CLINICAL REVIEW

Application Number	BLA 761080
Application Type	Original 351(k)
Priority or Standard	Standard
Submit Date(s)	9/21/2017
Received Date(s)	9/21/2017
BSUFA Goal Date	7/21/2018
Review Date	6/12/2018
Office / Division	Office of Hematology and Oncology Products / Division of Hematology Products
Primary Reviewer	Lea Cunningham, MD
Team Leader	Donna Przepiorka, MD, PhD
Nonproprietary Name	Filgrastim.aafi (referred to as "PF-06881893" by the applicant)*
Trade Name	Nivestym (proprietary, conditionally acceptable)
Therapeutic Class	Leukocyte Growth Factor
Applicant	Hospira, Inc.
Formulation(s)	Injection - 300 mcg/0.5 mL PF-06881893 - 480 mcg/0.8 mL PF-06881893
Indication(s)	• To decrease the incidence of infection, as manifested by febrile neutropenia, in patients with nonmyeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a significant incidence of severe neutropenia with fever • To reduce the time to neutrophil recovery and the duration of fever, following induction or consolidation chemotherapy treatment of patients with acute myeloid leukemia (AML) • To reduce the duration of neutropenia and neutropenia-related clinical sequelae, e.g., febrile neutropenia, in patients with nonmyeloid malignancies undergoing myeloablative chemotherapy followed by bone marrow transplantation • To reduce the incidence and duration of sequelae of neutropenia (e.g., fever, infections, oropharyngeal ulcers) in symptomatic patients with congenital neutropenia, cyclic neutropenia, or idiopathic neutropenia • Mobilize autologous hematopoietic progenitor cells into the peripheral blood for collection by leukapheresis

*We refer to the product as PF-06881893 throughout this review.

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Table of Abbreviations

AE	Adverse Event
AESI	Adverse Event of Special Interest
ALT	Alanine Aminotransferase
ANC	Absolute Neutrophil Count
AST	Aspartate Aminotransferase
AUC	Area Under Curve
BID	Twice daily
BLA	Biologics License Application
BPD	Biological Product Development
CFR	Code of Federal Regulations
CI	Confidence Interval
CMax	Maximal concentration
CRP	C-reactive protein
CTCAE	Common Terminology Criteria for Adverse Events
CTD	Common Technical Document
DSN	Duration of Severe Neutropenia
EU	European Union
G-CSF	Granulocyte-Colony Stimulating Factor
GGT	Gamma Glutamyl Transferase
IND	Investigational New Drug Application
ISS	Integrated Summary of Safety
iv	Intravenous
MedDRA	Medical Dictionary for Regulatory Activities
PD	Pharmacodynamic
PF	Prefilled Syringe
PK	Pharmacokinetic
PT	Preferred Term
SAE	Serious Adverse Event
SAF	Safety Analysis Population
SC	Subcutaneous
SD	Standard Deviation
SMQN	Standardized MedDRA Narrow Query
SOC	System Organ Class
TAC	Docetaxel, Doxorubicin Cyclophosphamide
US	United States

1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

Biologics License Application (BLA) BLA761080 for PF-06881893 was submitted by Hospira, Inc. under Section 351(k) of the Public Health Service Act. PF-06881893 is a proposed biosimilar to US-licensed Neupogen,[†] and Hospira is seeking licensure of PF-06881893 for the following five indications for which US-licensed Neupogen is currently approved:

- To decrease the incidence of infection, as manifested by febrile neutropenia, in patients with nonmyeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a significant incidence of severe neutropenia with fever
- To reduce the time to neutrophil recovery and the duration of fever, following induction or consolidation chemotherapy treatment of patients with acute myeloid leukemia (AML)
- To reduce the duration of neutropenia and neutropenia-related clinical sequelae, e.g., febrile neutropenia, in patients with nonmyeloid malignancies undergoing myeloablative chemotherapy followed by bone marrow transplantation
- Mobilize autologous hematopoietic progenitor cells into the peripheral blood for collection by leukapheresis
- To reduce the incidence and duration of sequelae of neutropenia (e.g., fever, infections, oropharyngeal ulcers) in symptomatic patients with congenital neutropenia, cyclic neutropenia, or idiopathic neutropenia

Upon review, three clinical studies were performed in healthy volunteers. All three studies were adequate and well controlled providing meaningful safety data. There are no clinically meaningful differences between PF-06881893 and US-licensed Neupogen for safety endpoints.

1.2 Basis for the Regulatory Recommendation

The clinical studies used to support this BLA for PF-06881893 as a proposed biosimilar to US-licensed Neupogen include:

Clinical Trial Identifier	Clinical Trial Title
C1121012 US	A Phase I, Randomized Open-Label, 2-Period, Parallel Arm Study to Assess the Immunogenicity of Multiple Subcutaneous (SC) Doses of "PF-06881893" (US) or US-Approved Neupogen® Reference Product in Healthy Volunteers
ZIN-FIL-1501 (C1121003) US	A randomized open-label, multiple-dose, crossover study evaluating the pharmacokinetics and pharmacodynamics of Filgrastim to US-approved Neupogen®
ZIN-FIL-1502 (C1121002) US	A randomized open-label, single-dose, crossover study evaluating the pharmacokinetics and pharmacodynamics of Filgrastim to US-approved Neupogen® (Amgen) following subcutaneous administration to healthy volunteers.

Study C1121012 was a phase I, randomized multicenter, open-label, 2-period, parallel arm study to Assess the Immunogenicity of Multiple Subcutaneous (SC) Doses of PF-06881893 (US) or US-

[†] Throughout this review, US-licensed Neupogen refers to the product licensed in the United States, and EU-approved Neupogen refers to the product approved by the European Medicines Agency.

Approved Neupogen Reference Product in Healthy Volunteers. The primary objective was to determine the proportion of subjects with a negative baseline ADA test result and confirmed post dose positive ADA test result at any time during the study. This was a well-controlled study and no clinically significant safety differences were identified between PF-06881893 and US-Approved Neupogen.

