CLINICAL REVIEW

Application Type	Original 351(k)
Application Number	**BLA 125553**
Priority or Standard	Standard
Submit Date	5/8/2014
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Review Date	2/6/2015
Office / Division	Office of Hematology and Oncology Products / Division of Hematology Products
Primary Reviewer	Donna Przepiorka, MD, PhD
Team Leader	Albert Deisseroth, MD, PhD
Proper Name	To be determined
Established Name	EP2006
(Proposed) Trade Name	Zarxio
Therapeutic Class	Leukocyte Growth Factor
Applicant	Sandoz, Inc
Formulation(s)	Injection (300 mcg PFS, 480 mcg PFS)
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 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

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ALT	Alanine Aminotransferase
ANC	Absolute Neutrophil Count
ANCOVA	Analysis Of Covariance
AST	Aspartate Aminotransferase
AUC	Area Under Curve
BLA	Biologics License Application
BPD	Biological Product Development
CI	Confidence Interval
CMC	Chemistry, Manufacturing And Controls
CTCAE	Common Terminology Criteria For Adverse Events
DSN	Duration Of Severe Neutropenia
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCTD	Electronic Common Technical Document
FAS	Full Analysis Set
G-CSF	Granulocyte-Colony Stimulating Factor
G-CSFR	Granulocyte-Colony Stimulating Factor Receptor
GGT	Gamma Glutamyl Transferase
IND	Investigational New Drug Application
ISR	Injection Site Reaction Scale
iv	Intravenous
PD	Pharmacodynamic
PFS	Prefilled Syringe
PK	Pharmacokinetic
PP	Per Protocol
SAE	Serious Adverse Event
SAF	Safety Analysis Population
sc	Subcutaneous
SD	Standard Deviation
SE	Standard Error
SMQ	Standardized MedDRA Query
SOC	System Organ Class
TAC	Docetaxel, Doxorubicin Cyclophosphamide
TEAE	Treatment-Emergent Adverse Event
ULN	Upper Limit Of Normal
VAS	Visual Analog Scale

1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

Biologics License Application (BLA) 125553 for EP2006 (Zarxio) was submitted by Sandoz, Inc., under section 351(k) of the Public Health Service Act. EP2006 is a proposed biosimilar to US-licensed Neupogen, and Sandoz is seeking licensure of EP2006 in all five indications for which US-licensed Neupogen is approved currently. The findings within this review of the clinical data would support the demonstration of biosimilarity based on the analytical comparisons and the assessment of pharmacokinetic and pharmacodynamic parameters in healthy subjects as described by the Product Quality and Clinical Pharmacology Reviewers.

1.2 Basis for the Regulatory Action Recommended

The clinical studies used to support this BLA for EP2006 as a proposed biosimilar to US-licensed Neupogen include:

- Study EP06-302, a randomized, double-blind comparison of EP2006 to US-licensed Neupogen in patients with breast cancer
- Study EP06-109, a randomized, double-blind, cross-over study of EP2006 and US-licensed Neupogen in healthy volunteers
- Five additional randomized, double-blind, cross-over studies of various doses and schedules of EP2006 and EU-approved Neupogen

None of the studies submitted was designed prospectively to assess equivalence of EP2006 and US-licensed Neupogen for a clinical efficacy or safety endpoint in an intended population.

Study EP06-302 was a randomized, double-blind comparison of EP2006 and US-licensed Neupogen for prevention of severe neutropenia in patients with breast cancer being treated with up to 6 cycles of combination chemotherapy using docetaxel, doxorubicin, and cyclophosphamide (TAC). Chemotherapy was administered on day 1 of each 21-day cycle, and EP2006 or US-licensed Neupogen 5 μg/kd/day sc was given from day 2 until neutrophil recovery. There were 218 subjects randomized equally into one of four groups to receive EP2006 for all cycles, US-licensed Neupogen for all cycles, EP2006 then US-licensed Neupogen in alternate cycles, or US-licensed Neupogen then EP2006 in alternate cycles. Baseline demographics and disease characteristics were adequately balanced between arms.

The primary endpoint was duration of severe neutropenia (DSN) in Cycle 1. Although Study EP06-302 was designed as a noninferiority trial, FDA conducted a post hoc 2-sided analysis to ensure there were no clinically meaningful differences between EP2006 and US-licensed Neupogen with regard to the primary endpoint. The between-group analysis of the primary endpoint of Cycle 1 DSN included 101 subjects treated with EP2006 and 103 subjects treated with US-licensed Neupogen. The DSN difference (control-experimental) was 0.04 days with a 90% confidence interval (CI) of -0.21 to 0.28 days. It was estimated that the results represented

no more than a 3% increase or decrease in the incidence of febrile neutropenia, and this was considered clinically insignificant.

Key secondary endpoints, including febrile neutropenia, days of fever, absolute neutrophil count (ANC) nadir, and time to ANC recovery in Cycle 1 and across all cycles, were to be reported descriptively. The between-group comparisons and within-subject comparisons of the key secondary endpoints showed similar results for EP2006 and US-licensed Neupogen.

Study EP06-302 was conducted in a patient population addressed by only one of the five indications approved for US-licensed Neupogen. The applicant proposed to use extrapolation based on the mechanism of action along with a demonstration of biosimilarity to obtain the other four indications for which US-licensed Neupogen is currently licensed.

The safety outcomes were assessed for similarity in all seven clinical studies. The Product Quality Reviewer indicated that the data submitted by the applicant provided an adequate scientific bridge to justify the relevance of the clinical studies that used EU-approved Neupogen as a comparator to support a demonstration of biosimilarity in this application.

Safety outcomes were assessed in Study EP06-302 in 53 subjects with breast cancer randomized to treatment with EP2006, 52 subjects to treatment with US-licensed Neupogen, and 109 subjects to treatment with both study agents in an alternating fashion. The incidence of the cardinal adverse events musculoskeletal pain (25% vs 29%) and injection site reaction (2% vs 1%) were similar between subjects treated with EP2006 or US-licensed Neupogen in Cycle 1. Results were comparable across Cycles 1-6, and there was no excess discordance for either of these cardinal adverse events in a within-subject comparison.

Common treatment emergent adverse events (TEAE) at the Preferred Term level as well as related TEAE were similar in incidence when compared between subjects treated with EP2006 or US-licensed Neupogen in Cycle 1 or across Cycles 1-6, and when compared within subjects who alternated treatments. There were too few grade $\geq$ 3 TEAE or grade $\geq$ 3 laboratory abnormalities for a meaningful comparison. There were no related TEAE with allergic reaction event terms specifically. The broad standardized MedDRA query (SMQ) analysis showed a similar incidence of nonspecific signs and symptoms of hypersensitivity events for both study agents when compared in Cycle 1 and across Cycles 1-6.

Among the 204 healthy volunteers in the six studies comparing EP2006 and either US-licensed Neupogen or EU-approved Neupogen in a cross-over fashion using various single- or multiple-dose schedules, the incidences of any TEAE or any TEAE in the System Organ Class (SOC) Musculoskeletal and connective tissue disorders were similar for both treatment periods.

In summary, the analysis of Study EP06-302 showed no clinically meaningful differences between EP2006 and US-licensed Neupogen with respect to DSN in cycle 1, and safety outcomes were similar for patients treated with either EP2006 or US-licensed Neupogen. These results would support the demonstration of biosimilarity based on the analytical comparisons and the assessment of pharmacokinetic and pharmacodynamic parameters in healthy subjects. The

use of extrapolation to support all five currently-approved indications based on mechanism of action is reasonable in conjunction with a finding of biosimilarity for this product.

1.3 Recommendations for Labeling

I agree with the applicant that the labeling for EP2006 should be comparable to the current prescribing information for US-licensed Neupogen other than drug product information specific to EP2006. I recommend that labeling be revised to address the limitations for dosing in patients less than 36 kg in weight.

1.4 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

None

1.5 Recommendations for Postmarket Requirements and Commitments

At the time of completion of this review, final recommendations for postmarket requirements and commitments were pending completion of the review of the final Pediatric Study Plan by the Pediatric Review Committee.

2 Introduction and Regulatory Background

2.1 Product Information

Proper Name:	To be determined
Established Name:	EP2006
Proposed Trade Name:	Zarxio
Dosage Forms:	Injection (300 mcg in a single-use, prefilled syringe, 480 mcg in a single-use, prefilled syringe)
Therapeutic Class:	Leukocyte Growth Factor
Chemical Class:	Recombinant Protein
Mechanism of Action:	EP2006 acts on hematopoietic cells by binding to specific cell surface receptors. Signaling through the receptor affects neutrophil progenitor proliferation, differentiation, and selected end-cell functional activation, including enhanced phagocytic ability, priming of the cellular metabolism associated with respiratory burst, antibody dependent killing, and the increased expression of some functions associated with cell surface antigens.
Proposed Indication:	• Cancer patients receiving myelosuppressive chemotherapy • Patients with acute myeloid leukemia receiving induction or consolidation chemotherapy

- Cancer patients receiving bone marrow transplant
- Patients undergoing peripheral blood progenitor cell collection and therapy
- Patients with severe chronic neutropenia

Proposed Dose-Schedule:

(b) (4)

2.2 Availability of Proposed Active Ingredient in the United States

EP2006 is not marketed in the US.

2.3 Reference Agent

Neupogen (filgrastim) was approved in the United States in 1991, and four 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)
- To mobilize 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)

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 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 allergic reactions, splenic rupture, acute respiratory distress syndrome, alveolar hemorrhage, sickle cell crisis and thrombocytopenia (Neulasta Prescribing Information, June, 2011; Neupogen Prescribing Information, March, 2013; Granix Prescribing Information, May, 2013). These drugs 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

Clinical development of EP2006 was initiated outside the US. The biologic product received approval by EMA in 2009. No trials have been performed in the US. The key events in the US presubmission regulatory activities include a pre-IND meeting 9/28/2010 and a BPD Type 4 meeting 11/19/2013.

FDA provided the following advice and comments to the sponsor regarding the clinical aspects of a BLA submission:

- FDA indicated that the sponsor should address the possibility that more limited functional capacity of the bone marrow in the patient populations for which US-licensed Neupogen is indicated would unveil differences in potency between a proposed biosimilar product and the reference product that would not be detectable in normal volunteers *[PIND]*.

- FDA advised that Sandoz should provide some clinical data comparing EP2006 with US-licensed Neupogen in each of the populations relevant to the indications for which it was seeking licensure or provide adequate scientific justification for extrapolation of data to support licensure for one or more additional indications for which the reference product is licensed *[PIND]*.

2.6 Other Relevant Background Information

Cycle 1 DSN is accepted as a surrogate measure of clinical benefit for use in studies of leukocyte growth factors used prophylactically in patients treated with chemotherapy for nonmyeloid malignancies (Gootenberg, 2002). The risk of severe neutropenia and adverse events is known to be highest in Cycle 1 of chemotherapy in this setting (Crawford, Dale, et al. 2008).

Blackwell and Crawford (1994) reported a correlation between DSN and risk of febrile neutropenia that was approximately linear over a DSN range of 3-7 days. The treatment benefit was approximately a 10% reduction in febrile neutropenia for each fewer day of severe neutropenia. No other surrogate for effectiveness or safety endpoints have been characterized is this fashion.

For noninferiority comparisons of leukocyte growth factors to US-licensed Neupogen, a loss of more than one day of treatment effect (about 10% in the incidence of febrile neutropenia) is considered clinically meaningful (Gootenberg, 2002). The limits of clinical meaningfulness for testing equivalence to US-licensed Neupogen have not been established.

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 Pediatric Review Committee concurred with the initial Pediatric Study Plan on 4/9/2014. The final Pediatric Study Plan was pending at the time of finalization of this review

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

BLA 125553 was received 5/8/2014 as an electronic submission is CTD format. Following receipt of missing information provided in response to information requests, the submission was found to be complete and was filed on 7/7/2014. Additional amendments are listed in Table 1.

Table 1: BLA Submission and Amendments

SDN	Received	Category	Subcategory
1	5/8/2014	Original	BLA
3	6/05/2014	Clinical	Response To Information Request
5	6/16/2014	Clinical	Response To Information Request
6	6/18/2014	Clinical/Biometrics	Response To Information Request
7	6/24/2014	Clinical	Response To Information Request
11	8/22/2014	Clinical	Response To Information Request
12	9/4/2014	Clinical	Safety Update
19	10/31/2014	Clinical	Clinical Information
21	12/2/2014	Clinical/Labeling	Clinical Information
22	12/5/2014	Clinical	Clinical Information
23	12/19/2014	Clinical	Response To Information Request

There were two major data integrity issues identified. The first issue regarded documentation of investigational product in Study EP06-302. As described in Section 5.3.1, the clinical site staff preparing study drug for administration in Study EP06-302 was not blinded, but they were to keep a record of the actual product drawn up for use in a blinded syringe. The applicant submitted the data file ex.xpt with exposure identity variable EXCAT denoting only "Study Drug Administration" as the data element. FDA requested a revised data file that indicated the actual

identity of the agent administered. The applicant submitted a revised ex.xpt in SDN 5 with a new variable for the actual agent administered, EXSCAT, but the data elements were limited to only leukocyte growth factors that were not study agents. For the purposes of identifying the actual agent administered, this reviewer imputed the identity of the treatment administered as the agent planned for the cycle for 98% of the doses administered. The verity of this approach was confirmed at FDA's inspection (see Section 3.2).

