Secondary (Team Leader) Review

Date	February 3, 2015
From	Albert Deisseroth, MD, PhD
Subject	Secondary Review
BLA Number	125553
Applicant	Sandoz
Date of Submission	May 8, 2014
PDUFA Goal Date	March 8, 2015
Proprietary Name	Zarxio
Dosage Regimen	300 mcg/0.5 mL PFS, 480 mcg/0.8 mL PFS
Approved Indications	Patients with cancer receiving myelosuppressive chemotherapy; Patients with AML receiving induction or consolidation chemotherapy; Patients with cancer receiving bone marrow transplant; Patients undergoing peripheral blood progenitor cell collection; Patients with severe chronic neutropenia.
Recommendation:	Approval of EP2006 as a biosimilar to US-licensed Neupogen for all 5 indications for which US-licensed Neupogen is currently licensed

Material Reviewed/Consulted	Reviewer/Author
Medical Officer Review	Donna Przepiorka, MD, PhD
Clinical Pharmacology	Sarah Schrieber, PhD, Anshu Marathe, PhD, and NAM Atiqur Rahman, PhD
Biostatistics	Kyung Lee, PhD, and Lei Nie, PhD
Pharmacology/Toxicology	Christopher M Sheth, PhD, Haw-Jyh Chiu, PhD, and John Leighton, PhD
Immunogenicity	Farouk Sheikh, PhD, Frederick Mills, PhD, and Susan Kirshner, PhD
CMC Statistics	Xiaoyu Dong, PhD, Meiyu Shen, PhD, and Yi Tsong, PhD
OC/OMPQ/DGMPA/BMAB	Bo Chi, PhD, Steve Fong, PhD, and Patricia Hughes, PhD
Chemistry Manufacturing and Controls	Maria-Teresa Gutierrez-Lugo, PhD, Gibbes Johnson, PhD, and Steven Kozlowski, MD
Project Manager	Jessica Boehmer

Reference ID: 3699309

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1. EXECUTIVE SUMMARY:

On May 8, 2014, Sandoz submitted BLA 125553 requesting licensure of EP2006 as a biosimilar to US-licensed Neupogen under Section 351(k) of the Public Health Service Act. The proposed proprietary name is Zarxio. Filgrastim is an N-methionyl analog of granulocyte colony-stimulating factor (G-CSF) which is a hematopoietic growth factor that induces proliferation and differentiation of neutrophil committed progenitor cells into neutrophils. Filgrastim also induces the release of neutrophils as well as CD34+ hematopoietic progenitor cells from the marrow into the peripheral blood. Filgrastim is made up of 175 amino acids without glycosylation so that from a molecular perspective, this product is relatively simple.

In this application, Sandoz requested that EP2006 be licensed as a biosimilar to US-licensed Neupogen for all of the five currently approved indications held by US-licensed Neupogen. These include: decreasing the incidence of infections in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs; reducing the duration of neutropenia in patients with non-myeloid malignancies undergoing myeloablative chemotherapy followed by marrow transplantation; reducing the incidence and duration of sequelae of neutropenia in symptomatic patients with congenital neutropenia, cyclic neutropenia, or idiopathic neutropenia; mobilization of hematopoietic progenitor cells into the peripheral blood for collection by leukapheresis; and reducing the time to neutrophil recovery and the duration of fever, following induction or consolidation chemotherapy treatment of adults with AML.

EP2006 was approved in 2009 under the trade name Zarzio for marketing in the European Union as a biosimilar product to EU-approved Neupogen. Marketing experience with Zarzio outside of the USA includes in excess of 7.5 million days of patient exposure.