Study ZIN-FIL-1501 was a randomized open-label, single center multiple-dose crossover study evaluating the pharmacodynamics and pharmacokinetics of PF-06881893 compared to US-approved Neupogen following subcutaneous administration to healthy volunteers. The primary objective was to determine the area under the effect curve for CD34+count, and the maximum observed CD34+ count. The secondary objective was to determine the time to the maximum observed CD34+ count. This was a well-controlled study and no clinically significant PK/PD differences were identified between PF-06881893 and US-Approved Neupogen.

Study ZIN-FIL-1502 was a randomized open-label, single center, single-dose crossover study evaluating the pharmacodynamics and pharmacokinetics of PF-06881893 compared to US-approved Neupogen following subcutaneous administration to healthy volunteers. The primary objective was to determine the area under the effect curve for CD34+count, and the maximum observed CD34+ count. The secondary objective was to determine the time to the maximum observed CD34+ count. This was a well-controlled study and no clinically significant PK/PD differences were identified between PF-06881893 and US-Approved Neupogen.

For all three clinical studies in healthy volunteers, there were no clinically meaningful differences between PF-06881893 and US-licensed Neupogen. The recommendation to approve PF-06881893 is based upon its non-inferior performance compared to US-licensed Neupogen and similar PK/PD results in the other two clinical studies.

1.3 Recommendations for Labeling

If a determination of biosimilarity is made based on the reviews of other disciplines, we agree with the applicant's proposal that labeling for PF-06881893 be comparable to the relevant sections of the current prescribing information for US-licensed Neupogen other than drug product information specific to PF-06881893.

1.4 Recommendations for Post Market Risk Evaluation and Mitigation Strategies

None.

1.5 Recommendations for Post Market Requirements and Commitments

None.

2 Introduction and Regulatory Background

2.1 Product Information

Nonproprietary Name:	PF-06881893
Proposed Trade Name:	Nivestym
Also Known As:	PF-06881893 Vial: • Injection: 300 mcg/mL in a single-dose vial • Injection: 480 mcg/1.6 mL in a single-dose vial Prefilled Syringe: • Injection: 300 mcg/0.5 mL in a single-dose prefilled syringe • Injection: 480 mcg/0.8 mL in a single-dose prefilled syringe
Therapeutic Class:	Leukocyte Growth Factor
Chemical Class:	Recombinant Protein
Mechanism of Action:	Colony-stimulating factors are glycoproteins which act on hematopoietic cells by binding to specific cell surface receptors and stimulating proliferation, differentiation commitment, and some end-cell functional activation. Endogenous G-CSF is a lineage-specific colony-stimulating factor that is produced by monocytes, fibroblasts, and endothelial cells. G-CSF regulates the production of neutrophils within the bone marrow and affects neutrophil progenitor proliferation, differentiation, and selected end-cell functions (including enhanced phagocytic ability, priming of the cellular metabolism associated with respiratory burst, antibody-dependent killing, and the increased expression of some cell surface antigens).

Proposed Indications:

- Patients with cancer receiving myelosuppressive chemotherapy or induction and/or consolidation chemotherapy for AML
  - Recommended starting dose is 5 mcg/kg/day subcutaneous injection, short intravenous infusion (15 to 30 minutes), or continuous intravenous infusion. See Full Prescribing Information for recommended dosage adjustments and timing of administration
- Patients with cancer undergoing bone marrow transplantation
  - 10 mcg/kg/day given as an intravenous infusion no longer than 24 hours. See Full Prescribing Information for recommended dosage adjustments and timing of administration
- Patients undergoing autologous peripheral blood progenitor cell collection and therapy
  - 10 mcg/kg/day subcutaneous injection

- Administer for at least 4 days before first leukapheresis procedure and continue until last leukapheresis
- Patients with congenital neutropenia
  - Recommended starting dose is 6 mcg/kg subcutaneous injection twice daily
- Patients with cyclic or idiopathic neutropenia
  - Recommended starting dose is 5 mcg/kg subcutaneous injection daily

2.2 Availability of Proposed Active Ingredient in the United States

PF-06881893 is not marketed in the US.

2.3 Reference Agent

US-approved Neupogen (filgrastim) was approved in the United States in 1991, and five additional indications were approved subsequently based on supplements to the BLA. The indications are:

- To decrease the incidence of infection, as manifested by febrile neutropenia, in patients with nonmyeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a significant incidence of severe neutropenia with fever (Approved 2/20/1991)
- To reduce the time to neutrophil recovery and the duration of fever, following induction or consolidation chemotherapy treatment of patients with acute myeloid leukemia (AML) (Approved 4/2/1998)
- To reduce the duration of neutropenia and neutropenia-related clinical sequelae, e.g., febrile neutropenia, in patients with nonmyeloid malignancies undergoing myeloablative chemotherapy followed by bone marrow transplantation (BMT) (Approved 6/15/1994)
- For the mobilization of autologous hematopoietic progenitor cells into the peripheral blood for collection by leukapheresis (Approved 12/28/1995)
- To reduce the incidence and duration of sequelae of neutropenia (e.g., fever, infections, oropharyngeal ulcers) in symptomatic patients with congenital neutropenia, cyclic neutropenia, or idiopathic neutropenia (Approved 12/19/1994)
- To increase survival in patients acutely exposed to myelosuppressive doses of radiation (Approved 3/30/2015)

2.4 Important Issues with Consideration to Related Drugs

Class-specific safety issues were established in studies using Neupogen or Neulasta. In healthy volunteers, the most common severe toxicities attributed to these drugs were bone pain, headache and nausea; life-threatening events were rare (<1%) (Kroschinsky, Holig, et al. 2005; Pulsipher, Chitphakdithai, et al. 2009, 2013). One large study showed no increased risk of myeloid leukemia or other cancers after a single course of Neupogen in healthy volunteers (Pulsipher, Chitphakdithai, et al. 2009). In a placebo-controlled trial to prevent chemotherapy- induced neutropenia, there were no serious, life-threatening or fatal reactions attributed to Neupogen (Neupogen Prescribing Information, March, 2013).