The second data integrity issue regarded major errors in the datasets identified by the applicant after filing the BLA. On 12/2/2014, the applicant submitted revised data files for Studies EP06-101, EP06-102, EP06-104, EP06-105 and EP06-301 due to errors that occurred in the process of mapping the clinical datasets to CDISC standards. An explanation submitted 12/19/2014 revealed that the errors affected critical files, including demographics, exposure, safety data and pharmacokinetics. The revised data sets came late in the review cycle and were not subject to verification by FDA inspection.

3.2 Compliance with Good Clinical Practices

All clinical study reports stated that the protocols were conducted in compliance with Good Clinical Practice (GCP). Audits were conducted by an independent agent, and no adverse audit findings were reported by the applicant for any of the studies. All clinical studies used in this review were conducted solely outside the US. The information required to demonstrate compliance with 21 CFR 312.120 was included in the application.

The Office of Scientific Investigations Division of Good Clinical Practice Compliance conducted inspections for Study 302 at one clinical site in Hungary (Site 204) and of the applicant's study records (Sandoz Pharmaceuticals, Hozkirchen, Germany). At Site 204, no regulatory issues were identified, and the raw data was verified. Review of the applicant's records revealed that commercial leukocyte growth factor was substituted for the study biologic in 33 cycles for 26 subjects. Most of these events occurred at Site 703, involving 76% of the randomized subjects at that single site. The applicant indicated that such substitutions occurred for ethical reasons when deviations in storage conditions prohibited use of the study supply after subjects had already received myelosuppressive chemotherapy. How these substitutions were handled in the analysis of the study outcomes is discussed in Sections 6.1.4 and 6.1.5.

3.3 Financial Disclosures

The applicant obtained financial disclosure forms from 129 investigators for Study EP06-302, 2 investigators for Study EP06-101, 4 investigators for Study EP06-102, 5 investigators for Study EP06-103, 4 investigators for Study EP06-104, 4 investigators for Study EP06-105, and 8 of the 10 investigators listed for Study EP06-109. None of the investigators in any of the studies was identified as an employee of the applicant, and no disclosable financial interests or arrangements were identified on any of the financial disclosure forms. To ensure no bias was introduced as a result of an undeclared financial conflict of interest at the clinical site for Study EP06-109, a request for inspection of the records for this study was submitted to the Office of Scientific Investigations Division of Bioequivalence and Good Laboratory Practice, but the records were

not available for audit at the time of the inspection. Since the clinical data from Study EP06-109 were utilized only as supporting information in this review, no further action was taken.

4 Significant Issues Related to Other Review Disciplines

At the time of completion of this review, only preliminary reports of significant issues were available from other review disciplines.

4.1 Product Quality

4.1.1 Chemistry Manufacturing and Controls

The applicant proposed to use clinical studies comparing EP2006 to US-licensed Neupogen or to EU-approved Neupogen to support its claim that EP2006 is a US-licensed Neupogen biosimilar. A three-way analytical comparison was performed by the applicant. The CMC Reviewer indicated that the results provided adequate scientific justification for use of either US-licensed Neupogen or EU-approved Neupogen as a comparator in studies for this application.

The applicant described several manufacturing processes used to produce EP2006 for the clinical studies and a final commercial manufacturing process. The CMC Reviewer confirmed that products from these processes were shown to be comparable.

Lastly, the CMC Reviewer indicated that the analytical comparisons showed the EP2006 and US-licensed Neupogen were highly similar. It was noted that EP2006 is formulated in a buffer that differs from that used for US-licensed Neupogen, and the analytical studies could not predict how this difference in buffer might affect the pharmacokinetics of EP2006 in humans.

4.1.2 Immunogenicity

The Immunogenicity Reviewer indicated that anti-G-CSF antibody was not detected in any of the study subjects tested, whether the subject was treated with EP2006, US-licensed Neupogen or EU-approved Neupogen, in any of the six studies with immunogenicity data available.

4.1.3 Device

The DMEPA Reviewer indicated that the needle safety device obstructed the gradations on the syringe below 0.3 mL. The applicant proposed (b) (4) . At the time of this review, it was not clear how labeling would address administration of EP2006 from the prefilled syringe for children using doses less than 0.3 mL.

4.2 Preclinical Pharmacology/Toxicology

The Preclinical Reviewer identified no issues in the preclinical pharmacodynamics, toxicity, toxickinetics, and local tolerance studies.

4.3 Clinical Pharmacology

The Clinical Pharmacology Reviewer identified no issues in the pharmacokinetic and pharmacodynamics studies in healthy volunteers. The Clinical Pharmacology Reviewer did note that in the PK substudy of Study EP06-302 in the patients with breast cancer, the exposure of EP2006 was lower than that observed for US-licensed Neupogen. The Reviewer noted further that this substudy was not designed as a definitive PK study, the inter-subject coefficient of variability was relatively large in comparison to that in the healthy volunteers, and the difference in exposures in the patients did not appear to translate into a clinically meaningful difference in PD.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

Table 2. Clinical Trials of EP2006

Study	Design	Population	Primary Endpoint
EP06-101	Randomized, double-blind, multiple-dose, 2-way crossover •EP2006 10 ug/kg/d sc x 7 •EU-approved Neupogen 10 ug/kg/d sc x 7	Healthy volunteers - 40 subjects randomized 1:1	AUC Ratio and Cmax Ratio for test product to reference product
EP06-102	Randomized, double-blind, single-dose, 2-way crossover •EP2006 5 ug/kg iv x 1 •EU-approved Neupogen 5 ug/kg iv x 1	Healthy volunteers - 26 subjects randomized 1:1	AUC Ratio and Cmax Ratio for test product to reference product
EP06-103	Randomized, double-blind, 2-dose level, multiple-dose, 2-way crossover •EP2006 2.5 or 5 ug/kg/d sc x 7 •EU-approved Neupogen 2.5 or 5 ug/kg/d sc x 7	Healthy volunteers - 56 subjects with 28 in each dose group randomized 1:1	AUC ANC Ratio for test product to reference product
EP06-104	Randomized, double-blind, single-dose, 3-way crossover •EP2006 acetate 2.5 ug/kg sc x 1 •EP2006 glutamate 2.5 ug/kg sc x 1 •EU-approved Neupogen 2.5 ug/kg sc x 1	Healthy volunteers - 30 subjects randomized equally into each of 6 arms	AUC Ratio and Cmax Ratio for glutamate product to acetate product
EP06-105	Randomized, double-blind, single-dose, 2-way crossover •EP2006 1 ug/kg sc x 1 •EU-approved Neupogen 1 ug/kg sc x 1	Healthy volunteers - 24 subjects randomized 1:1	AUC ANC Ratio for test product to reference product
EP06-106	Randomized, double-blind, single-dose, 2-way crossover •EP2006 5 ug/kg sc x 1 •Gran 5 ug/kg sc x 1	Healthy volunteers - 24 subjects randomized 1:1	AUC Ratio, Cmax Ratio, and AUC ANC Ratio for test product to reference product

Study	Design	Population	Primary Endpoint
EP06-107	Randomized, double-blind, single-dose, 2-way crossover •EP2006 2.5 ug/kg iv x 1 •Gran 2.5 ug/kg iv x 1	Healthy volunteers - 24 subjects randomized 1:1	AUC Ratio, Cmax Ratio, and AUC ANC Ratio for test product to reference product
EP06-108	Randomized, double-blind, multiple-dose, 2-way crossover •EP2006 5 ug/kg BID sc x 3 days •Gran 5 ug/kg BID sc x 3 days	Healthy volunteers - 34 subjects randomized 1:1	AUC CD34 Ratio for test product to reference product
EP06-109	Randomized, double-blind, single-dose, 2-way crossover •EP2006 10 ug/kg/d sc x 1 •US-licensed Neupogen 10 ug/kg/d sc x 1	Healthy volunteers · 28 subjects randomized 1:1	AUC ANC Ratio, AUC Ratio and Cmax Ratio for test product to reference product
EP06-110	Randomized, double-blind, multiple-dose, 2-way crossover •EP2006 5 ug/kg BID sc x 3 days •Gran 5 ug/kg BID sc x 3 days	Healthy volunteers - 78 subjects randomized 1:1	AUC CD34 Ratio for test product to reference product
EP06-301	Open-label, single-arm, multi-center •EP2006 300 or 480 ug/d sc x 14 (Dosing based on weight category)	Adult females with breast cancer scheduled to receive doxorubicin and docetaxel chemotherapy for 4 cycles - 170 subjects enrolled	Incidence of adverse events
EP06-302	Randomized, double-blind, 4-arm, noninferiority and interchangeability trial •EP2006 5 ug/kg/d x 14 •US-licensed Neupogen 5 ug/kg/d x 14	Adult females with breast cancer scheduled to receive TAC chemotherapy for 6 cycles - 214 subjects randomized 1:1:1:1	Duration of severe neutropenia in cycle 1
EP06-501	Prospective, observational study •EP2006 as per EU labeling	Healthy donors · 121 subjects enrolled	Incidence of adverse events

5.2 Review Strategy

The key materials used for the review of EP2006 include:

- BLA 125553
- Relevant published literature
- Relevant information in the public domain

There was no clinical trial submitted that was designed as a comparative clinical study to test equivalence with regard to a clinical efficacy endpoint. The primary efficacy endpoint of Study EP06-302 was utilized to determine if there was a clinically meaningful difference between

EP2006 and US-licensed Neupogen on the basis of a post hoc analysis. For the assessment of similarity with regard to clinical safety, only protocols that included US-licensed Neupogen or EU-approved Neupogen as a control were used. Studies using other controls and studies without controls (noncomparative studies) provided limited supporting safety information.

5.3 Discussion of Individual Studies/Clinical Trials

5.3.1 Study EP06-302

A Randomized, Double-Blind, Parallel-Group, Multi-Center Phase III Study Comparing The Efficacy And Safety Of EP2006 And Neupogen® In Breast Cancer Patients Treated With Myelosuppressive Chemotherapy

Design

The protocol is a randomized, double-blind, noninferiority comparison of EP2006 and US-licensed Neupogen given subcutaenously for prevention of chemotherapy-induced severe neutropenia. Eligible patients were women with breast cancer scheduled for neoadjuvant or adjuvant treatment with TAC chemotherapy for 6 cycles. The study subjects were randomized equally into one of four groups to receive EP2006 for all cycles, US-licensed Neupogen for all cycles, EP2006 then US-licensed Neupogen in alternate cycles, or US-licensed Neupogen then EP2006 in alternate cycles as shown in Table 3. Follow-up was through 4 weeks after the last dose of study drug.

Table 3: Study Drug Sequence by Study Arm

Study Arm		Cycle 1	Cycle 2	Cycle 3	Cycle 4	Cycle 5	Cycle 6
1	(EP)	EP2006	EP2006	EP2006	EP2006	EP2006	EP2006
2	(EPNEU)	EP2006	US-Neupogen	EP2006	US-Neupogen	EP2006	US-Neupogen
3	(NEUEP)	US-Neupogen	EP2006	US-Neupogen	EP2006	Neupogen	EP2006
4	(NEU)	US-Neupogen	US-Neupogen	US-Neupogen	US-Neupogen	US-Neupogen	US-Neupogen

Objectives

The primary objective of the study was to compare the mean DSN in Cycle 1 with EP2006 vs US-licensed Neupogen. DSN was defined as the number of consecutive days that a subject's ANC is <0.5 Gi/L in Cycle 1. For subjects who do not experience any severe neutropenia in Cycle 1, the DSN was set to 0.

Secondary objectives included the incidence of febrile neutropenia, days of fever, ANC nadir, time to ANC recovery, frequency of infections, incidence and duration of hospitalization due to febrile neutropenia, incidence, occurrence, and severity of adverse events, assessment of local tolerability at the injection site, systemic tolerance (physical examination and safety laboratory assessments), and anti-rhG-CSF antibody formation.

Key Eligibility Criteria

- Women ≥ 18 years of age
- Histologically proven breast cancer
- Eligible for neoadjuvant or adjuvant TAC chemotherapy
- Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2
- ANC ≥ 1.5 Gi/L
- Platelet count ≥ 100 Gi/L
- Hemoglobin ≥ 10 g/dL
- Total bilirubin within normal limits
- Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) level ≤ 2x ULN
- Liver-derived alkaline phosphatase level ≤ 3x ULN
- Creatinine ≤ 1.5 x ULN
- No history of myelogenous leukemia, myelodysplastic syndrome, sickle cell disease, previous or concurrent malignancy (except nonmelanoma skin cancer or cancer treated with curative intent), or any serious illness or medical condition
- No concurrent or prior radiotherapy within four weeks of randomization, anti-cancer treatment for breast cancer
- No prior bone marrow or stem cell transplant
- No previous therapy with any rhG-CSF product
- No known hypersensitivity to E. coli proteins or any of the excipients used in the IMPs
- No documented HIV, Hepatitis B or Hepatitis C infection
- No participation in any other clinical study using an investigational product or device within three months

Treatment Plan

Chemotherapy (TAC) consisted of doxorubicin 50 mg/m², cyclophosphamide 500 mg/m², and docetaxel 75 mg/m² given intravenously on day 1 of each 21-day cycle.

Blinded study drug (EP2006 or US-licensed Neupogen) was administered at 5 µg/kg subcutaneously from day 2 of each cycle until the ANC recovered to at least 10 Gi/L or for a maximum of 14 days, whichever occurs first. Study drugs were supplied to the clinical sites openly labelled. The staff preparing study drug for administration were not blinded. The patient, investigator and all other staff involved in study assessments were blinded.

Schedule of Assessments

For the assessment of the primary endpoint, a complete blood count was performed in Cycle 1 from day 1 until the ANC recovered to 10 Gi/L or day 15, whichever occurred first. For Cycles 2-6, the complete blood count was performed on day 1 and daily only from day 7 until recovery.