BLA 125553:

CMC: The foundation of all biosimilar applications and the first hurdle to surmount is whether the proposed biosimilar product is “highly similar” to the reference product from an analytic perspective. Sandoz concluded on the basis of its extensive studies of the physical and functional properties of EP2006 and US-licensed Neupogen, that EP2006 is “highly similar” to US-licensed Neupogen. In addition, Sandoz carried out a three way analytical comparison of US-licensed Neupogen, EU-approved Neupogen, and EP2006 to establish a scientific bridge to justify the relevance of data obtained using EU-approved Neupogen to support a demonstration of biosimilarity to US-licensed Neupogen. Sandoz demonstrated that these three products were all highly similar based on meeting pre-specified acceptance criteria for analytical similarity across all three pairwise comparisons.

Non-clinical Studies: Sandoz concluded on the basis of their nonclinical studies comparing the toxicity, pharmacokinetic, and pharmacodynamic properties of EP2006 and EU-approved Neupogen, that EP2006 was similar to Neupogen.

Clinical Pharmacology Studies: On the basis of two studies in which the pharmacokinetics and pharmacodynamics of EP2006 was compared in normal human subjects to US-licensed Neupogen, as well as 4 studies in which the pharmacokinetics and pharmacodynamics of EP2006 was compared to EU-approved Neupogen at doses ranging from 1, 2.5, 5 and 10 mcg/kg in normal human subjects, that there are no clinically meaningful differences between EP2006 and US-licensed Neupogen.

Immunogenicity and Safety: Sandoz also summarized immunogenicity and safety studies which had been carried out in normal human subjects. On the basis of these studies, Sandoz concluded that there are no clinically meaningful differences between EP2006 and US-licensed Neupogen,.

Additional Efficacy, Safety and Immunogenicity Studies: Finally, Sandoz presented safety, efficacy and immunogenicity data from a study that randomized patients with breast cancer receiving TAC chemotherapy between EP2006 and US-licensed Neupogen. On the basis of these studies, Sandoz concluded that there are no clinically meaningful differences between EP2006 and US-licensed Neupogen.

Reviewer Comment: *The study in patients with breast cancer was conducted as part of the clinical development program to support the approval of Zarzio in the EU in 2009. A study in patients with breast cancer would not be necessary to support development of EP2006 as a proposed biosimilar to Neupogen..*

Regulatory Recommendation: This secondary reviewer recommends that EP2006 be licensed for all five of the indications for which US-licensed Neupogen is currently licensed, due to the same mechanism of action for all of these indications and the totality of the evidence presented by Sandoz.

2. BACKGROUND: (This section was derived in part from the review of Dr. Donna Przepiorka).

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.

3. CHEMISTRY MANUFACTURING AND CONTROLS (CMC):

Based on a review of an extensive series of comparisons of the structural and functional properties of EP2006 and US-licensed Neupogen, the CMC review team concluded that EP2006 is highly similar to US-licensed Neupogen. Sandoz also provided structural and functional data

for EU-approved Neupogen, and established a robust analytical bridge between EP2006, US-licensed Neupogen and EU-approved Neupogen, to justify the relevance of data obtained using EU-approved Neupogen to support a demonstration of biosimilarity to US-licensed Neupogen. For details, please see the CMC review.

Regulatory Recommendation of the CMC Review Team: Approval.

4. PHARMACOLOGY/TOXICOLOGY: (This section was excerpted from the review of Dr. Christopher M. Sheth).

The nonclinical data submitted to the BLA demonstrate the similarity (i.e., similar PD characteristics and similar safety) of EP2006 and EU-approved Neupogen. The PD study (EP06-004) examined the hematological response in normal and neutropenic rats for 12 days following administration of either EP2006 or Neupogen. In normal rats, EP2006 and EU-approved Neupogen produced similar relatively sustained dose-related increases in ANC from Days 2 to 5. Both EP2006 and EU-approved Neupogen produced similar biphasic increases in ANC in neutropenic rats with two peak responses occurring on Days 2 and 5 with lower values on Days 3 and 4. Local tolerance study (EP06-003) was conducted to assess for potential erythema, edema, hematomas, pain reactions, gross pathology, and histopathology in rabbits administered undiluted EP2006 or EU-approved Neupogen via the SC, intravenous (IV), perivascular (PV), intraarterial (IA) and intramuscular (IM) routes. No definitive drug related changes occurred in the local tolerance study.