Potential but rare life-threatening events attributed to this class include serious allergic reactions, splenic rupture, acute respiratory distress syndrome, alveolar hemorrhage/hemoptysis, capillary

leak syndrome, cutaneous vasculitis, sickle cell crisis glomerulonephritis, leukocytosis and thrombocytopenia (Neulasta Prescribing Information, October, 2016; Neupogen Prescribing Information, June, 2016; Granix Prescribing Information, June, 2017; Zarxio Prescribing Information, February, 2017). These biologics are known to be immunogenic, but neutralizing antibodies have not been reported. Current labeling also cites a theoretical potential for stimulation of growth of malignant cells in patients with cancer.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

The key events in the US presubmission regulatory activities include:

Meeting/ Correspondence Date	Meeting/Correspondence Type	Meeting/Correspondence Objective
11 Mar 2011	Pre-IND Meeting	Discuss the development plan for PF-06881893 in the context of a proposed biosimilar biological product under section 351(k) of the PHS Act.
27 Mar 2014	FDA Correspondence	FDA recommendation that Hospira join the BPD program and request a BPD Type 2 or 3 Meeting to discuss the clinical development program.
25 Feb 2015	BPD Type 2 Meeting	Discuss the preliminary analytical biosimilarity assessment, future analytical plans, the proposed nonclinical study, immunogenicity and clinical development program
04 Sept 2015	IND submission	IND 109991 to support initiation of single-dose PK/PD clinical study ZIN-FIL-1502
28 Oct 2015	IND Amendment	To add the protocol for multiple-dose PK/PD study ZIN-FIL-1501
04 Feb 2016	Teleconference with FDA	Discuss the proposed proprietary name
24 June 2016	Request for SPA	Request for FDA review of the clinical study protocol, C1121012, for the comparative immunogenicity study under a SPA
30 Aug 2016	BPD Type 3 Meeting	Review of the interim analytical similarity data comparing PF-06881893 to the reference product and to obtain concurrence from FDA on the suitability of the immunogenicity methods and validations.
21 Sept 2016	Protocol Amendment	Revised clinical study protocol C1121012 (Comparative Immunogenicity study) based on feedback received during the SPA review
22 Sept 2016	Request for FDA Feedback	Submitted use-related risk analysis along with the draft protocol for the Summative Human Factors study to validate the safe and effective use of the PF-06881893 product in the prefilled syringe presentation
21 Oct 2016	iPSP	Submitted an Initial Pediatric Study Plan for FDA Written Agreement
28 Dec 2016	FDA Correspondence	FDA provided feedback after their review of the use-error risk analysis (UERA). FDA did not identify any new or unique use-related risks and determined that a Human Factors Validation study is not warranted. FDA also provided recommendations on revisions to the Prefilled Syringe Instructions for Use labeling

		regarding clarification of instructions, comprehension, readability and patient friendly language.
08 Feb 2017	BPD Type 4 Meeting	Discuss and obtain concurrence from the FDA on the overall content, format and procedural considerations of the 351(k) BLA for PF-06881893, a potential biosimilar for US-licensed Neupogen reference product.
10 Mar 2017	Revised iPSP	Submitted a revised iPSP based on comments received from the FDA
15 Mar 2017	Pre-NDS Meeting with Health Canada	To discuss the overall PF-06881893 development program in support of a future NDS
31 May 2017	Agreed iPSP	Submitted an agreed iPSP incorporating FDA feedback received during review
11 Jul 2017	FDA agreement on iPSP	Received FDA agreement on the iPSP

2.6 Other Relevant Background Information

None.

2.7 Compliance with the Pediatric Research Equity Act

The applicant provided justification for extrapolation to the pediatric populations from available data for the reference product. The Agency responded to the Sponsor's iPSP with comments on January 19, 2017 (the pediatric review committee discussed the iPSP on January 11, 2017). The Sponsor then submitted the agreed iPSP on May 31, 2017. The agreed initial pediatric study plan was finalized and issued on July 11, 2017.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

BLA 761080 was received 9/21/2017 as an electronic submission in eCTD format. Following receipt of a response to an information request on 11/1/17, the submission was found to be complete and was filed on 11/20/2017. Additional amendments regarding clarification of methodology used to decipher anti-drug antibody levels are listed below.

BLA Submission and Amendments

SDN	Received	Category	Subcategory
1	09/21/2017	Original	BLA
3	11/01/2017	Clinical	Response to Information Request
17	3/1/2018	Clinical	Response to Information Request
19	3/14/2018	Clinical	Response to Information Request

3.2 Compliance with Good Clinical Practices

Zin-Fil-1501 and ZIN-FIL-1502 GCP compliance statements were reviewed and are adequate. The C1121012 GCP study also has a compliance section which was reviewed and adequate. OSI inspected the facilities in (b) (4) and issued a report 4/2/18. The final inspection classification is Voluntary Action Indicated (VAI). This did not impact the credibility of the study results.

3.3 Financial Disclosures

The applicant submitted a Form FDA 3454 certifying that they had not entered financial arrangements with the listed clinical investigators, and that none of the clinical investigators reported a financial conflict of interest. The listing of clinical investigators covered all three studies submitted in the BLA. There were no disclosable conflicts of interest.

4 Significant Issues Related to Other Review Disciplines

4.1 Product Quality (from midcyle meeting)

4.1.1 Chemistry Manufacturing and Controls

At the time of completion of this review, the final determination of similarity based on the analytical comparisons of PF-06881893 and US-licensed Neupogen was pending.

4.1.2 Immunogenicity

The sponsor performed immunogenicity assays for both PF-06881893 and US-licensed Neupogen. Validation of the assays was still pending at the time of completion of this review.

4.1.3 Device

At the time of completion of this review, the CDRH reviewer had not identified any significant issues with the proposed prefilled syringe presentations. The final CDRH review was still pending.

4.2 Preclinical Pharmacology/Toxicology

As of the mid-cycle meeting, the Preclinical Pharmacology/Toxicology reviewer had not identified significant issues.