Table :Schedule of Study Assessments

	Cycle 1, 2, 3, 4, 5, 6																				End of Treatment	End of Study[4]
		Week 1							Week 2							Week 3							
Study Procedure	Screening (D -21 to D -1)	C# D1 Visit	C# D2	C# D3	C# D4	C# D5	C# D6	C# D7	C# D8	C# D9	C# D10	C# D11	C# D12	C# D13	C# D14	C# D15	C# D16	C# D17	C# D18	C# D19	C# D20	C# D21	C# D21 / Early Termination	Study Termination
Informed consent	X																						
Demographics	X																						
Medical and surgical history	X																						
Previous treatment	X																						
ECOG status	X	X																				X	
Physical examination	X	X																				X	X
Vital signs	X	X																				X	X
Height, weight, BSA	X	X[5]																					
ECG	X																					X	
Echocardiography or MUGA	X																						
CBC[1]	X	X[7]	X	X	X	X	X	X	X	X	X	X	X	X	X	X						X	
PK sample - see table 7.2																							
Clinical chemistry[2]	X	X[7]																				X	
Urinalysis	X	X[7]																				X	
Serum pregnancy test	X																					X	
Serology for HIV, Hepatitis B+C	X																						
Anti-rhG-CSF antibody sample collection		X																				X	X
Chemotherapy administration		X																					
Randomization[3]			X																				
IMP administration[3]			X	X	X	X	X	X	X	X	X	X	X	X	X	X								
Injection site assessment[3]			X	X	X	X	X	X	X	X	X	X	X	X	X	X							X	
Body temperature measurements		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Concomitant medication		X	Assessed at every visit																			X	X	
AE assessment		X	Assessed at every visit																			X	X	

From Study EP06-302 Table 7-1

Statistical Analysis Plan

The primary efficacy endpoint was DSN in Cycle 1. The accrual target was 192 subjects. With a 1:1 randomization, an assumption of 10% dropouts, and a noninferiority margin of 1 day, the applicant calculated that the sample size had 90% power to test the primary endpoint with a 2.5% one-sided Type 1 error.

The populations planned for analyses included (From Study EP06-302 Clinical Study Report Table 9-5):

- Safety set (SAF) - The safety set consists of all patients who received at least one dose of study drug and had at least one post-baseline safety assessment.
- Full analysis set (FAS) - All randomized patients who received at least one dose of study medication. Patients are analyzed according to the treatment they were assigned to at randomization.
- Per protocol (PP) set - Those patients who completed the first chemotherapy cycle without major protocol deviations (deviation from entry criteria, errors in treatment assignment, use of excluded/forbidden/un-allowed medication, poor compliance, loss to follow-up, missing ANC data).
- Safety interchangeability (SAF-I) set - All randomized patients who received at least one dose of study drug after Cycle 1.
- PP interchangeability (PP-I) set - All randomized patients who completed all six chemotherapy cycles without major protocol violations.

- Pharmacokinetic (PK) analysis set - All patients participating in the PK sub-study with a valid PK profile.

The primary analysis was to be based on Cycle 1 ANC data for patients in the PP population (those who completed the first cycle without major protocol deviations). The Statistical Analysis Plan indicated that main efficacy parameter would be analyzed by ANCOVA with factor treatment group, strata adjuvant vs neo-adjuvant, and the covariate baseline ANC. Non-inferiority of EP2006 would be concluded if the lower limit of the two-sided 95% CI of the treatment difference did not exceed the -1 day margin. The same analysis using the FAS population were planned to ensure robustness.

All secondary efficacy parameters were to be evaluated descriptively by treatment group in the per protocol population, the completer population (PP-I) and the full analysis set as indicated in the Statistical Analysis Plan.

Key Study Revisions

There were two amendments to Study EP06-302, Amendment 1 on 8/2/2011 and Amendment 2 on 5/30/2012. None of the revisions was considered major with regard to impact on the analysis of the primary endpoint.

5.3.2 Studies in Healthy Volunteers

5.3.2.1 *Study EP06-101* - A *Randomized, Double-Blind, Multiple-Dose, 2-Way Crossover Study To Compare The Pharmacokinetics, Pharmacodynamics, Safety, And Local Tolerance Of 10 Mg/Kg/Day Filgrastim Sandoz And Filgrastim (Neupogen®) Following Multiple Subcutaneous (S.C.) Administration In Healthy Adult Subjects*

The protocol was a randomized, double-blind, multiple-dose, 2-way crossover study comparing EP2006 to EU-approved Neupogen in healthy volunteers. There were 2 administration periods for each subject during which the leukocyte growth factor was given at 10 ug/kg/day sc x 7 days followed by a 28-day washout period. Subjects were randomized 1:1 to 1 of the 2 cross-over sequences in the study. The primary objective was to compare the PK of the 2 agents following single and multiple doses. A secondary objective was to compare PD measures of ANC and CD34+ cells. Subjects were assessed clinically on days 1, 7 and 10 of each administration period. Safety laboratory testing was performed on days 1, 4, 7 and 10, and ultrasound of the spleen at baseline and on day 10. Forty subjects were randomized, 8 dropped out early, and 32 subjects completed both administration periods.

5.3.2.2 *Study EP06-102* - *A Single Center, Randomized, Double-Blind, Two-Way Cross-Over Study To Determine The Pharmacokinetics And Pharmacodynamics Of Filgrastim Sandoz And Filgrastim (Neupogen) Administered At A Dose Of 5 Mg/Kg Body Weight As Intravenous Infusion To Healthy Male And Female Subjects*

The protocol was a randomized, double-blind, single-dose, 2-way crossover study comparing EP2006 to EU-approved Neupogen in healthy volunteers. There were 2 administration periods

for each subject during which the leukocyte growth factor was given at 5 ug/kg/day iv over 30 minutes once followed by a 14- to 21-day washout period. Subjects were randomized 1:1 to 1 of the 2 cross-over sequences in the study. The primary objective was to compare the single-dose PK of the 2 agents. A secondary objective was to compare PD measures of ANC. Subjects were assessed clinically and safety laboratory testing was performed on day 1 of each administration period and 7-14 days after the last dose. Twenty-six subjects were randomized, 2 dropped out early, and 24 subjects completed both administration periods.

5.3.2.3 *Study EP06-103 - A Single Center, Randomized, Double-Blind, Multiple-Dose, Two-Way Cross-Over Study To Determine The Pharmacodynamics And Pharmacokinetics Of Filgrastim Sandoz And Neupogen® At Two Dose Levels (2.5 And 5.0 Mg/Kg Body Weight) Administered To Two Groups (Group 1: 2.5 Mg/Kg Body Weight, Group 2: 5 Mg/Kg Body Weight) As Single And Multiple Subcutaneous Injections To Healthy Male And Female Subjects*

The protocol was a randomized, double-blind, 2 dose-level, multiple-dose, 2-way crossover study comparing EP2006 to EU-approved Neupogen in healthy volunteers. There were 2 administration periods for each subject during which the leukocyte growth factor was given at either 2.5 ug/kg/day sc x 7 days followed by a 28-day washout period (group 1) or at 5 ug/kg/day sc x 7 days followed by a 28-day washout period (group 2). Subjects were randomized 1:1 to 1 of the 2 cross-over sequences within each group in the study. The primary objective was to compare the PD measure of ANC at each dose level. Secondary objectives were to compare PD measure of CD34+ cells and PK. Subjects were assessed clinically prior to dose 1 and 11-15 days after the last dose of each administration period. Safety laboratory testing was performed on days -1, 4, 7, 10, and 11-15 days after the last dose of each administration period. Ultrasound of the spleen on day -1 of each administration period. Fifty-six subjects were randomized (28 in each dose-level group), 1 dropped out early, and 55 subjects completed both administration periods.

5.3.2.4 *Study EP06-104 - A Single Center, Randomized, Double-Blind, Three-Way Cross-Over Study To Determine The Pharmacokinetics And Pharmacodynamics Of Two Formulations Of EP2006 And Neupogen® Administered At A Single Dose Of 2.5 Mg/Kg Body Weight As Subcutaneous Injection To Healthy Male And Female Subjects*

The protocol was a randomized, double-blind, single-dose, 3-way crossover study comparing two different formulations of EP2006 and EU-approved Neupogen in healthy volunteers. There were 3 administration periods for each subject during which the leukocyte growth factor was given at 2.5 ug/kg/day sc over 30 minutes once followed by a 14- to 21-day washout period. Subjects were randomized equally to 1 of the 6 cross-over sequences in the study. The primary objective was to compare the single-dose PK of the EP2006 formulations. Secondary objectives included compares of PK and PD measures of ANC between the EP2006 formulations and EU-approved Neupogen. Subjects were assessed clinically and safety laboratory testing was performed prior to dose 1 and 7-14 days after the last dose. Thirty subjects were randomized, 1 dropped out early, and 29 subjects completed all three administration periods.

5.3.2.5 *Study EP06-105 - A Single Center, Randomized, Double-Blind, Two-Way Cross-Over Study To Determine The Pharmacokinetics And Pharmacodynamics Of EP2006 And Neupogen®*

Administered At A Single Dose Of 1.0 Mg/Kg Body Weight As Subcutaneous Injection To Healthy Male And Female Subjects

The protocol was a randomized, double-blind, single-dose, 2-way crossover study comparing EP2006 to EU-approved Neupogen in healthy volunteers. There were 2 administration periods for each subject during which the leukocyte growth factor was given at 1 ug/kg/day sc over 30 minutes once followed by a 10- to 20-day washout period. Subjects were randomized 1:1 to 1 of the 2 cross-over sequences in the study. The primary objective was to compare PD measures of ANC. A secondary objective was to compare the single-dose PK of the 2 agents. Subjects were assessed clinically and safety laboratory testing was performed prior to dose 1 and 7-14 days after the last dose. Twenty-four subjects were randomized, and all completed both administration periods.

5.3.2.6 *Study EP06-109 - A Randomized, Double-Blind, Two-Way Crossover Study To Determine The Pharmacodynamics, Pharmacokinetics And Safety Of EP2006 And Neupogen® (US-Licensed) Following A Single Subcutaneous Injection In Healthy Subjects*

The protocol was a randomized, double-blind, single-dose, 2-way crossover study comparing EP2006 to US-licensed Neupogen in healthy volunteers. There were 2 administration periods for each subject during which the leukocyte growth factor was given at 10 ug/kg sc once followed by a 28-day washout period. Subjects were randomized 1:1 to 1 of the 2 cross-over sequences in the study. The primary objectives were to compare PD measures of ANC and single-dose PK of the 2 agents. A secondary objective was to compare PD measures of CD34+ cells. Subjects were assessed clinically on day -1 of each administration period and 28 days after the last dose. Safety laboratory testing was performed on days -1 and 3 of each administration period and 28 days after the last dose. Twenty eight subjects were randomized, 2 dropped out early, and 26 subjects completed both administration periods.

6 Review of Efficacy Endpoints

Summary

The comparison of EP2006 with US-licensed Neupogen with regard to an efficacy endpoint in an intended population was based on Study EP06-302, a randomized, double-blind, comparison of EP2006 and US-licensed Neupogen for prevention of severe neutropenia in patients with breast cancer being treated with up to 6 cycles of combination chemotherapy using docetaxel, doxorubicin, and cyclophosphamide (TAC). There were 218 subjects randomized equally into one of four groups to receive EP2006 for all cycles, US-licensed Neupogen for all cycles, EP2006 then US-licensed Neupogen in alternate cycles, or US-licensed Neupogen then EP2006 in alternate cycles. Baseline demographics and disease characteristics were adequately balanced between arms.

The per protocol (PP) populations were used for between-group analyses of the efficacy endpoints. The primary endpoint was DSN in Cycle 1. Although Study EP06-302 was designed as a noninferiority trial, FDA conducted a post hoc 2-sided analysis to ensure there were no clinically meaningful differences between EP2006 and US-licensed Neupogen with regard to the primary endpoint. Key secondary endpoints, including febrile neutropenia, days of fever, ANC nadir, and time to ANC recovery in Cycle 1 and across all cycles, were planned to be reported descriptively by treatment arm.

Results of the efficacy analyses showed the following:

- The between-group analysis of the primary endpoint of Cycle 1 DSN included 101 subjects treated with EP2006 and 103 subjects treated with US-licensed Neupogen. The DSN difference (control-experimental) was 0.04 days with a 90% confidence interval of -0.21 to 0.28 days. Among the primary analysis, supporting analysis and key sensitivity analyses, the upper and lower bounds of the 90% confidence interval for difference in Cycle 1 DSN were no greater than 0.28 days.

- The between-group analyses of the key secondary endpoints included 40 subjects treated with EP2006 in all cycles and 46 subjects treated with US-licensed Neupogen in all cycles. Although there were small numerical differences between groups for each endpoint when assessed by cycle, neither the absolute difference nor the direction of the difference was consistent across the cycles.

- The within-subject analyses of time to ANC recovery, a secondary endpoint, included 91 subjects who had at least 2 cycles using EP2006 and at least 2 cycles using US-licensed Neupogen. The ratio (EP2006: US-licensed Neupogen) of the mean time to ANC recovery was 1.01 (90% CI 0.99-1.04).

Overall, Study EP06-302 demonstrated no clinically meaningful differences between EP2006 and US-licensed Neupogen with respect to DSN in cycle1, and the secondary endpoints were similar for patients treated with EP2006 vs US-licensed Neupogen. Study EP06-302 was conducted in a patient population addressed by only one of the five indications approved for US-

licensed Neupogen. The applicant proposed to use extrapolation based on the mechanism of action to claim the other four indications.

6.1 Cancer Patients Receiving Myelosuppressive Chemotherapy

Zarxio is indicated 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.