The 14-day TK study (EP06-002) showed that the toxicokinetics of EP2006 and EU-approved Neupogen at dose levels between 20 and 500 μg/kg are relatively similar in rats following single (on Day 0) and repeated (on Day 13) subcutaneous dosing. Two 28-day toxicity/TK studies (EP06-001 and EP06-006) with 6-week recovery periods were conducted in rats. Both studies were essentially identical in design, however the EP06-006 study was the most informative (pivotal) as it was conducted with the formulation of EP2006 (to be marketed in the US) containing L-glutamic acid as the buffering agent.

The EP06-001 study is supportive as it was conducted with EP2006 formulated in acetic acid which is the same buffer system used in the EU-approved Neupogen comparator. No drug-related deaths occurred in either 28-day study. Dose- and time-related increases in white blood cells, notably neutrophils, were observed in males and females treated with ≥ 20 μg/kg EP2006 or EU-approved Neupogen on Days 3, 14 and 28.

Other noteworthy findings were similar between EP2006 and EU-approved Neupogen in both studies and included: swollen joints and paralysis and/or some hind leg dysfunction at 500 μg/kg; dose-related increases in alkaline phosphatase up to 9-fold greater than controls; dose-related increases in spleen weights; hyperplasia of myeloid cells, increased hematopoietic cells in bone marrow and spleen, myeloid hyperplasia in the liver (EP06-006) and riddled compacta or myelofibrosis in the femur bone (EP06-001). Exposures to rhG-CSF were similar in animals

receiving equivalent dose levels of EP2006 or EU-approved Neupogen during the 28-day studies. On the basis of these results, the review team concluded that EP2006 was similar to EU-approved Neupogen.

Regulatory Recommendation of the Non-clinical Reviewer: Recommend approval.

5. CLINICAL PHARMACOLOGY: (This section was excerpted from the review of Dr. Sarah Schrieber).

This Biologic License Application (BLA) for EP2006, a recombinant human granulocyte stimulating factor (G-CSF) has been submitted under Section 351(k) of the Public Health Service Act (42 U.S.C. 262(k)). The applicant is seeking approval for EP2006 as a proposed biosimilar to US-licensed Neupogen licensed under BLA 103353 by Amgen Inc., and is seeking licensure for all the indications for which US-licensed Neupogen is currently approved. EP2006 drug product was developed as a liquid for injection, filled in a pre-filled syringe in the strengths of 300 mcg/0.5 mL and 480 mcg/0.8 mL.

The applicant submitted four pharmacokinetic (PK) and pharmacodynamic (PD) studies that evaluated subcutaneous (SC) doses of 1-10 mcg/kg in healthy subjects to evaluate the PK and PD similarity of EP2006 with US-licensed Neupogen. In addition to PK, these studies evaluated absolute neutrophil counts (ANC) and CD34+ cell counts as relevant and sensitive PD markers for the similarity assessment. Among these, three studies utilized EU-approved Neupogen. As such, adequate data and information was needed to scientifically justify the relevance of these comparative data to an assessment of biosimilarity to the US-licensed reference product.

The pairwise comparisons of EP2006, US-licensed Neupogen, and EU-approved Neupogen met the pre-specified criteria for analytical similarity and established a scientific bridge to justify the relevance of the PK/PD data generated using EU-approved Neupogen (refer to CMC review). The 90% CI for AUC and Cmax after a single dose were within the pre-defined limits of 80-125%. Similarly, the 95% CI for AUEC and ANCmax for ANC after a single dose were within the pre-defined limits of 80-125%. The 95% CI for AUEC and CD34max for CD34+ cell counts after multiple doses were within the limits of 80-125%.

Overall, the PK and PD studies support a demonstration of PK and PD similarity between EP2006 and US-licensed Neupogen. The PK and PD studies results add to the totality of the evidence to support a demonstration of biosimilarity of EP2006 and US-licensed Neupogen.