4.3 Clinical Pharmacology

Based upon PK and PD (ANC and CD34+ cell mobilization) study data, PK and PD similarity was met between PF-06881893 and US-licensed Neupogen according to the Clinical Pharmacology reviewer midcycle meeting discussion.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

Table 1: PF-06881893 PK/PD Studies in Healthy Volunteers			
Protocol	**Design**	**Population**	**Endpoints**
C1121012	Multicenter, randomized, open-label, 2-period, parallel arm study **Period 1**: PF-06881893 5 mcg/kg/d iv x 5 OR US-approved Neupogen 5 mcg/kg/d iv x 5 **Period 2 (same drug as period 1)**: PF-06881893 5 mcg/kg/d iv x 1 OR US-licensed Neupogen 5 mcg/kg/d iv x 1	Healthy volunteers 256 subjects randomized 1:1	The primary endpoint was the proportion of subjects with a negative baseline ADA test result and confirmed post dose positive ADA test result at any time during the study. Presence of anti-filgrastim antibody x 6 time points per subject Period 1 on Days 0, 10 and 26 +/- 1, and in Period 2 on Days 0, 10 and 31 +/- 2
ZIN-FIL-1501	Single-center, randomized, open-label, multiple-dose, 2-way crossover study in healthy subjects. **Period 1** PF-06881893 5 mcg/kg/d iv x 5 OR US- licensed Neupogen 5 mcg/kg/d iv x 5 **Period 2** (opposite drug as period 1) PF-06881893 5 mcg/kg/d iv x 5 OR US- licensed Neupogen 5 mcg/kg/d iv x 5	Sequence Group 1: PF-06881893 (in Period 1) followed by US-licensed Neupogen RP (in Period 2): 5 mcg/kg as a single SC dose 60 subjects randomized 1:1	Primary: Area under the effect curve for CD34+count, and the maximum observed CD34+ count. Secondary: Time to maximum observed CD34+ count.
ZIN-FIL-1502	A single-center, randomized, open-label, single-dose, 2-way crossover study in healthy subjects **Period 1** PF-06881893 5 mcg/kg/d iv x 1 OR US- licensed Neupogen 5 mcg/kg/d iv x 1 **Period 2** (opposite drug as period 1) PF-06881893 5 mcg/kg/d iv x 5 OR US- licensed Neupogen 5 mcg/kg/d iv x 1	Sequence Group 1: PF-06881893 followed by US-licensed Neupogen RP: 5 mcg/kg as a single SC dose. Sequence Group 2: opposite 24 subjects randomized 1:1	Primary: Area under the effect curve for CD34+count, and the maximum observed CD34+ count. Secondary: Time to maximum observed CD34+ count.

5.2 Review Strategy

The key materials used for the review of efficacy and safety included BLA 761080, relevant published literature, and relevant information in the public domain.

There was no clinical trial in an intended population that was designed as a comparative clinical study to test equivalence in a clinical efficacy endpoint for any of the proposed indications. The methodological approach to the assessment of effectiveness is discussed in Section 6.1.1. For the assessment of clinically meaningful differences in safety, data were reviewed from all studies listed in Table 2. The methodological approach to the assessment of safety is discussed in Section 7.1.

Statistical analyses by the clinical reviewer were performed using JMP 13.1 (SAS Institute, Inc., Cary, NC). MedDRA Adverse Events Diagnostic (MAED) (Clinical Trials & Surveys Corporation, Owings Mills, MD) was used to assess for safety signals. Unless stated otherwise, all other p-values are unadjusted for multiplicity and should be interpreted with caution.

5.3 Discussion of Individual Studies/Clinical Trials

Study C1121012 was a phase I, randomized multicenter, open-label, 2-period, parallel arm study to Assess the Immunogenicity of Multiple Subcutaneous (SC) Doses of "PF-06881893" (US) or US-Approved Neupogen Reference Product in Healthy Volunteers.

There were 2 administration periods for each subject during which the leukocyte growth factor was given at 5 mcg/kg/day IV x 5 doses in the first period and one dose of the same drug in the second period with a 4-week washout period between administrations. Subjects were randomized 1:1 to one of the two parallel sequences to receive either PF-06881893 or US-approved Neupogen. The primary objective was to determine the proportion of subjects with a negative baseline ADA test result and confirmed post dose positive ADA test result at any time during the study. Subjects were assessed clinically during screening and at the final study visit. Blood was drawn for antibody testing in period 1 on Days 0, 10 and 26 +/- 1, and in Period 2 on Days 0, 10 and 31 +/- 2. There were no substantial protocol amendments after the start of the study. The study was initiated on 18 October 2016 and completed on 31 January 2017. 256 subjects were randomized. A total of 255 subjects were treated; 1 subject (assigned to the US-licensed Neupogen group) was not dosed due to a personal emergency. Fifteen subjects dropped out of the study (9 subjects in the PF-06881893 group and 6 subjects in the US-licensed Neupogen group). Two subjects in the PF-06881893 group discontinued due to TEAE (diverticular perforation and back pain). One subject in the US-licensed Neupogen group discontinued due to TEAE (back pain). Two hundred and forty patients completed both administration periods.

Study ZIN-FIL-1501 was a randomized open-label, single center multiple-dose crossover study evaluating the pharmacodynamics and pharmacokinetics of PF-06881893 compared to US-approved Neupogen following subcutaneous administration to healthy volunteers. There were two administration periods for each subject during which the leukocyte growth factor was given at 5 mcg/kg/day iv x 5 doses in the first period and 5 doses of the opposite drug in the second period with a 4-week washout period between administrations. Subjects were randomized 1:1 to one of

the two cross-over sequences to receive either PF-06881893 or US-approved Neupogen. The primary objective was to determine the area under the effect curve for CD34+count, and the maximum observed CD34+ count. The secondary objective was to determine the time to the maximum observed CD34+ count. Subjects were assessed clinically during screening and at the final study visit. Blood was drawn for PK/PD studies on Day 6, 7-10, 12 and 33 of each period. Blood was drawn for CD34+ cell counts on days 1-5 and at 24, 48, 72, 96 and 120 hours following dose administration on day 5. There were no substantial protocol amendments after the start of the study. The study was initiated on 29 March 2016 and completed on 10 June 2016. 60 subjects were randomized. All 60 enrolled patients received at least one dose of at least one of the study drugs and were included in the total safety population; 59 subjects received at least one does of PF-06881893 and 58 subjects received at least one dose of the Neupogen reference product. Three subjects (10.0%) in Sequence Group 1 prematurely discontinued (1 lost to follow-up after treatment in period 2, one had a protocol deviation (positive for cotinine on period 2 admission) and one withdrew consent after PF-06881893 treatment in period 1). Fifty-six patients completed both administration periods.