6.1.1 Methods

The comparison of EP2006 with US-licensed Neupogen with regard to a clinical efficacy endpoint for this indication was based on Study EP06-302. The details of the protocol design were described in Section 5.3.1. The dose of EP2006 chosen for study, 5 µg/kg/day, was based on the dose approved for the reference product, US-licensed Neupogen. The main objective of the study as designed was to establish noninferiority of EP2006 relative to US-licensed Neupogen in Cycle 1 DSN. The PP population was planned for use in the primary analysis of the primary endpoint, and the FAS population was to be used for the secondary analysis. Noninferiority would be concluded if the lower limit of the two-sided 95% CI of the treatment difference did not exceed one day.

Review Comments:

- ***Without leukocyte growth factor support, the chemotherapy regimen in this protocol is known to cause febrile neutropenia in a median of 29% (range, 22-34%) of patients (Martin, Pienkowski, et al, 2005; Nabholtz, Mackey, et al. 2001; Naboholtz, Smylie, et al. 1997;O'Regan, Von Roenn, et al. 2005; von Minckwitz, Kummel, et al, 2008) and a median 7 days of severe neutropenia (Nabholtz, Mackey, et al. 2001), so it is sufficiently myelosuppressive to allow for a comparison that would support the stated indication.***

- ***Since there is a potential for increased toxicity of EP2006 with an increase in potency, dose and/or exposure with a supratherapeutic dose (Engelhardt , Bertz, et al. 1999), a noninferiority analysis as used in the applicant's statistical analysis plan would not be sufficient to exclude clinically meaningful differences between EP2006 and US-licensed Neupogen. A two-sided analysis to assess equivalence would be a better approach.***

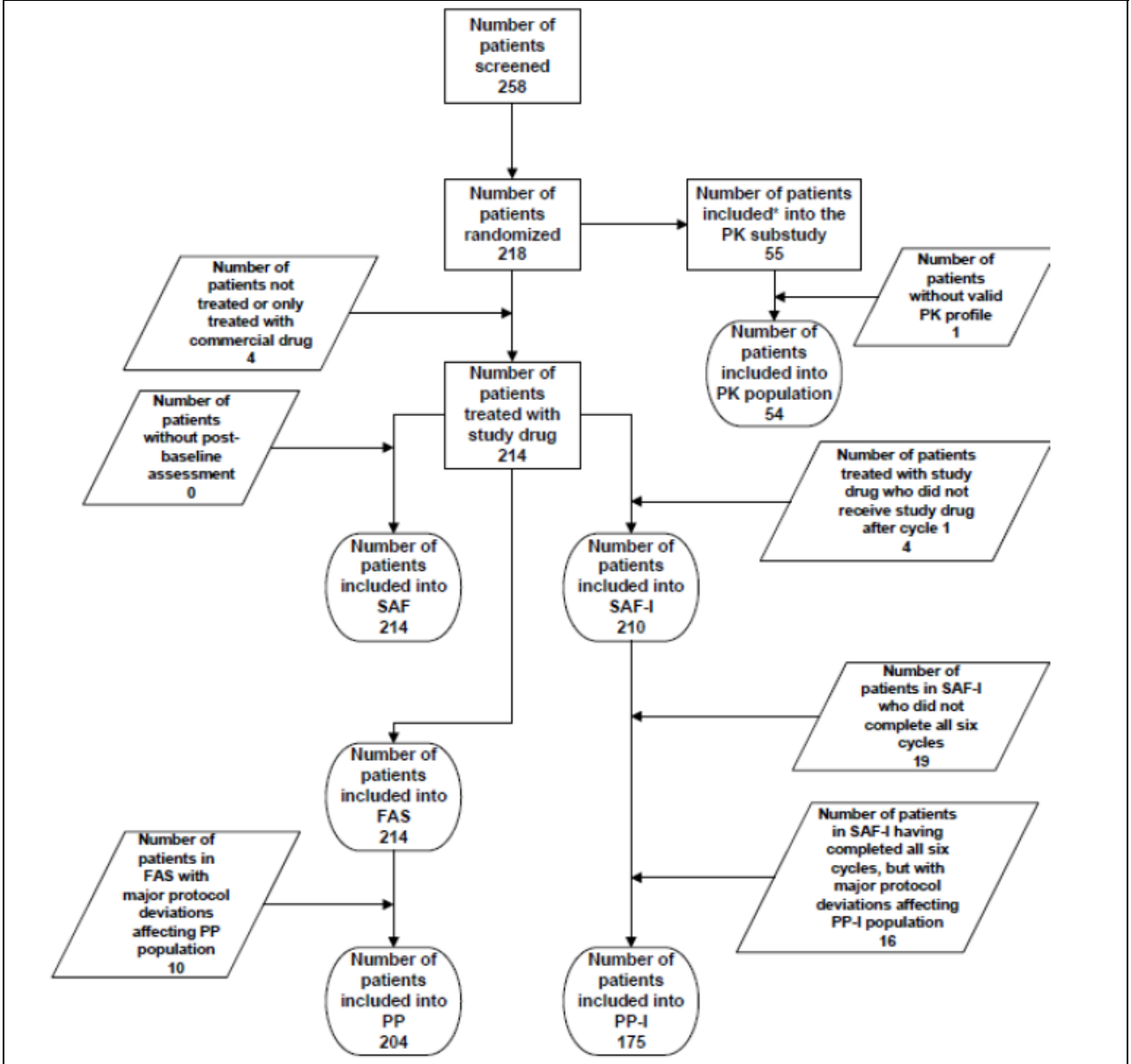
- ***As discussed in Section 2.6, Cycle 1 DSN is a clinically relevant endpoint for the objective of this comparison. Since the statistical analysis plan does not provide for equivalence limits, the results of the analysis will be a review issue.***

- ***For an assessment of equivalence for an efficacy endpoint, there are inherent biases when using either the PP or the FAS population for analyses. Use of the PP population for the primary analysis is considered acceptable, but a positive secondary analysis in the FAS population is needed in order to support robustness.***

6.1.2 Subject Disposition

A total of 258 women were enrolled. The first subject was enrolled on 12/26/2011, and the last subject completed follow-up on 6/17/2013. A diagram of the analysis populations as defined in Section 5.3.1 is shown in Figure 1.

Figure 1: Study Populations



Source: Study EP06-302 Clinical Study Report Figure 11-1

There were 40 screen failures. A total of 218 patients were randomized. Fourteen subjects were subsequently excluded from the randomized population; one did not receive any study drug, four did not complete the course of study drug in Cycle 1 as prescribed, and nine received commercial product rather than study drug for all or for part of Cycle 1. The protocol deviations

are discussed further in Section 6.1.4 below. The remaining 204 subjects comprised the PP population. The disposition of the subjects in the PP population by study arm is shown in Table 4. An additional 29 subjects withdrew from the PP population, and the most common reason was withdrawal of consent. The arm receiving EP2006 alone had the lowest rate of study completion (78%).

Table 4: Disposition of Subjects

	Study Arm				
	EP	**EPNEU**	**NEUEP**	**NEU**	**All**
Enrolled					258
Screen Failure					40
Randomized	54	55	54	55	218
Excluded at Cycle 1	4	4	3	3	14
Per Protocol (PP) Population	50	51	51	52	204
Discontinued Early	11	5	8	5	29
Completed Study (PP-I)	39	46	43	47	175
Early Discontinuation Reasons					
Withdrew Consent	4	2	3	2	11
Refused Further Treatment	2	2	0	1	5
Lost To Follow-Up	1	0	2	1	4
Disease Progression	1	0	2	0	3
Missed Visits	2	0	0	1	3
Adverse Event	0	0	1	0	1
Death	1	0	0	0	1
Other-Planned Surgery	0	1	0	0	1

Source: FDA analysis

6.1.3 Demographics

The characteristics of the PP population are shown in Table 5. All subjects were female and Caucasian. There was one Hispanic subject in the NEU arm, and the remainder were non-Hispanic. Few (10%) of the subjects were ≥ 65 years old, and none had metastatic breast cancer. There were no substantial differences in the patient characteristics when compared by study arm or by treatment given in Cycle 1.

Table 5: Demographics (Per Protocol Population)

	Study Arm				Cycle 1 by Treatment		
	EP (N=50)	**EPNEU (N=51)**	**NEUEP (N=51)**	**NEU (N=52)**	**EP2006 (N=101)**	**US-licensed Neupogen (N=103)**	**All (N=204)**
Median Age (years) (range)	53 (24 - 74)	50 (26 - 73)	50 (26 - 71)	47 (23 - 76)	51 (24 - 74)	48 (23 - 76)	50 (23 - 76)
Age ≥65 years	6 (12%)	3 (6%)	7 (13%)	4 (8%)	9 (9%)	11 (11%)	20 (10%)
Female	50 (100%)	51 (100%)	51 (100%)	47 (100%)	101 (100%)	103 (100%)	204 (100%)
Caucasian	50 (100%)	51 (100%)	51 (100%)	47 (100%)	101 (100%)	103 (100%)	204 (100%)
Performance Status							
0	38 (76%)	41(80%)	43 (83%)	38 (75%)	79 (78%)	81 (79%)	160 (78%)
1	12 (24%)	10 20%)	9 (17%)	13 (25%)	22 (22%)	22 (21%)	44 (22%)
Stratum							
Adjuvant	29 (58%)	29 (57%)	29 (56%)	29 (57%)	58 (57%)	58 (56%)	116 (57%)
Neoadjuvant	21 (42%)	22 (43%)	23 (44%)	22 (43%)	43 (43%)	45 (44%)	88 (43%)
Stage							
1	5 (10%)	1 (2%)	4 (8%)	4 (8%)	6 (6%)	8 (8%)	14 (7%)
2	24 (48%)	32 (63%)	26 (50%)	24 (47%)	56 (55%)	50 (49%)	106 (52%)
3	21 (42%)	18 (35%)	22 (42%)	23 (45%)	39 (39%)	45 (44%)	84 (41%)
Country							
Russia	37 (74%)	37 (73%)	40 (77%)	42 (82%)	74 (73%)	82 (80%)	156 (76%)
Ukraine	8 (16%)	9 (18%)	8 (15%)	8 (16%)	17 (17%)	16 (16%)	33 (16%)
Hungary	4 (8%)	3 (6%)	3 (6%)	1 (2%)	7 (7%)	4 (4%)	11 (5%)
Latvia	0	1 (2%)	1 (2%)	0	1 (1%)	1 (1%)	2 (1%)
Czech Republic	1 (2%)	0	0	0	1 (1%)	0	1 (<1%)
Slovakia	0	1 (2%)	0	0	1 (1%)	0	1(<1%)

Source: FDA analysis

6.1.4 Protocol Deviations

A total of 300 protocol deviations were reported for 124 subjects in Study EP06-302. Table 6 lists the number of deviations by broad criterion for the total randomized population and the deviations in Cycle 1 for the PP population. Issues with study agent (leukocyte growth factor or chemotherapy) at any time during the trial accounted for 23% of the protocol deviations and affected 20% of the randomized population.

Table 6: Protocol Deviations

	Randomized Population by Study Arm				Per Protocol Population by Cycle 1 Agent		
	EP (N=54)	EPNEU (N=55)	NEUEP (N=55)	NEU (N=54)	EP2006 (N=101)	US-licensed Neupogen (N=103)	All
Subjects with Deviations	33 (61%)	31 (56%)	30 (55%)	28 (52%)	24 (24%)	14 (14%)	124
Deviations	100	75	61	60	41	18	300
Deviations by Criterion							
Lab Test Missed, Late or Problematic	38	21	11	15	16	7	89
Study Agent Missed, Late or Problematic	23	16	17	14	8	3	70
Study Visit Out of Window	16	12	11	12	2	0	51
Procedure Missed, Late or Problematic	16	9	14	10	8	7	49
CBC Missed, Late or Problematic	4	15	7	6	6	1	32
Concomitant Medication Issue	2	1	0	0	0	0	3
Administrative Issue	0	1	0	1	0	0	2
Eligibility Issue	1	0	0	1	1	0	2
Randomization Issue	0	0	1	1	0	0	2

Source: FDA analysis

The major study agent-related protocol deviation was use of commercial leukocyte growth factor in place of EP2006 or US-licensed Neupogen supplied by the applicant. In some cases, only one or a few doses of the study agent were substituted during a single cycle, but in other cases, all doses for the cycle were substituted. Either scenario was considered a major protocol deviation, and the subjects who received commercial leukocyte growth factor were excluded from the primary analyses of efficacy endpoints. The numbers of subjects in the randomized population who received commercial leukocyte growth factor in place of study agent by cycle is shown in Table 7.

Table 7: Numbers of Subjects Treated with Commercial Leukocyte Growth Factor

Planned Study Agent	Cycle 1	Cycle 2	Cycle 3	Cycle 4	Cycle 5	Cycle 6
EP2006	5	4	2	1	2	3
US-licensed Neupogen	4	2	4	0	2	4

Source: FDA analysis

To assess the extent of the errors in dosing chemotherapy, an analysis was performed to determine what percentage of the planned dose was actually administered in the PP population. As shown in Table 8, a median of essentially 100% of the planned doses of chemotherapy was administered in Cycle 1, and no subject received less than 80% of the planned doses. For those subjects treated in Cycles 2-6 (excluding cycles where subjects received commercial drug), the chemotherapy doses were less than 80% of those planned for 5 subjects during 10 (2%) cycles

using EP2006 and 6 (1%) cycles using US-licensed Neupogen. All other subjects received at least 80% of the planned chemotherapy doses.

