confidence intervals for mean difference
Red dashed line: Equivalence margin

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Table 6. Equivalence Test Results for In Vitro Potency Data Using MWCMLE Method

Comparison	Number of DP lots	Mean Difference, %	90% CI for Mean Difference, %	Equivalence Margin, %	Statistical Equivalence
PF-06881894 vs. US-licensed Neulasta	(10,14)	-2.13	(-7.36, 4.72)	(-11.59, -11.59)	**Yes**
PF-06881894 vs. EU-approved Neulasta	(10,14)	-0.91	(-5.84, 4.66)	(-9.54, 9.54)	**Yes**
EU-approved Neulasta vs. US-licensed Neulasta	(14,14)	-1.21	(-6.12, 4.33)	(-11.59, -11.59)	**Yes**

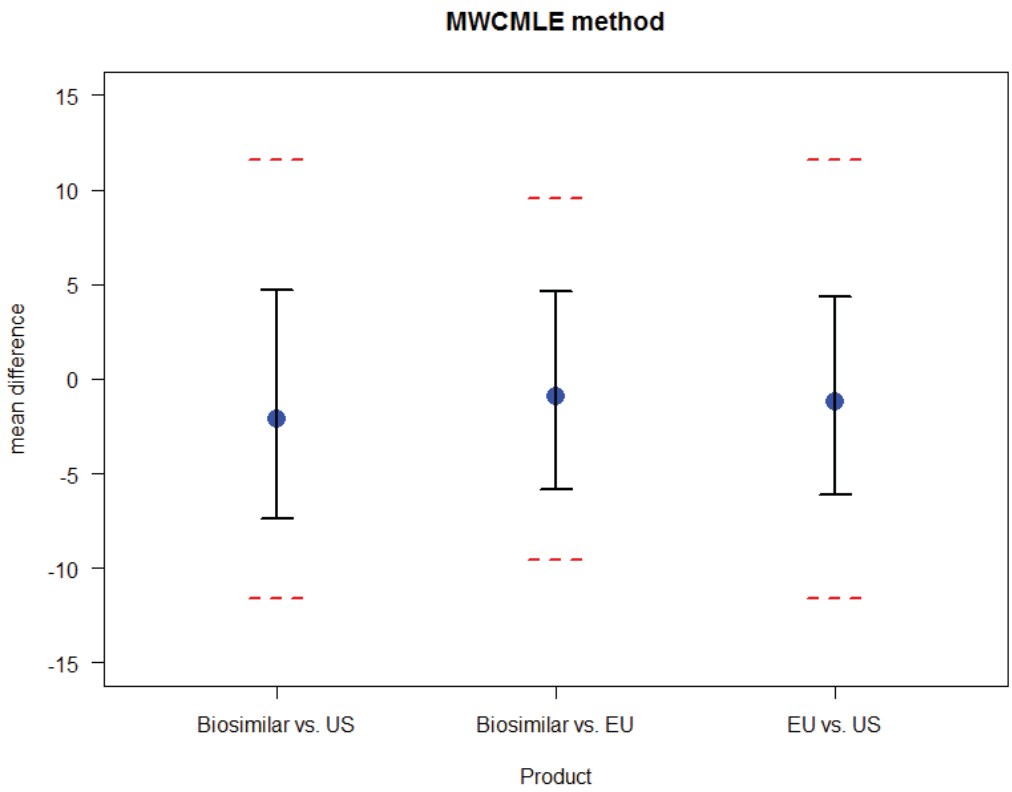

Figure 3. Equivalence Test Results for In Vitro Potency Data Using MWCMLE Method
Black solid line: 90% confidence intervals for mean difference
Red dashed line: Equivalence margin

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4. Conclusion and recommendation

The results from the statistical equivalence analyses for the Tier 1 QA In Vitro Potency support a demonstration that the proposed biosimilar PF-06881894 is highly similar to US-licensed Neulasta and also support the analytical bridge between US-licensed Neulasta and EU-approved Neulasta.

References

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Tsong, Yi, Xiaoyu Dong, and Meiyu Shen. 2017. "Development of Statistical Methods for Analytical Similarity Assessment." Journal of Biopharmaceutical Statistics 27 (2). Taylor & Francis: 197–205.

Weng, Yu-Ting, Yi Tsong, Meiyu Shen, Chao Wang. 2018. "Improved Wald Test for Reference Scaled Equivalence Assessment of Analytical Biosimilarity". International Journal of Clinical Biostatistics and Biometrics. DOI: 10.23937/2469-5831/1510016

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