Study ZIN-FIL-1502 was a randomized open-label, single center, single-dose crossover study evaluating the pharmacodynamics and pharmacokinetics of PF-06881893 compared to US-approved Neupogen following subcutaneous administration to healthy volunteers. There were two administration periods for each subject during which the leukocyte growth factor was given at 5 mcg/kg/day IV x 1 doses in the first period and 5 doses of the opposite drug in the second period with a 4-week washout period between administrations. Subjects were randomized 1:1 to one of the two cross-over sequences to receive either PF-06881893 or US-approved Neupogen. The primary objective was to determine the area under the effect curve for CD34+count, and the maximum observed CD34+ count. The Secondary objective was to determine the time to the maximum observed CD34+ count. Subjects were assessed clinically during screening and at the final study visit. Blood for PK sampling was collected 1 hour (60 minutes) prior to each dose administration and 1, 2, 3, 4, 6, 8, 10, 12, 16, 24, and 48 hours after each dose administration. Blood for PD assessments was collected hour (60 minutes) prior to each dose administration and 0.5, 1, 2, 4, 6, 8, 24, 48, 72, 96, and 120 hours after each dose. There were no substantial protocol amendments after the start of the study. The study was initiated on 18 December 2015 and completed on 01 March 2016. Twenty-four subjects were randomized. All 24 enrolled patients received at least one dose of each of the study drugs and were included in the total Safety Population. Twenty-three patients completed both administration periods. One patient was lost to follow up after treatment period 1.

6 Review of Efficacy Endpoints

Efficacy Summary

There were no comparative clinical trials in an intended population submitted in this BLA or in the published literature that tested the equivalence of PF-06881893 and US-licensed Neupogen for a clinical efficacy endpoint. The finding of no clinically-meaningful differences will be based solely on the analytical comparisons and the PK/PD analyses.

6.1 All Neutropenia-Related Indications

PF-06881893 is a leukocyte growth factor indicated to:

- To decrease the incidence of infection, as manifested by febrile neutropenia, in patients with nonmyeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a significant incidence of severe neutropenia with fever
- To reduce the time to neutrophil recovery and the duration of fever, following induction or consolidation chemotherapy treatment of patients with acute myeloid leukemia (AML)
- To reduce the duration of neutropenia and neutropenia-related clinical sequelae, e.g., febrile neutropenia, in patients with nonmyeloid malignancies undergoing myeloablative chemotherapy followed by bone marrow transplantation
- Mobilize autologous hematopoietic progenitor cells into the peripheral blood for collection by leukapheresis
- To reduce the incidence and duration of sequelae of neutropenia (e.g., fever, infections, oropharyngeal ulcers) in symptomatic patients with congenital neutropenia, cyclic neutropenia, or idiopathic neutropenia

6.1.1 Methods

There was no clinical trial in an intended population submitted that was designed as a comparative clinical study to test equivalence in a clinical efficacy endpoint for any of the proposed indications.

In the absence of data from an adequate and well-controlled clinical trial, Sections 6.1.2 through 6.1.10 are omitted from this review.

6.1.11 Literature Review

PubMed searches for "filgrastim" and "Hospira" conducted as late as 5/29/2018 yielded no publications of clinical effectiveness data. The only studies are about Nivestim, the EU-licensed Neupogen biosimilar which has not been proven to be the same API as PF-06881893. Any literature referring to the EU-approved product is not applicable to PF-06881893.

7 Review of Safety

Safety Summary

The immunogenicity study C1122012 comparing PF-06881893 to US-licensed Neupogen demonstrated that safety and immunogenicity incidence observed between PF-06881893 and US-licensed Neupogen appeared similar. ZIN-FIL-1501 and ZIN-FIL-1502 provided supportive evidence for safety. There were no deaths or high grade AEs in any of the three clinical studies.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The clinical review of safety for this BLA was based on the safety data from the 3 healthy volunteer studies C1121012, ZIN-FIL-1501 and ZIN-FIL-1502 compared to US-licensed Neupogen. Table 2 in Section 5.1 describes the design of the protocols used in the safety analyses. The results of the analyses of safety data from the healthy volunteer studies are described in Sections 7.2-7.4. Overall PF-06881893 and Neupogen had similar safety profiles. Most of the AE's reported during the studies were expected given the known biologic effects of filgrastim-based products. No deaths were reported in the clinical trials submitted to support the biosimilarity of PF-06881893 and US-licensed Neupogen.

Sections 7.5 through 7.6 of the review template are omitted due to lack of applicable information

7.1.2 Categorization of Adverse Events

AEs reported throughout the study were coded to a preferred term and body system using version 18.0 of the MedDRA dictionary; severity was not categorized. In response to an Information Request received 11/1/2017 missing grades were imputed by the applicant as mild (corresponding to Common Terminology Criteria for Adverse Events [CTCAE] Grade 1), moderate (Grade 2), or severe (Grade 3) or life-threatening (Grade 4) as requested.

7.1.3 Pooling of Data

No data pooling was provided by the applicant.

Study ZIN-FIL-1501 and ZIN-FIL-1502 comparing PF-06881893 to US-licensed Neupogen used similar dose schedules. The incidences of any TEAE or any TEAE in the SOC Musculoskeletal and connective tissue disorders were similar for both treatment periods in these studies. No clinically significant differences were noted in the rates of adverse events of special interest between PF-06881893 and US-licensed Neupogen. In summary, safety outcomes appeared similar for healthy volunteers treated with either PF-06881893 or US licensed Neupogen. The impact of ADAs on AEs was not assessed in this review.

7.2 Adequacy of Safety Assessments

7.2.1 Safety Population

Safety data were available for 279 unique subjects with 279 randomizations. The safety population for analysis was comprised of all subjects who received at least one dose of PF-06881893 or US licensed Neupogen. Relevant demographic, treatment and safety outcomes information is displayed in the tables below as determined by the analysis of comparisons rather than by unique participant. The demographics of the healthy volunteer safety population used for comparative analyses are shown in Table 2. Male and female subjects were evenly distributed. Most subjects were Caucasian followed by African American. There were

slightly more patients over the age of 45 years in the PF-06881893 group as compared to the US-licensed Neupogen group (N =40 vs 29). This difference is not clinically significant.