Table 8: Median Percentage of Planned Chemotherapy Dose (Range)

	Cycle 1		Cycles 2-6	
	EP2006 (N=101)	US-licensed Neupogen (N=103)	EP2006 (N=461)	US-licensed Neupogen (N=479)
Cyclophosphamide	100 (95 - 105)	100 93 - 104	100 76 - 105	100 76 - 105
Docetaxel	100 94 - 104	100 87 - 106	100 70 - 106	100 76 -106
Doxorubicin	99 95 - 105	100 93 - 104	99. 76 - 105	100 76 - 104

For the PP population.
Source: FDA analysis

6.1.5 Primary Efficacy Endpoint

6.1.5.1 Measurement of the Primary Endpoint

Severe neutropenia was defined as ANC <0.5 Gi/L. The duration of severe neutropenia was defined as the number of days from the first day in which the ANC fell below 0.5 Gi/L after beginning a chemotherapy cycle until the ANC was 0.5 Gi/L or higher in the same cycle. According to the protocol, for the PP population, subjects with missing ANC data were excluded, and for the FAS population, missing data was imputed by linear interpolation (Protocol EP06-302 version dated 5/30/2012, Section 10.4.3). According to the Clinical Study Report (dated 12/19/2013, Section 9.7.5.3), missing ANC data was assigned according to the following rules:

- The ANC before and after the missing day was ≥ 0.5 Gi/L: the day could be ignored as a potential day of severe neutropenia.
- If at both neighboring days the ANCs were < 0.5 Gi/L, then the missing day was to be set to severe neutropenia.
- If the day before was < 0.5 Gi/L and the day after ≥ 0.5 Gi/L, then the missing day was to be set to severe neutropenia.
- If the day before was ≥ 0.5 Gi/L and the day after < 0.5 Gi/L, then the missing day was to be set to severe neutropenia.
- If any of the neighboring days was also missing, severe neutropenia could not be determined and remained missing.

FDA identified 4 subjects in the PP population for whom DSN was assigned according to these rules (subjects 603-03, 706-30, 801-01 and 809-08).

6.1.5.2 Analysis of the Primary Endpoint

The applicant provided results from the noninferiority analysis of the primary endpoint. The difference (US-licensed Neupogen - EP2006) in Cycle 1 DSN was 0.04 days (one-sided 97.5% bound, -0.26 days) in the PP population and 0.02 days (one-sided 97.5% bound, -0.27 days) in the FAS population. Since the one-sided 97.5% bound was within the 1-day margin, the applicant concluded that noninferiority was established.

Results of the analyses of Cycle 1 DSN by the FDA statistician are shown in Table 9 (see the FDA Statistician's review for details of the methodology used for the analyses of the efficacy endpoints). The Cycle 1 DSN was slightly shorter for subjects treated with EP2006 with a difference in mean DSN of 0.04 days in comparison to US-licensed Neupogen. The 90% confidence interval for the difference in DSN was -0.21 to 0.28 days. Since DSNs were not normally distributed, the ANCOVA was also performed using a negative binomial distribution assumption (Table 9), and the 90% confidence interval was -0.18 to 0.24. The FDA statistician indicated that alternate methods, such as Poisson regression and bootstrapping, yielded similar results.

Table 9: FDA's Analyses of the Primary Efficacy Endpoint

	Cycle 1 Mean DSN (SD)			
Population[a]	**EP2006**	**US-licensed Neupogen**	**DSN Difference[b]**	**90% CI**
Primary Analysis				
PP	1.17 (1.11) days	1.20 (1.02) days	0.04 days	-0.21 to 0.28
PP, binomial distribution	-	-	0.03 days	-0.18 to 0.24
Key Sensitivity Analyses				
FAS	1.18 (1.12) days	1.20 (1.02) days	0.02 days	-0.22 to 0.26
FAS, excluding Site 703 and subjects with study agent protocol violations	1.15 (1.12) days	1.13 (1.02) days	-0.01 days	-0.28 to 0.25
PP, DSN as ANC < 1.0 Gi/L	1.76 (1.23) days	1.84 (1.25) days	0.08 days	-0.21 to 0.37

[a]The PP population included 101 subjects on EP2006 and 103 subjects on US-licensed Neupogen. The FAS population included 107 subjects on EP2006 and 107 on US-licensed Neupogen. The FAS population excluding all subjects at Site 703 and subjects who received commercial leukocyte growth factor included 92 subjects on EP2006 and 89 subjects on US-licensed Neupogen.
[b]Difference = DSN with US-licensed Neupogen (control) minus DSN with EP2006 (experimental). A positive difference indicates a greater treatment effect with EP2006.
Source: FDA statistician's analysis

The results for three of the sensitivity analyses performed by the FDA statistician are also shown in Table 9. First, the Cycle 1 DSN difference in the FAS population was similar to that in the PP population. Second, the Cycle 1 DSN difference in the FAS population excluding Site 703 fell into the negative range (-0.01 days) with a lower bound (-0.28 days) of the 90% confidence interval, only slightly lower than in the PP population. Lastly, using an alternate level of ANC (ANC <1.0 Gi/L) to determine Cycle 1 DSN in the PP population, the DSN difference and the upper bound (0.37 days) of the 90% confidence interval were slightly higher than in the PP population.

As an additional supporting analysis, the applicant also provided a tabulation of DSN by cycle. However, since ANC was not measured consistently prior to day 7 in Cycles 2-6, the start day for the DSN interval cannot be determined reliably, so these results were not considered further.

Review Comment: The results of the primary analysis and the key sensitivity analyses of the difference in Cycle 1 DSN at the grade 4 level, including an analysis excluding a clinical site with potential to contribute bias, all yielded similar point estimates and 90% confidence intervals with bounds no greater than 0.28 days. The consistency suggests that the results are robust. With the assumption of the correlation between DSN and incidence of febrile neutropenia (see Section 2.6), the bounds of 0.28 days represents approximately a 3% difference in the rate of febrile neutropenia. In the judgment of this reviewer, a 3% increase or decrease in the rate of febrile neutropenia is not clinically meaningful in the intended population.

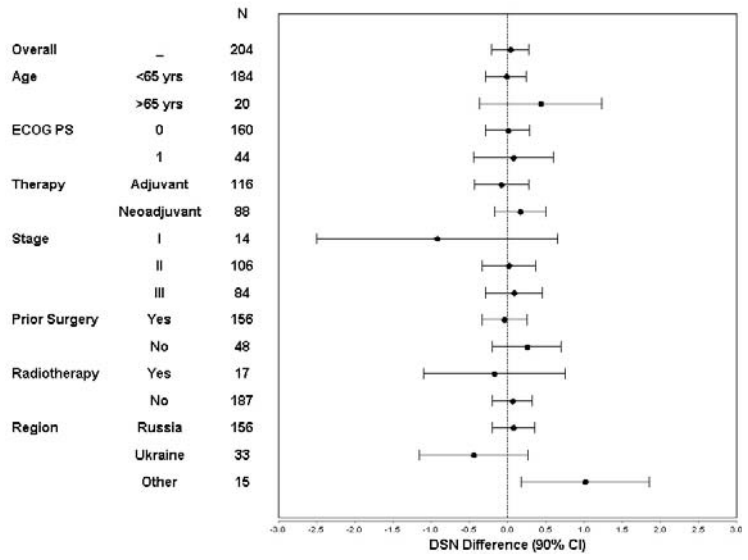
6.1.6 Subpopulations

The applicant provided subgroup analyses of the difference in Cycle 1 DSN by age group, geographic location, chemotherapy stratum, stage at diagnosis, prior breast cancer surgery, prior radiotherapy, and ECOG performance status. They reported that the lower bound of the one-sided 97.5% confidence interval was greater than 1 day in both the PP and FAS populations for the subgroups with Stage 1 disease, prior radiotherapy and in the Ukraine.

The FDA statistician calculated the difference in Cycle 1 DSN and 90% confidence interval by subgroup. These are shown in Figure 2.

Figure 2: Difference in Cycle 1 DSN By Subgroup in the PP Population

Differences in DSN (days) and 90% CI are shown for US-licensed Neupogen DSN minus EP2006 DSN. A positive difference indicates a greater treatment effect with EP2006.



Source: FDA statistician's analysis

Review Comments:

- ***The statistician's calculations confirm the report of the applicant with regard to the lower bound in the subgroups with Stage 1 disease, prior radiotherapy and in the Ukraine. Additionally, two subgroups with relatively high upper bounds were also identified (age ≥ 65 years and geographic region other than Russia and Ukraine). However, there is an inverse correlation between subgroup size and deviation of the point estimate from that for the total population as well as with the width of the 90% confidence interval, supporting the conclusion that the outliers result from small sample size rather than a biological effect.***

- ***There were no subgroup analyses performed by gender or race due to the paucity of males and noncaucasians in the study population. Statistically significant but clinically minor differences in CD34 mobilization and collection by race and gender have been found (Bertani, Santoleri, et al. 2014; Hsu, Wingard, et al. 2015), but there are no reports to date that such differences have occurred with use of filgrastim class products for prevention of neutropenia in patients receiving myelosuppressive chemotherapy, so the omission of such analyses in this application should not alter any conclusions regarding clinically meaningful differences in the primary endpoint.***

6.1.7 Analysis of the Secondary Efficacy Endpoints

The key secondary endpoints planned to support the primary efficacy analysis were febrile neutropenia, days of fever, ANC nadir, time to ANC recovery, frequency of infections, and incidence and duration of hospitalization due to febrile neutropenia. The applicant performed the between-group analyses by assigned study arm and grouping by arms EP+EPNEU vs NEUEP+NEU. The results of the applicant's analysis of febrile neutropenia, days of fever, and ANC nadir are shown in Table 10.

For time to ANC recovery, the applicant provided a summary for the interval from day of nadir to day ANC ≥2 Gi/L (Study EP06-302 Clinical Study Report Section 11.4.2.5). However, the time to ANC recovery was defined by the protocol and SAP as the number of days from chemotherapy administration until the ANC increases to ≥ 2 Gi/L after the nadir. The results for the time to ANC recovery listed in Table 10 are the FDA's analysis based on the definition in the protocol and SAP. For this analysis, the result was set to day 7 for those subjects whose nadir was ≥ 2 Gi/L, and it was set to day 15 for those who did not recover to ≥ 2 Gi/L by day 15.

Table 10: Results of Key Secondary Efficacy Endpoints (Between-Group Comparison)

	Study Agent[a]	Incidence of Febrile Neutropenia (n, %)	Mean (SD) Days with Fever	Mean (SD) ANC Nadir (Gi/L)	Mean (SD) Time to ANC Recovery (Day)
PP Population[b] (Arms EP + EPNEU vs Arms NEU + NEUEP)					
Cycle 1	E	4 (4.0%)	0.1 (0.29)	0.73 (1.14)	9.2 (1.2)
	N	2 (1.9%)	0 (0.24)	0.76 (1.31)	9.0 (1.0)
PP-1 Population[c] (Arm EP vs Arm NEU)					
Cycle 1	E	1 (2.5%)	0 (0.16)	0.57 (0.91)	9.3 (1.0)
	N	0	0 (0)	0.73 (1.34)	9.2 (0.9)
Cycle 2	E	0	0.1 (0.30)	1.36 (2.31)	8.9 (1.0)
	N	0	0 (0)	0.92 (0.86)	9.1 (1.4)
Cycle 3	E	0	0 (0)	0.72 (0.65)	9.6 (1.3)
	N	0	0 (0.15)	1.43 (2.33)	9.1 (1.1)
Cycle 4	E	0	0 (0)	1.03 (1.39)	9.3 (1.4)
	N	0	0 (0)	1.03 (1.40)	9.2 (1.4)
Cycle 5	E	0	0 (0)	1.05 (1.19)	9.1 (1.2)
	N	0	0.1 (0.32)	1.26 (1.66)	9.2 (1.5)
Cycle 6	E	1 (2.5%)	0 (0)	1.03 (1.35)	9.3 (1.4)
	N	0	0 (0)	1.86 (2.89)	9.1 (2.3)

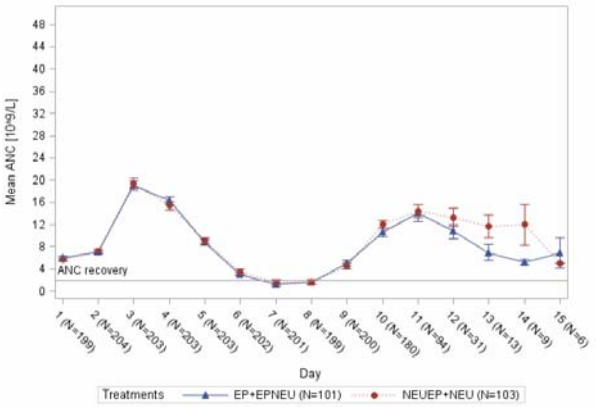
[a]Study agent E=EP2006 and N=US-licensed Neupogen.
[b]The PP population includes 101 subjects on EP2006 (arms EP and EP-NEU) (E) and 103 subjects on US-licensed Neupogen (arms NEU and NEU-EP) (N) in Cycle 1.
[c]The PP-I population includes 40 subjects on EP2006 (arm EP) (E) and 46 subjects on US-licensed Neupogen (arm NEU) (N) across all 6 cycles.
Source: The data for the incidence of febrile neutropenia, days of fever and ANC nadir was taken from Study EP06-302 Clinical Study Report Tables 11-7, 14.2.4.7.3, 14.2.5.2.1, 14.2.3.1.2, 14.2.4.7.2, and 14.2.5.1.2. Mean time to ANC recovery is an FDA analysis.

Review Comment: Although there are numerical differences for many of the comparisons in Table 10, the differences are small and not in a consistent direction, so it is reasonable to conclude that the results are similar.