Table 2 Healthy Volunteer Safety Population Demographics

	STUDYID							
	C1121012				ZIN-FIL-1501		ZIN-FIL-1502	
	TRT01A 2				TRT01A 2		TRT01A 2	
	PF-06881893		Neupogen		PF-06881893		PF-06881893	
Sex	N	Column %	N	Column %	N	Column%	N	Column%
F	64	50%	65	51%	21	35%	11	46%
M	64	50%	62	49%	39	65%	13	54%

Race	N	Column %	N	Column %	N	Column%	N	Column%
Black or African American	25	20%	22	18%	9	15%	2	8%
Native Hawaiian or Other Pacific Islander	1	1%	0	0%	0	0%	0	0%
White	99	79%	101	82%	51	85%	22	92%

Ethnic	N	Column %	N	Column %	N	Column%	N	Column%
Hispanic or Latino	109	85%	114	90%	59	98%	24	100%
Not Hispanic or Latino	19	15%	13	10%	1	2%	0	0%

		STUDYID			
		C1121012		ZIN-FIL-1501	ZIN-FIL-1502
		TRT01A 2		TRT01A 2	TRT01A 2
		PF-06881893	US-approved Neupogen	PF-06881893	PF-06881893
Age	Median	38	35	45.5	41.5
	Min	19	18	23	23
	Max	61	65	63	58

Source: FDA Analysis

7.2.2 Explorations for Dose Toxicity Relationship

Not applicable.

7.2.3 Special Animal and/or In Vitro Testing

There were no findings in the preclinical studies that warranted special comparisons for the analysis of clinical safety. This finding was reassessed during the midcycle meeting.

7.2.4 Routine Clinical Testing

The schedule of safety evaluations is described in section 5.3 above. The frequency of monitoring dictated by the protocols was considered adequate to assess the safety profile.

7.2.5 Metabolic, Clearance, and Interaction Workup

There were no findings in the pharmacology studies that warranted special comparisons for the analysis of clinical safety.

7.2.6 Adverse Events of Special Interest

The criteria used to ascertain adverse events of special interest is described in Table 3.

Table 3 Search Strategy for Adverse Events of Special Interest

AESI	Search Terms used for AESI	Terms Used By FDA
Allergic Reactions	Angioedema, Dermatitis allergic, Drug hypersensitivity, Hypersensitivity, Rash, Rash pruritic, Urticaria	Hypersensitivity (SMQN), Anaphylactic reaction (SMQN)
Musculoskeletal events	Arthralgia, Back pain, Bone pain, Musculoskeletal pain, Myalgia, Neck pain, Pain in extremity	Musculoskeletal and connective tissue disorders (SOC)
Injection site reaction	-	Injection site reactions (HLT)

7.3 Major Safety Results

7.3.1 Deaths

There were no fatal adverse events reported.

7.3.2 Serious Adverse Events

There were no serious adverse events reported.

7.3.3 Dropouts and/or Discontinuations

On immunogenicity study C1121012 fifteen patients of 256 (6%) discontinued therapy. Nine (7%) were in the PF-06881893 group and 6 (4.7%) were in the US-licensed Neupogen group (Table 4). One subject in the US-licensed Neupogen group was not dosed due to a personal emergency.

Table 4 Reasons for Study C1121012 Discontinuation

	PF-06881893	US-licensed Neupogen
	N (%)	N (%)
Discontinued from treatment	9 (7.0)	06 (4.7)
Reasons for discontinuation from treatment		
Adverse event	2 (1.6)	1 (0.8)
Lost to follow-up	2 (1.6)	2 (1.6)
Protocol deviation	1 (0.8)	1 (0.8)
Withdrawal by subject	4 (3.1)	1 (0.8)
Other	0	1 (0.8)
Source: FDA Analysis		

One patient in each group withdrew due to back pain and one in the PF-06881893 group due to diverticular perforation (table 5). No subjects on cross-over studies ZIN-FIL-1501 and ZIN-FIL-1502 withdrew due to adverse drug reactions.

Table 5 Adverse Events in Subjects Not Completing Study C1121012				
AEDECOD	PF-06881893	PF-06881893 %	US-approved Neupogen	Neupogen_%
Back pain	1	1%	1	1%
Diverticular perforation	1	1%	0	0%
Source: FDA Analysis				

7.3.4 Significant Adverse Events

The applicant reported no substantial differences in bone pain between those who received PF-06881893 vs those who received US-licensed Neupogen. Allergic reactions were reported in several subjects and considered related by the applicant.

FDA evaluated AESI (musculoskeletal pain, allergic reactions and injection site reactions) as described in Section 7.2.6. Table 6 shows the incidence of adverse events in the SOC Musculoskeletal and connective tissue disorders by study drug and dose in the safety population where paired data were available. No subjects in study single dose study ZIN-FIL-1502 had adverse events of special interest because they only received one dose of either drug.

Table 6 Adverse Events of Special Interest for All Three Clinical Studies						
	C1121012		ZIN-FIL-1501		ZIN-FIL-1502	
AESI	PF-06881893 # (%)	Neupogen	PF-06881893	Neupogen	PF-06881893	Neupogen
Allergic Reactions	1 (0.78)	0 (0)	0 (0)	1(2)	1 (8)	0(0)
Musculoskeletal events	44 (34.38)	45 (35.43)	7 (12)	9 (15)	0(0)	0(0)
Injection site reaction	2 (1.56)	13(10.24)	0 (0)	0 (0)	0(0)	0(0)
Source: FDA analysis						

Thirteen subjects (10%) on immunogenicity study C1121012 who received US-licensed Neupogen had injection site reactions as compared to two subjects (1.5%) who received PF-06881893. The types of injection site reactions are detailed in table 7 and are comprised mostly of hemorrhage and erythema. These differences are not clinically significant and are not thought to be due to lack of potency of PF-06881893.