The applicant also provided a profile of the mean ANC in Cycle 1 for the PP population by treatment with EP2006 (arms EP and EPNEU) vs US-licensed Neupogen (arms NEU and NEUEP) (Figure 3). The profiles diverged only after day 11 where the number of subjects with results was quite small. Of the subjects with data available, none in either arm had an ANC < 2 Gi/L recorded for days 11-15. FDA also constructed profiles for ANC recovery by cycle for subjects treated with EP2006 (arm EP) vs US-licensed Neupogen (arm NEU) across all 6 cycles (Figure 3). The profiles generally overlapped, and any divergence was inconsistent between cycles.

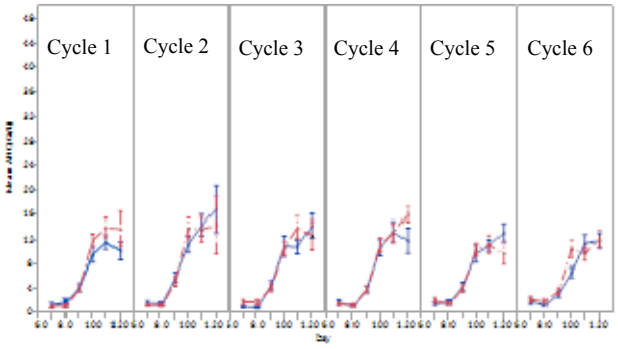
Figure 3: Time Course of Mean ANC (Between-Group Comparison)

Cycle 1 in PP Population (ANC Mean, SE)



Source: Study EP06-302 Clinical Study Report Figure 11-4

Cycles 1-6 in PP-I Population (ANC Mean, SE)



Treatments: EP2006, blue solid line,
US-licensed Neupogen, red dashed line

Source: FDA analysis

Review Comment: Although the curves for Cycle 1 in the PP population diverge after day 11, there is no evidence that this resulted from lack of ANC recovery in subjects treated with EP2006. Further, the ANC recovery profiles for Cycles 1-6 demonstrate no consistent differences between subjects treated with EP2006 or US-licensed Neupogen.

Lastly, FDA performed a within-subject comparison of time to ANC recovery using data from subjects who alternated treatments in arms EPNEU and NEUEP during Cycles 2-6. There were 91 subjects who had at least 2 cycles using EP2006 and at least 2 cycles using US-licensed Neupogen. Cycles in which commercial drug was used were excluded. The mean time to ANC recovery was 8.82 (SE 0.10) days with EP2006 and 8.75 (SE 0.10) days with US-licensed Neupogen. The ratio of the mean time to ANC recovery was 1.01 (90% CI 0.99-1.04).

For the endpoints frequency of infections and incidence or duration of hospitalization due to febrile neutropenia, the applicant provided summary analyses from adverse event data in the SAF population and no analyses in the efficacy population. As such, these outcomes are considered in the review of safety in Section 7.

Review Comment: The study was not designed to assess equivalence for any of the secondary endpoints. Nonetheless, the analyses did show that the secondary efficacy endpoints were generally similar for EP2006 and US-licensed Neupogen.

Since no studies addressing dose, persistence of efficacy, tolerance or other additional analyses for this indication were submitted, Sections 6.1.8 through 6.1.10 are omitted from this review.

6.1.11 Literature Review

Verpoort and Mohler (2012) reported a retrospective comparison of Zarzio and Neupogen (source not identified as US-licensed or EU-approved) as primary or secondary prophylaxis in patients with solid tumors or hematological malignancies receiving chemotherapy. In the 77 patients treated with Zarzio, 1% developed neutropenic fever, and 9% required chemotherapy dose reductions or discontinuation due to neutropenia. In the 25 patients treated with Neupogen, 4% developed neutropenic fever, and 16% required chemotherapy dose reductions or discontinuation due to neutropenia. The authors concluded that the effectiveness of Zarzio was similar to that of Neupogen in this setting.

6.2 Other Indications

Zarxio is indicated 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) .

- 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.

- 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.

6.2.1 Methods

There were no comparative clinical studies submitted that address the additional indications. The applicant proposed to use extrapolation based on the mechanism of action of EP2006 to support all indications. The applicant asserted that "the potency established in clinical PK/PD studies and the clinical efficacy and safety of EP2006 shown in the treatment of neutropenia in cancer patients receiving myelosuppressive chemotherapy can be extrapolated to all indications authorized for the reference product Neupogen" (Module 2.7.3 Summary of Clinical Efficacy Section 1.4).

Based on their review of the literature, the applicant concluded that "The filgrastim-induced production of neutrophils in neutropenia and the mobilization of hematopoietic progenitor cells are both mediated by selective binding of filgrastim to the G-CSFR....The treatment of neutropenic conditions and hematopoietic progenitor cell mobilization are different clinical indications and filgrastim shows more than one clinical effect. These effects are of different importance for each indication. The mobilization of hematopoietic progenitor cells to the peripheral blood is a byproduct in the treatment of neutropenia, just as the increase of neutrophils

is a byproduct in hematopoietic progenitor cell mobilization. The important point is that each of the different effects of filgrastim is the downstream result of one common original mechanism of action, i.e. the activation of the G-CSFR. The G-CSFR is a single affinity class of receptors, i.e. it is not different between cells which express it. No mechanism of action of filgrastim not related to the G-CSFR has been described. Accordingly, a biosimilar rhG-CSF with receptor binding characteristics that are highly similar to the reference product elicits the same response and the same downstream clinical effects as the reference product" (Module 2.7.3 Summary of Clinical Efficacy Section 1.4.4).

6.2.11 Literature Review

Lefrere et al reported a retrospective comparison of Zarzio and Neupogen (source not identified as US-licensed or EU-approved) in addition to chemotherapy for mobilization of autologous PBPC in patients with lymphoma or myeloma (Lefrere, Brignier, et al. 2011). The study included 40 patients who received Zarzio and 41 who received Neupogen. In the comparison of Zarzio vs Neupogen, they reported similar results for median number of day of leukocyte growth factor administration (5 vs 5), median preleukapheresis peripheral blood CD34 count (56 vs 60 per microliter), median CD34 collection in the first apheresis (5.5 vs 4.49 x 10^6/kg), median number of leukaphereses to collect 3 x 10^6 CD34/kg (1 vs 1), and the number of mobilization failures (3 vs 1). They also provided outcomes for 31 patients transplanted with CD34 cells collected using Zarzio and 33 patients transplanted with CD34 cells collected using Neupogen. Results were similar for the median time to ANC recovery (14 vs 15 days) and median time to platelet recovery (12 vs 11 days).

Manko et al reported a prospective randomized comparison of Zarzio and Neupogen (source not identified as US-licensed or EU-approved) in addition to chemotherapy for mobilization of autologous PBPC in patients with solid tumors or hematological malignancies (Manko, Walter-Cronek, et al. 2014). There were 54 subjects in each treatment arms. The leukocyte growth factor was administered at 10 ug/kg iv daily. In the comparison of Zarzio vs Neupogen, they reported similar results for median number of day of leukocyte growth factor administration (8 vs 8), median preleukapheresis peripheral blood CD34 count (62 vs 48 per microliter), median total CD34 collection (9.1 vs 9.4 x 10^6/kg), median number of leukaphereses to complete the collection (1 vs 1), and the number of mobilization failures (6 vs 5).

Review Comment: I agree with the applicant's conclusion that filgrastim class products exert their clinical effects solely through the G-CSF receptor. Extrapolation would be an acceptable approach to support all approved indications of the reference product if a) analytical testing demonstrates that that EP2006 and the reference product are highly similar, b) the PK and PD testing demonstrates equivalence, c) the PD endpoints are scientifically valid as indicators of the biological effects of this class, and d) all other comparisons show at least similarity between EP2006 and the reference product. The analyses in Sections 6.1.5 - 6.1.7 address only item d in this list, and the results are consistent with the prerequisite of similarity. Although the literature from Europe regarding EP2006 is sparse, no reports suggested a lack of similarity to EU-approved Neupogen for any of the indications.

7 Review of Safety Endpoints

Summary

A detailed analysis of safety outcomes was conducted using data from Study EP06-302, a randomized trial comparing EP2006 to US-licensed Neupogen for prevention of chemotherapy-induced neutropenia in patients with breast cancer. The patient population included 53 subjects randomized to treatment with EP2006, 52 subjects to treatment with US-licensed Neupogen, and 109 subjects to treatment with both study agents in an alternating fashion. The study agent regimen was consistent with the proposed dose-schedule for chemotherapy-induced neutropenia. The majority of the subjects (89%) received all six planned cycles of therapy. The study population was monitored for deaths, serious adverse events, adverse events of interest, common adverse events, immunogenicity and common laboratory tests. Follow-up was through 4 weeks after the last dose of study drug.

Analysis of the safety data for Study EP06-302 showed:

- There were no related fatal TEAE or related SAEs reported.

- The incidence of the cardinal adverse events musculoskeletal pain and injection site reaction were similar between subjects treated with EP2006 or US-licensed Neupogen in Cycle 1 and across Cycles 1-6. There was no excess discordance for either of these cardinal adverse events in a within-subject comparison.

- Common TEAE at the Preferred Term level were similar in incidence when compared between subjects treated with EP2006 or US-licensed Neupogen in Cycle 1 or across Cycles 1-6, and when compared within subjects who alternated treatments.

- The incidence of related TEAE was also similar between EP2006 and US-licensed Neupogen. There were too few grade ≥ 3 TEAE or grade ≥ 3 laboratory abnormalities for a meaningful comparison.

- There were no related TEAE with allergic reaction event terms specifically. The broad SMQ analysis showed a similar incidence of nonspecific signs and symptoms of hypersensitivity events for both study agents when compared in Cycle 1 and across Cycles 1-6.

There were 204 healthy volunteers in six studies comparing EP2006 and either US-licensed Neupogen or EU-approved Neupogen in a cross-over fashion using various single- or multiple-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.

In summary, safety outcomes were similar for patients or healthy volunteers treated with either EP2006 or US-licensed Neupogen.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The main clinical review of safety endpoints for this BLA was based on the safety from Study EP06-302. Six studies in healthy volunteers were used for supporting analyses. US-licensed Neupogen was used as the control in Study EP06-109, and EU-approved Neupogen was the control in Studies EP06-101, EP06-102, EP06-103, EP06-104 and EP06-105. Table 2 in Section 5.1 describes the design of the protocols used in the safety analyses.

Since the manufacturing reviewer concluded that EP2006 materials from all processes were comparable (see Section 4.1.1), the clinical data generated across studies was considered suitable for review. Additionally, as the analytical studies conducted by the applicant provided an adequate scientific bridge to justify using data from studies with EU-approved Neupogen as the control to support conclusions regarding the similarity of EP2006 and US-licensed Neupogen (see Section 4.1.1), data from Studies EP06-101, EP06-102, EP06-103, EP06-104 and EP06-105 were included in the review.

The results of the analysis of safety outcomes in Sections 7.2, 7.3, 7.4, 7.5 and 7.6 refer specifically to the subjects treated on Study EP06-302. Safety outcomes for the healthy volunteer studies are described in Section 7.7.

7.1.2 Categorization of Adverse Events

Adverse events were reported down to the verbatim term. The adverse events were coded using MedDRA version 16.0 for Study EP06-302 and by MedDRA version 15.1 for the five studies in healthy volunteers.

7.1.3 Pooling of Data

The results of prophylaxis studies of leukocyte growth factors have shown the incidence of events in Cycle 1 may differ from that in the remaining cycles, so safety comparisons in Study EP06-302 were assessed initially in Cycle 1 alone pooling results for arms EP + EPNEU and for arms NEU + NEUEP. For between-group comparisons across cycles, results considered for subjects only in arms EP and NEU, which are the arms in which subjects received the same study agent throughout the trial. Within-subject comparisons used arms EPNEU and NEUEP, and results by subject and actual treatment for the cycle (rather than by study arm) were pooled for the analyses.

There was no integrated data set for the healthy volunteer population submitted. Concerns regarding the accuracy of the data in the data sets available was discussed in Section 3.1. Based on these concerns, FDA's review of safety focused on relevant information that could be abstracted from the clinical study reports rather than the data sets.

7.1.4 Procedures

The populations used in the safety analyses are described in Sections 7.2.1 and 7.7.1. Since none of the studies was designed to assess equivalence for any of the safety outcomes, most results are reported descriptively. Data analyses were performed using JMP 10.0 (SAS Institute, Inc., Cary, NC), and Stata/IC 12.1 (Stata Corporation, College Station, MD). MedDRA Adverse Events Diagnostic (MAED) (Clinical Trials & Surveys Corporation, Owings Mills, MD) was used for between-group comparisons. In most cases, the assessments were performed at the Preferred Term level, but evaluations of some cardinal events utilized grouped terms as described in Section 7.2.6.

There was no analysis of similarity by dose, time, demographics, disease characteristics or concomitant medications submitted for review. There was no analysis of similarity with regard to carcinogenicity, human reproduction and pregnancy, effects in children, overdose, drug abuse potential, withdrawal or rebound submitted for review. Consequently, Sections 7.5 and 7.6 are omitted from this review. The applicant indicated that they planned to extrapolate from the reference product regarding this information (Module 2.7.4 Summary of Clinical Safety Section 5).

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses

The safety population in Study EP06-302 was comprised of all subjects who received at least one dose of study drug and had a subsequent safety assessment. Safety data were available for 214 subjects supported with EP2006 at the proposed dose-schedule (SAF population in Figure 1). It should be noted that the applicant described some safety outcomes in the SAF-I population, which excluded subjects who did not receive more than one cycle of study agent. This may account for small difference between FDA results and those of the applicant.