Table 7 Injection Site Reactions by Type for Study C1121012			
AEDECOD	**N Rows**	**N (PF-06881893)**	**N (US-approved Neupogen)**
Injection site erythema	4	0	4
Injection site hemorrhage	9	1	8
Injection site induration	1	0	1
Injection site pain	1	1	0
Injection site pruritus	1	1	0

Table 7 Injection Site Reactions by Type for Study C1121012			
AEDECOD	**N Rows**	**N (PF-06881893)**	**N (US-approved Neupogen)**
Source: FDA analysis			

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

Table 8 shows the numbers of subjects with adverse events by PT in decreasing order of incidence in the immunogenicity parallel group study C1121012. Only PTs that occurred in at least 2 subjects in either of the randomized arms are displayed. Most these events were considered related and mild (Grade 1-2)

Table 8 Treatment Emergent Adverse Events by SOC for Study C1121012					
	PF-06881893 N =128		Neupogen N=127		
SOC	Number of subjects	Proportion (%)	Number of subjects	Proportion (%)	RD (per hundred)
Cardiac disorders	5	3.91	4	3.15	0.76
Endocrine disorders	0	0	1	0.79	-0.79
Eye disorders	1	0.78	0	0	0.78
Gastrointestinal disorders	10	7.81	6	4.72	3.09
General disorders and administration site conditions (including local reactions)	6	4.69	19	14.96	-10.27
Infections and infestations	7	5.47	6	4.72	0.74
Injury, poisoning and procedural complications	1	0.78	1	0.79	-0.01
Musculoskeletal and connective tissue disorders	44	34.38	45	35.43	-1.06
Nervous system disorders	19	14.84	24	18.9	-4.05
Psychiatric disorders	1	0.78	1	0.79	-0.01
Renal and urinary disorders	1	0.78	0	0	0.78
Reproductive system and breast disorders	2	1.56	1	0.79	0.78
Respiratory, thoracic and mediastinal disorders	5	3.91	4	3.15	0.76
Skin and subcutaneous tissue disorders	3	2.34	2	1.57	0.77
Vascular disorders	1	0.78	1	0.79	-0.01
Source FDA Analysis					

Table 9 shows the numbers of subjects with adverse events by PT in decreasing order of incidence in the immunogenicity parallel group study C1121012. Most these events were considered related and mild.

Table 9 Study C1121012 Treatment Emergent Adverse Events by PT with Risk Difference = or >2%					
	PF-06881893 N =128		*Neupogen N=127*		
PT	*Number of subjects*	*Proportion (%)*	*Number of subjects*	*Proportion (%)*	*RD (per hundred)*
Injection site hemorrhage	1	0.78	8	6.3	-5.52
Injection site erythema	0	0	4	3.15	-3.15
Pain in extremity	4	3.13	7	5.51	-2.39
Dizziness	0	0	3	2.36	-2.36
Arthralgia	4	3.13	1	0.79	2.34
Source: FDA Analysis					

Table 10 shows treatment emergent adverse events by PT for cross-over study ZIN-FIL-1501. The common AEs reported in this study that were related included the preferred terms back pain, extremity pain, pain unspecified, arthralgia, neck pain, chest pain, and musculoskeletal pain. These AEs are all grade 1-2 and are not clinically meaningful.

Table 10 ZIN-FIL-1501 Treatment Emergent Adverse Events by PT for RD >1%					
AEDECOD	**PF-06881893**	**PF-06881893 %**	**US-approved Neupogen**	**Neupogen %**	**RD**
Abscess	0	0%	1	2%	-1.8%
Cellulitis	0	0%	1	2%	-1.8%
Cough	2	4%	3	5%	-1.8%
Dermatitis	0	0%	1	2%	-1.8%
Dizziness	0	0%	1	2%	-1.8%
Dyspnea	0	0%	1	2%	-1.8%
Erythema	0	0%	1	2%	-1.8%
Fatigue	0	0%	1	2%	-1.8%
Flatulence	0	0%	1	2%	-1.8%
Flushing	0	0%	1	2%	-1.8%
Oropharyngeal pain	1	2%	2	4%	-1.8%
Pain in extremity	0	0%	1	2%	-1.8%
Viral upper respiratory tract infection	0	0%	1	2%	-1.8%
Constipation	1	2%	0	0%	1.8%
Musculoskeletal pain	1	2%	0	0%	1.8%
Myalgia	1	2%	0	0%	1.8%
Tachycardia	1	2%	0	0%	1.8%
Back pain	7	13%	6	11%	1.8%
Chills	2	4%	0	0%	3.6%
Pyrexia	5	9%	3	5%	3.6%
Headache	5	9%	2	4%	5.4%
Source: FDA Analysis					

Table 11 shows treatment emergent adverse events by PT for cross-over study ZIN-FIL-1502. The common AEs reported in this study that were generally less than in study ZIN-FIL-1501 probably

because subjects on ZIN-FIL-1502 only received 1 dose of each drug separated by a 28-day washout period.

Table 11 ZIN-FIL-1502 Treatment Emergent Adverse Events by PT for Risk Difference >1%					
AEDECOD	**PF-06881893**	**PF-06881893 %**	**US-approved Neupogen**	**Neupogen %**	**RD**
Dry throat	0	0%	1	4%	-4%
Nasopharyngitis	0	0%	1	4%	-4%
Abdominal discomfort	1	4%	0	0%	4%
Nausea	1	4%	0	0%	4%
Oropharyngeal pain	1	4%	0	0%	4%
Rhinitis allergic	1	4%	0	0%	4%
Vertigo	1	4%	0	0%	4%
Vomiting	1	4%	0	0%	4%
Source: FDA Analysis					

7.4.2 Laboratory Findings

Relevant safety laboratory variables identified by the applicant were alanine aminotransferase (ALT), aspartate aminotransferase (AST) and alkaline phosphatase. Hematology parameters were also evaluated. The applicant reported no clinically relevant differences in the effect of study drugs. FDA evaluated laboratory abnormalities in terms of both the listing of adverse events (SOC Investigations) and the raw laboratory data. Table 12 summarizes the grade 1-2 adverse event terms that address laboratory test abnormalities for the immunogenicity study C1121012 and cross-over study ZIN-FIL-1501. There were no high grade AEs in these two studies. There were no abnormalities for study ZIN-FIL-1502 likely because the subjects only received one dose of each drug. Table 12 summarizes the incidence of laboratory studies by cross-over comparison for study ZIN-FIL-1501 or immunogenicity parallel comparison for study C1121012 respectively.