The demographics of the safety population from Study EP06-302 are shown in Table 11.

Table 11: Demographics (Safety Population)

	Study Arm				
	EP (N=53)	**EPNEU (N=54)**	**NEUEP (N=55)**	**NEU (N=52)**	**All (N=214)**
Median Age (years)	53	49	50	47	50
(range)	(24 - 74)	(26 - 73)	(26 - 71)	(23 - 76)	(23 - 76)
Age ≥65 years	6 (11%)	3 (6%)	7 (13%)	4 (8%)	20 (9%)
Female	53 (100%)	54 (100%)	55 (100%)	52 (100%)	214 (100%)
Caucasian	53 (100%)	54 (100%)	55 (100%)	52 (100%)	214 (100%)
Performance Status					
0	39 (74%)	43 (80%)	44 (80%)	38 (73%)	166 (77%)
1	14 (26%)	11 (20%)	11 (20%)	14 (27%)	50 (23%)
Stratum					
Adjuvant	31 (58%)	32 (59%)	31 (56%)	30 (58%)	124 (58%)
Neoadjuvant	22 (42%)	22 (41%)	24 (44%)	22 (42%)	90 (42%)

Table 11: Demographics (Safety Population)

		Study Arm				
		EP (N=53)	EPNEU (N=54)	NEUEP (N=55)	NEU (N=52)	All (N=214)
Stage		5 (9%)	2 (4%)	4 (7%)	4 (8%)	15 (7%)
	1	24 (45%)	33 (61%)	28 (51%)	25 (48%)	110 (52%)
	2	24 (45%)	19 (35%)	23 (42%)	23 (44%)	89 (42%)
	3					
Country						
	Russia	39 (74%)	40 (74%)	43 (78%)	43 (83%)	165 (77%)
	Ukraine	8 (15%)	9 (17%)	8 (15%)	8 (15%)	33 (15%)
	Hungary	4 (8%)	3 (6%)	3 (5%)	1 (2%)	11 (5%)
	Latvia	0	1 (2%)	1 (2%)	0	2 (1%)
	Slovakia	1 (2%)	1 (2%)	0	0	2 (1%)
	Czech Republic	1 (2%)	0	0	0	1 (<1%)

Source: FDA analysis

7.2.2 Explorations for Dose-Toxicity Relationship

In Study EP06-302, study agent was administered daily for up to 14 days per cycle in up to six cycles of chemotherapy. Subjects were treated using the randomized dose of study agent, and no modifications of the dose were planned, so no assessments of similarity of safety events by dose were performed.

At the time the dataset was locked, all subjects had completed the treatment portion of the protocols or withdrew early. A total of 1217 cycles were available for review. Table 12 shows the number of cycles of exposure to study agents for each study arm.

Table 12: Exposure by Arm and Study Agent

	Study Arm:	EP (N=53)	EPNEU/NEUEP (N=109)		NEU (N=52)
Total Cycles	Treatment:	EP2006	EP2006	US-licensed Neupogen	US-licensed Neupogen
1 Cycle		1[a]	8	2	1
2 Cycles		1	4	8	0
3 Cycles		0	97	97	1
4 Cycles		5	0	0	0
5 Cycles		1	0	0	1
6 Cycles		45	0	0	49

[a]Numbers of subjects
Source: FDA analysis

7.2.3 Special Animal and/or In Vitro Testing

Relevant results from the preclinical studies are discussed in Section 4.2. There were no findings in the preclinical studies that warranted additional clinical safety analyses.

7.2.4 Routine Clinical Testing

The schedule of safety evaluations is described in section 5.3.2 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

Relevant results from the pharmacology studies are discussed in Section 4.3. There were no findings in the pharmacology studies that warranted additional clinical safety testing.

7.2.6 Adverse Events of Special Interest (AESI)

The significant class-specific adverse events were described in Section 2.4. These are all considered in the analysis of treatment-related adverse events, and no additional assessments of these events were made.

FDA identified two cardinal safety events for closer scrutiny. The first was musculoskeletal pain, chosen because these events are the most common toxicity of leukocyte growth factors. The second was injection site reactions, assessed to ensure that the difference between the EP2006 and US-licensed Neupogen formulations did not impact the risk of local reactions. In order to capture all similar events, grouped terms, as defined in Section 7.3.4 and specific for this protocol, were used for these comparisons.

7.3 Major Safety Results

Table 13: Summary of Major Safety Events (Between-Group Comparison)

	Cycle 1 by Treatment		Cycles 1 - 6 Arm EP vs Arm NEU	
	EP2006 (N=107)	US-licensed Neupogen (N=107)	EP2006 (N=53)	US-licensed Neupogen (N=52)
TEAEs	87 (81%)	89 (83%)	52 (98%)	50 (96%)
Related TEAEs	22 (21%)	21 (20%)	19 (36%)	20 (39%)
SAEs	5 (5%)	2 (2%)	5 (9%)	2 (4%)
Related SAEs	0	0	0	0
Fatal TEAEs	1 (1%)	0	1 (1%)	0
Related Fatal TEAEs	0	0	0	0

Source: FDA analysis

7.3.1 Deaths

There were no related fatal TEAE (Table 13). The applicant reported one fatal event on study, a pulmonary embolism in the setting of pre-existing rheumatic heart disease in Cycle 1. FDA concurred that this event was not related to the study agent.

7.3.2 Nonfatal Serious Adverse Events

There were few SAEs reported, and none were considered related to the study agent (Table 13).

7.3.3 Dropouts and/or Discontinuations

There was one subject who withdrew due to an adverse event - fluctuating blood pressure in the setting of chronic hypertension. Since the event was not temporally related to administration of study drug it was considered unrelated, and FDA concurred with this conclusion.

7.3.4 Significant Adverse Events

As discussed in Section 7.2.6, musculoskeletal pain and injection site reactions were considered cardinal adverse events. Table 14 shows the incidence of these events in between-group comparisons using grouped terms as determined by FDA. The group terms include the Preferred Terms identified in the footnote of the table. The choice of Preferred Terms was based on the actual adverse events reported in Study EP06-302 and is therefore specific to this protocol.

Table 14: Cardinal Adverse Events (Between-Group Comparison)

	Cycle 1 by Treatment		Cycles 1 - 6 Arm EP vs Arm NEU	
Grouped Term	**EP2006 (N=107)**	**US-licensed Neupogen (N=107)**	**EP2006 (N=53)**	**US-licensed Neupogen (N=52)**
Musculoskeletal Pain[a]	27 (25%)	31 (29%)	21 (40%)	22 (42%)
Injection Site Reaction[b]	2 (2%)	1 (1%)	2 (4%)	1 (2%)

[a]Includes arthralgia, back pain, bone pain, musculoskeletal chest pain, musculoskeletal pain, myalgia, pain, pain in extremity or spinal pain
[b]Includes injection site erythema, extravasation, haematoma, pain or pruritus
Source: FDA analysis

A within-subject analysis was also performed using the 91 subjects from arms EPNEU and NEUEP who received at least 2 cycles of both study agents and no commercial leukocyte growth factor. Musculoskeletal pain was reported in 31% during an EP2006 cycle and in 36% during a cycle with US-licensed Neupogen. There were 17 subjects discordant in developing musculoskeletal pain. An injection site reaction was reported in 7% during an EP2006 cycle and in 5% during a cycle with US-licensed Neupogen. There were 3 subjects discordant in

developing an injection site reaction. The within-subject comparisons were negative by McNemar's test for both musculoskeletal pain and injection site reactions.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

In Cycle 1, a TEAE was reported for 81% of subjects treated with EP2006 and 83% treated with US-licensed Neupogen. Table 15 lists the nonhematological TEAE (excluding Alopecia) that occurred in at least 5% of subjects treated with EP2006. The proportion that was considered related to study agent is also listed. The only TEAE that were grade 3 or greater were a grade 5 embolism in a subject on EP2006 (see Section 7.3.1) and grade 3 hyperglycemia in a subject on US-licensed Neupogen.

Table 15: Common TEAE in Cycle 1 (Between-Group Comparison)

	Any TEAE		Suspected TEAE	
Preferred Term	**EP2006 (N=107)**	**US-licensed Neupogen (N=107)**	**EP2006 (N=107)**	**US-licensed Neupogen (N=107)**
Nausea	39 (36%)	43 (40%)	4 (4%)	2 (2%)
Asthenia	30 (28%)	42 (39%)	2 (2%)	1 (1%)
Bone pain	19 (18%)	22 (21%)	13 (12%)	16 (15%)
Fatigue	17 (16%)	12 (11%)	0 (0)	1 (1%)
Diarrhea	6 (6%)	12 (11%)	0 (0)	0 (0)
Vomiting	5 (5%)	9 (8%)	0 (0)	0 (0)
Musculoskeletal pain	5 (5%)	2 (2%)	3 (3%)	1 (1%)

Source: FDA analysis

In Cycles 1-6, a TEAE was reported for 98% of subjects treated with EP2006 and 96% treated with US-licensed Neupogen. Table 16 lists the nonhematological TEAE (excluding Alopecia) that occurred in at least 5% of subjects treated with EP2006 across Cycles 1-6 in arms EP and NEU. The proportion that was considered related to study agent is also listed. The only nonhematological TEAE in more than one subject that was grade 3 or greater was Febrile neutropenia which occurred in 3 subjects on EP2006 and 1 on US-licensed Neupogen.

Table 16: Common TEAE in Cycle 1-6 (Between-Group Comparison)

	Any TEAE		Suspected TEAE	
Preferred Term	**EP2006 (N=53)**	**US-licensed Neupogen (N=52)**	**EP2006 (N=53)**	**US-licensed Neupogen (N=52)**
Bone pain	12 (23%)	17 (33%)	12 (23%)	17 (33%)
Decreased appetite	8 (15%)	13 (25%)	0 (0)	0 (0)
Pyrexia	6 (11%)	1 (2%)	0 (0)	0 (0)
Diarrhea	5 (9%)	8 (15%)	0 (0)	0 (0)

Table 16: Common TEAE in Cycle 1-6 (Between-Group Comparison)

	Any TEAE		Suspected TEAE	
Preferred Term	**EP2006 (N=53)**	**US-licensed Neupogen (N=52)**	**EP2006 (N=53)**	**US-licensed Neupogen (N=52)**
Musculoskeletal pain	4 (8%)	1 (2%)	4 (8%)	1 (2%)
Stomatitis	3 (6%)	2 (4%)	0 (0)	0 (0)
Febrile neutropenia	3 (6%)	1 (2%)	0 (0)	0 (0)
Peripheral sensory neuropathy	3 (6%)	1 (2%)	0 (0)	0 (0)

EP2006 includes subjects in arm EP and US-licensed Neupogen includes subjects in arm NEU.
Source: FDA analysis

A within-subject comparison was also performed using the 91 subjects from arms EPNEU and NEUEP who received 2 cycles of both study agents and no commercial leukocyte growth factor. Table 17 lists the nonhematological TEAE (excluding Alopecia) that occurred in at least 5% of subjects in the cycles with EP2006. The proportion that were considered related to study agent is also listed. There was no nonhematological TEAE grade 3 or greater that occurred in more than one subject by treatment.

Table 17: Common TEAE in Cross-Over Cycles (With-Subject Comparison)

	Any TEAE		Suspected TEAE	
Preferred Term	**EP2006 (N=91)**	**US-licensed Neupogen (N=91)**	**EP2006 (N=91)**	**US-licensed Neupogen (N=91)**
Nausea	42 (46%)	40 (44%)	3 (3%)	2 (2%)
Asthenia	40 (44%)	37 (41%)	1 (1%)	4 (4%)
Bone pain	23 (25%)	28 (31%)	18 (20%)	22 (24%)
Fatigue	13 (14%)	12 (13%)	0 (0)	1 (1%)
Diarrhea	11 (12%)	8 (9%)	1 (1%)	1 (1%)
Vomiting	10 (11%)	9 (10%)	1 (1%)	0 (0)
Erythema	6 (7%)	5 (5%)	0 (0)	0 (0)
Decreased appetite	5 (5%)	2 (2%)	0 (0)	0 (0)

Includes subjects in arms EPNEU and NEUEP by treatment period as listed in the column header.
Source: FDA analysis

7.4.2 Laboratory Findings

The applicant made several observations regarding the laboratory testing results (Study EP06-302 Clinical Study Report Section 12.4):

- Clinically significant abnormalities were observed for each of the hematological parameters.
- The mean changes in hematological parameters from baseline did not differ markedly between EP2006 and US-licensed Neupogen.
- Clinically significant abnormalities were observed for ALT, AST, GGT, glucose and uric acid.

- There were no clinically relevant trends noted in the clinical chemistry parameters.

FDA chose to assess ALT, bilirubin, creatinine, neutrophils and platelets as clinically relevant to treatment with a leukocyte growth factor. The data file did not include grading. Where reference ranges were available, the results were graded according to CTCAE v4 by FDA. Clinically significant abnormalities were considered grade 3 or worse. Chemistry testing results were largely provided only on day 1 of each cycle, so the analysis for Cycle 1 refers specifically to the results reported for Cycle 2 day 1 (prior to Cycle 2 chemotherapy).

In the between-group assessment for Cycle 1, there were no grade ≥3 elevations in ALT, bilirubin or creatinine. Grade ≥3 neutropenia occurred in 77% on EP2006 vs 79% on US-licensed Neupogen, and grade ≥3 thrombocytopenia occurred in 2% on EP2006 vs no subjects on US-licensed Neupogen. Given the low rate of clinically significant laboratory abnormalities other the neutropenia, which was assessed as an efficacy endpoint, no further comparisons of laboratory testing was performed.

7.4.3 Vital Signs

The applicant reported no clinically significant abnormalities in vital signs expect for one subject with tachycardia Cycle 1 day 1 of the EPNEU arm (Study EP06-302 Clinical Study Report Section 12.5.1). In view of the paucity of abnormalities in vital signs, no further analyses were conducted.

7.4.4 Electrocardiograms (ECGs)

The applicant reported no clinically significant abnormalities in ECG recordings (Study EP06-302 Clinical Study Report Section 12.5.2), so no further analyses of ECGs were conducted.

7.4.5 Special Safety Studies

There were no special studies for similarity of safety endpoints submitted for review.

7.4.6 Immunogenicity

The applicant reported that no anti-G-CSF antibodies were detected in subjects in Study EP06-302 (Study EP06-302 Clinical Study Report Section 12.5.4), and the Immunogenicity Reviewer concurred with this conclusion (see Section 4.1.2). FDA also assessed events potentially denoting hypersensitivity reactions using standardized MedDRA queries (SMQs). There were no related adverse events reported with allergic reaction terms specifically. As such, the narrow and algorithmic SMQs, which emphasize specificity, were noninformative. Table 18 shows the between-group comparisons for the broad SMQs anaphylactic reaction and hypersensitivity. The broad SMQs include the general signs and symptoms that might occur with hypersensitivity reactions, increasing the sensitivity in case there was underreporting of specific allergic event terms. The comparison showed no substantial differences between treatment groups for either of the broad SMQs by treatment in Cycle 1 or across Cycles 1-6 for arm EP vs arm NEU. Since cross-over between EP2006 and US-licensed Neupogen occurred every 21 days in arms EPNEU

and NEUEP, assessment of immunological response might be confounded, so no within-subject comparison was performed.

Table 18: Hypersensitivity by Broad SMQ (Between-Group Comparison)

	Cycle 1 by Treatment		Cycles 1 - 6 Arm EP vs Arm NEU	
Broad SMQ	**EP2006 (N=107)**	**US-licensed Neupogen (N=107)**	**EP2006 (N=53)**	**US-licensed Neupogen (N=52)**
Anaphylactic Reaction	8 (7%)	8 (7%)	8 (15%)	10 (19%)
Hypersensitivity	11 (10%)	8 (7%)	9 (17%)	9 (17%)

Source: FDA analysis

Review Comment: Overall, the results of the analysis of Study EP06-302 showed that safety outcomes were similar in subjects treated with EP2006 or US-licensed Neupogen to prevent neutropenia after chemotherapy for breast cancer.

7.7 Additional Submissions / Safety Issues

7.7.1 Cross-Over Studies in Healthy Volunteers

Six studies of EP2006 in healthy volunteers were also submitted. All six studies had a cross-over design in which subject received treatment with both EP2006 and the comparator but in different time periods. US-licensed Neupogen was used as the comparator in Study EP06-109, and EU-approved Neupogen was the comparator in Studies EP06-101, EP06-102, EP06-103, EP06-104 and EP06-105. Table 2 in Section 5.1 describes the design of these protocols.

In their review of the individual studies, the applicant did not find that the safety profile of EP2006 differed from that of the comparator used (Module 2.7.4 Summary of Clinical Safety Section 2.1.1).

The randomized population in these studies included 204 subjects of median age 37 years (range, 19-54 years). There were 116 (57%) males and 88 (43%) females. Fewer than 1% of the subjects were not Caucasian. The study agent was administered intravenously only in Study EP06-102 and subcutaneously in the remainder of the studies. Dose-schedules for each study are shown in Table 19 below.

Eight subjects were noted to have withdrawn early from study due to an adverse reaction. The adverse events that resulted in withdrawal included 3 cases of ALT elevation and 1 case each of pregnancy, influenza, allergic rhinitis, headache with nausea and vomiting and viral infection. The clinical study reports were not clear with regard to which treatment period was associated with the early withdrawals.

Table 19 shows the incidence of any adverse event during treatment with either EP2006 or the comparator. The table also shows the reported incidence of adverse events in the SOC Musculoskeletal and connective tissue disorders, used as a surrogate for musculoskeletal pain, the cardinal event grouped term describe in Section 7.3.4. Since the raw data were not available to identify discordance in paired outcomes, a within-subject analysis could not be performed.

Table 19: Adverse Events in Healthy Volunteer Cross-Over Studies

Study	Regimen[a]	Agent[b]	Subjects[c]	Any Adverse Event	Musculoskeletal[d] SOC Adverse Event	Source[e]
EP06-105	1 µg/kg sc x 1	EP2006	24	13 (54%)	2 (8%)	12-2
		Comparator	24	11 (46%)	4 (17%)	
EP06-104	2.5 µg/kg sc x 1	EP2006	29	16 (52%)	3 (10%)	14.3.1.3
		Comparator	30	19 (63%)	5 (17%)	
EP06-109	10 µg/kg sc x 1	EP2006	27	13 (48%)	3 (11%)	14.3.1.1.1
		Comparator	27	14 (52%)	3 (11%)	
EP06-102	5 µg/kg iv x 1	EP2006	24	15 (63%)	5 (21%)	47
		Comparator	26	16 (62%)	4 (15%)	
EP06-103	2.5 µg/kg/d sc x 7	EP2006	28	28 (100%)	11 (39%)	54
		Comparator	28	28 (100%)	10 (36%)	
EP06-103	5 µg/kg/d sc x 7	EP2006	28	28 (100%)	16 (57%)	59
		Comparator	28	28 (100%)	14 (50%)	
EP06-101	10 µg/kg/d sc x 7	EP2006	36	30 (83%)	27 (75%)	27
		Comparator	36	33 (92%)	30 (83%)	

[a]Study agent dose regimen was the same in both treatment periods.
[b]The comparator is US-licensed Neupogen in Study EP06-109 and EU-approved Neupogen in the remainder of the studies listed.
[c]Although the results are for the same subjects from different treatment periods, the number of subjects treated may vary by agent due to dropouts or withdrawals prior to completion of the cross-over treatment.
[d]SOC Musculoskeletal and connective tissue disorders.
[e]Table number in the respective study Clinical Study Report from which the data were abstracted.

In four of the studies, local tolerance was assessed by the subject using a visual analog scale of 0 mm to 100 mm (VAS) and by the investigator using a standardized 3-point scale (Injection Site Reaction Score, ISR). No statistical comparisons were made. The applicant reported the following:

- In Study EP06-105 (dose-schedule 1 µg/kg sc x 1), the mean VAS was 0 mm with EP2006. Two subjects reported a VAS >0 (1 mm and 3 mm) on EU-approved Neupogen, and the remainder of the VAS on EU-approved Neupogen were 0. All ISRs were 0. (Study EP06-105 Clinical Study Report Section 12.4)
- In Study EP06-109 (dose-schedule 10 µg/kg sc x 1), the mean VAS scores were <2 mm with either EP2006 or US-licensed Neupogen. An injection site reaction was reported by 2 subjects on EP2006 and 2 on US-licensed Neupogen. Using the ISR, all reactions were graded as mild. (Study EP06-105 Clinical Study Report Section 12.5.3)

- In Study EP06-103 (dose-schedule 2.5 or 5 μg/kg sc x 7), the mean VAS score was 10 mm with EP2006 and 4 mm with EU-licensed Neupogen in the 2.5 μg/kg, and the mean VAS score was 4 mm with either treatment in the 5 μg/kg group. The ISR scores were rated 0 for more than 85% with either product in the 2.5 μg/kg group and for more than 91% with either product in the 5 μg/kg. (Study EP06-105 Clinical Study Report Sections 12.5.5 and 12.5.6)
- In Study EP06-101 (dose-schedule 10 μg/kg sc x 7), the mean VAS scores were <2 mm with EP2006 and <5 mm with EU-approved Neupogen. There were 11 mild reactions reported on EP2006 and 5 mild reactions on EU-approved Neupogen. (Study EP06-105 Clinical Study Report Section 12.5.5)

The applicant concluded that there were no relevant differences in local tolerance between EP2006 and the comparators in these studies (Module 2.7.4 Summary of Clinical Safety Section 2.1.5).

7.7.2 Other Clinical Studies

The submission included reports for four healthy volunteer studies (EP06-106, EP06-107, EP06-108 and EP06-110; see Table 2 in Section 5.1) of EP2006 in comparison to Gran, a filgrastim class product approved in Japan. The applicant reported that in these studies they found little or no difference between EP2006 and Gran in the type and incidence of adverse events which were suspected as due to the study agent. Since Gran is not considered a scientifically valid comparator for the purposes of this application, FDA performed no further review of these studies.

Study EP06-301 was a single-arm trial of EP2006 as primary prophylaxis of chemotherapy-induced neutropenia in patients with breast cancer. The applicant found that the adverse events reported during the study were consistent with known toxicities of either the filgrastim class products or the study chemotherapy. Study EP06-501 is an observational study of healthy volunteers who received EP2006 for mobilization of peripheral blood stem cells for donation. The applicant indicated that the observed pattern of drug-related adverse events in these donors was consistent with the side effect profile of the G-CSF product class. Since there was no comparator used in these protocols, FDA performed no further review of these studies.

7.7.3 Literature Review

In the report of Verpoort and Mohler (2012) as described in Section 6.1.11, the authors reported simply that there were no unexpected safety findings.

In the report of Manko et al (Manko, Walter-Cronek, et al. 2014) as described in Section 6.2.11, the authors reported that during the mobilization period, the incidences of adverse events were similar with Zarzio vs Neupogen as reported for bone pain (31% vs 35%), nausea or vomiting (11% vs 7%), diarrhea (11% vs 9%), neutropenic fever (20% vs 19%), and skin rash (0% vs 2%).

Review Comment: The additional studies and literature review provide no evidence to alter the conclusions drawn from the review of safety outcomes in Study EP06-302.

8 Postmarket Experience

EP2006 was first approved on 2/6/2009. Marketing authorization was granted in the European Economic Area and in 29 additional countries under the trade names Zarzio and Filgrastim HEXAL. All authorizations are as a biosimilar or follow-on biological. Estimated cumulative exposure is shown in Table 20.

Table 20: Estimated Cumulative Exposure to EP2006 as of 31-Jan-2014

Country	Strengths (in pre-filled syringes)	Filgrastim sold in million units	Patient-exposure (patient-days)
EEA		(b) (4)	
SubTotal EEA	30 MIU/0.5 mL		3,690,296
	48 MIU/0.5 mL		2,061,297
Non-EEA*	30 MIU/0.5 mL		363,145
	48 MIU/0.5 mL		51,533
Total	30 MIU/0.5 mL		4,053,441
	48 MIU/0.5 mL		2,112,831
Total			**6,166,272**

Source: Module 2.7.4 Summary of Clinical Safety Table 6-2

There were no safety issues with EP2006 reported that resulted in modification of the prescribing information. Updates to the prescribing information were made as requested by regulatory authorities in order to maintain consistency with the prescribing information of the innovator product.

The applicant has received 177 serious adverse event reports covering 591 adverse drug reactions. Of these, 251 adverse drug reactions were listed, and 340 were unlisted. The majority of the unlisted reactions were the subject of only a single report. The applicant identified no adverse events clearly related to EP2006 that were not known or expected.

There were no reports of anti-G-CSF antibodies received by the applicant. However, there have been 13 cases of hypersensitivity reactions, including 2 anaphylactic reactions. Of the 13 reported cases, 9 patients recovered from the event, and outcome was not reported for 4 patients. Based on the information available, the applicant concluded that 4 of the cases were related to EP2006.

Review Comment: I agree that the postmarketing information revealed no safety events related to EP2006 not known to occur with US-licensed Neupogen. Conclusions regarding similarity that can be drawn from this experience are limited by the lack of quantitative comparative data for the US-licensed Neupogen. Of additional note are the cases of hypersensitivity reactions. Although such reactions were not reported in the clinical studies of EP2006, the postmarketing data suggest that the risk is actual (albeit expected), and the incidence may be too low to be detected in small studies.

9 Appendices

9.1 Advisory Committee Meeting

BLA 125553 was discussed at the Oncologic Drugs Advisory Committee Meeting held January 7, 2015. The committee was asked to discuss the following issues:

Discussion Question 1: Does the committee agree that EP2006 is highly similar to the reference product, US-licensed Neupogen, notwithstanding minor differences in clinically inactive components?

The committee members agreed that EP2006 was highly similar to US-licensed Neupogen based on the evidence provided. The Chairperson asserted that the applicant had satisfied the required components to demonstrate similarity, and that robust safety and effectiveness data from extensive use outside of the United States provided further comfort with this conclusion. One member noted specifically that EP2006 was identical in terms of amino acid composition, and that although it was formulated differently in comparison to US-licensed Neupogen, the chemical differences were minor in terms of clinical activity.

Discussion Question 2: Does the committee agree that there are no clinically meaningful differences between EP2006 and US-licensed Neupogen?

Overall, the committee agreed that there were no clinically meaningful differences between EP2006 and US-licensed Neupogen. The committee raised a question regarding the difference between ANC recovery profiles in Cycle 1 between EP2006 and US-licensed Neupogen in Study EP06-302 as presented by FDA, since the results differed from that presented by the applicant. Members agreed that this issue may be resolved by clarifying which set of data was accurate. The committee also articulated that they saw no differences in the common and expected adverse events, but pointed out that differences in rare or late events were not assessed.

The results of the voting question are as follows:

Voting Question: Does the committee agree that based on the totality of the evidence, EP2006 should receive licensure as a biosimilar product for each of the five indications for which US-licensed Neupogen is currently licensed?

Yes – 14 and No - 0

9.2 Literature Reviewed/ References

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