Table 12 Abnormal Laboratory Results for Studies ZIN-FIL-1501 & C1121012				
ZIN-FIL-1501 Abnormal Laboratory Results				
Laboratory Name	PF06881893	PF-06881893 %	US-approved Neupogen	Neupogen %
Alkaline Phosphatase (U/L) HIGH	38	68%	41	73%
Low Hemoglobin (g/dL) LOW	16	29%	12	21%
Platelets (10^3/uL) LOW	14	25%	16	29%
Glucose (mg/dL) HIGH	3	5%	3	5%
Low Glucose (mg/dL) LOW	1	2%	2	4%
Phosphate (mg/dL) LOW	1	2%	2	4%
Aspartate Aminotransferase (U/L) HIGH	1	2%	1	2%
C1121012 Abnormal Laboratory Results				
Laboratory Name	PF-06881893	PF-06881893 %	US-approved Neupogen	Neupogen %
Alkaline Phosphatase (U/L) HIGH	36	28%	46	36%
Alanine aminotransferase (U/L) HIGH	10	8%	17	13%
Aspartate aminotransferase (U/L) HIGH	9	7%	10	8%
Platelets (10^3/mm^3) LOW	9	7%	19	15%

C1121012 Abnormal Laboratory Results

Laboratory Name	PF-06881893	PF-06881893 %	US-approved Neupogen	Neupogen %
Creatinine (mg/dL) LOW	7	5%	3	2%
Gamma glutamyl transferase (U/L) HIGH	5	4%	5	4%
Bilirubin (mg/dL) HIGH	3	2%	3	2%
Potassium (Meq/L) HIGH	3	2%	3	2%
Hemoglobin (g/dL) HIGH	1	1%	0	0%

7.4.3 Vital Signs

We reviewed all vital signs including temperature, heart rate, respiratory rate and blood pressure. There were no clinically significant changes in vital signs according to FDA analysis. The sponsor performed similar analysis of the four aforementioned vital sign parameters and similarly concluded there were no clinically significant changes in vital signs.

7.4.4 Electrocardiograms (ECGs)

The ECG data in ADEG data files for all three clinical studies were evaluated. There were no clinically significant ECG abnormalities in any of the three studies. The sponsor did not report clinically significant ECG findings in any of the three studies.

7.4.5 Special Safety Studies/Clinical Trials

For the immunogenicity study C1122012, the statistical reviewer concluded that "the risk difference of the proportion of subjects with a negative baseline anti-drug antibody (ADA) test result and confirmed post-dose positive ADA test result at any time during the study was 2.56% with 90% exact confidence interval between -2.72% and 8.36%. The sensitivity analyses performed using different methods to construct the 90% CI of the risk difference as well as including both ADA negative and positive subjects and increased titer from baseline as an event of interest agree with the primary analysis result. The results based on ITT population also appear to support the non-inferiority result. Since the upper bound of the CIs were below pre-specified margin of 10% for all analyses, the study demonstrated non-inferiority of the proportion of subjects with a negative ADA and a positive ADA at any time during the study between the PF-06881893 and the US-Licensed Neupogen".

7.4.6 Immunogenicity

In study C1122012 all 256 randomized subjects (128 subjects in each arm) were used to calculate the proportion of subjects with baseline negative and baseline positive ADA as a sensitivity analysis. The upper bound of the 90% CI is 9.63% which is within the prespecified non-inferiority margin of 10%. This result indicates that there are no meaningful differences in immunogenicity results for PF-06881893 as compared to US-licensed Neupogen.

Table 13 Study C1122012 Anti-Drug Antibody Evaluation						
	PF-06881893 5 mcg/kg (N=128)		US-licensed Neupogen® 5 mcg/kg (N=127)		Risk Difference (%)	90% CI
	N*	n (%)	N*	n (%)		
Proportion with positive ADA	125	11 (8.8)	127	8 (6.3)	2.5	(-4.37, 9.63)
Source: FDA Statistical reviewer						

N = number of subjects in FAS cohort. N*=the number of subjects included in analysis for immunogenicity. The difference between N* and N is that subjects with missing values at baseline or during treatment were not included in N* cohort; n is the number of subjects with negative baseline ADA and post-dose positive ADA test result or positive baseline ADA and has an increase titer from baseline. Percentages were based on the number of subjects in the N* population.

7.7 Additional Submissions / Safety Issues

7.7.1

Literature Review

A PubMed search for filgrastim and Hospira yielded no information relevant to this review. The only available information is regarding EU-approved Nivestim. Nivestim has not been shown to be the same active pharmaceutical ingredient as PF-06881893.

8 Postmarket Experience

PSURS were submitted. There were no unexpected safety issues observed. It should be noted however that Nivestim, the EU-approved product, can not be compared to PF-06881893 for clinically meaningful differences.

9 Appendices

9.1 Advisory Committee Meeting

This application was not discussed by an Advisory Committee.

9.2 Literature Reviewed/ References

Kroschinsky F, Hölig K, Poppe-Thiede K, et al. (2005) Single-dose pegfilgrastim for the mobilization of allogeneic CD34+ peripheral blood progenitor cells in healthy family and unrelated donors. Haematologica 90:1665-71.

Pulsipher MA, Chitphakdithai P, Logan BR, et al. (2013) Acute toxicities of unrelated bone marrow versus peripheral blood stem cell donation: results of a prospective trial from the National Marrow Donor Program. Blood 121:197-206.

Pulsipher MA, Chitphakdithai P, Miller JP, et al. (2009) Adverse events among 2408 unrelated donors of peripheral blood stem cells: results of a prospective trial from the National Marrow Donor Program. Blood 113:3604-11.

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/s/

LEA C CUNNINGHAM
06/12/2018

DONNA PRZEPIORKA
06/12/2018
The TL comments are incorporated in the CDTL review.