Regulatory Recommendation: The Office of Clinical Pharmacology has determined that the PK and PD results support a demonstration of no clinically meaningful differences between EP2006 and US-licensed Neupogen and recommends approval of EP2006.

6. EFFICACY (This section is excerpted from the reviews of Dr. Kyung Lee.)

This review evaluates the results of the clinical study, EP06-302 (PIONEER) which was a randomized, double-blind, parallel-group, multi-center study of EP2006 and US-licensed Neupogen in histologically proven patients with breast cancer. Patients eligible for neoadjuvant or adjuvant treatment were treated with myelosuppressive TAC chemotherapy (Taxotere® [docetaxel 75 mg/m^2] in combination with Adriamycin® [doxorubicin 50 mg/m^2] and Cytoxan® [cyclophosphamide 500 mg/m^2]), all given IV on day 1 of each of six 21-day cycles).

A total of 192 patients were planned to be assigned into four arms (48/group) randomly; Group 1: EP2006 for Cycle 1 through 6; Group 2: EP2006 for Cycles 1, 3, and 5 and US-licensed Neupogen for Cycles, 2, 4, and 6; Group 3: US-licensed Neupogen cycles 1, 3, and 5 and EP2006 for Cycles 2, 4, and 6; Group 4: US-licensed Neupogen for Cycles 1 through 6 (See Table 2). The pre-specified primary objective of this study was to demonstrate non-inferiority of EP2006 versus US-licensed Neupogen with respect to the mean duration of severe neutropenia (DSN), which was defined as the number of consecutive days with grade 4 neutropenia (absolute neutrophil count [ANC] less than 0.5 × 109/L), during Cycle 1 of the neoadjuvant or adjuvant TAC regimen in patients with breast cancer.

The primary endpoint was the duration of severe neutropenia (DSN) in days in cycle 1 and analysis conducted in the per-protocol population (PP) (101 patients in the EP2006 group and 103 patients in the US-licensed Neupogen group). The randomization stratification factor was kind of therapy (adjuvant therapy vs. neoadjuvant therapy). The primary analysis was analysis of covariance with covariates treatment status (adjuvant vs neoadjuvant) and baseline absolute neutrophil count, based on the per-protocol population (the subgroup of subjects who received treatment and had no major protocol violations). No similarity margins for equivalence testing were proposed by the sponsor.

The data provided in the submission could be used to evaluate the claim that the products are similar by considering the width of the confidence interval for the difference in mean DSN. If the difference is sufficiently small (±1 day) with a narrow confidence interval, one might conclude that the difference is not clinically meaningful. We conclude that there was no clinically meaningful difference between the EP2006 group and the US-licensed Neupogen group with respect to the efficacy endpoint results. The mean DSN in Cycle 1 was 1.17 days and 1.20 days for EP2006 and US-licensed Neupogen, respectively. The 90% CI of the mean difference is (-0.21, 0.28). The analysis showed that EP2006 is equivalent to US-licensed Neupogen in terms of efficacy as measured by the mean difference of DSN between EP2006 and US-licensed Neupogen being less than 1 day for both the upper and lower bounds of the 90% CI.

Regulatory Recommendation: On the basis of the efficacy results, the recommendation is for approval.

7. SAFETY (This section is excerpted from the review of Dr. Donna Przepiorka):

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 $\geq$ 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 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.

Regulatory Recommendation: Based on this analysis of safety, approval is recommended.

8. IMMUNOGENICITY:

The Immunogenicity Review Team concluded on the basis of its review of BLA 125553 that the results from the immunogenicity studies support a demonstration of no clinically meaningful differences between EP2006 and US-licensed Neupogen. For details, please see the Immunogenicity Review.

Regulatory Recommendation: Approval.

9. ADVISORY COMMITTEE MEETING: The Advisory Committee voted unanimously for approval.

10. POST MARKETING COMMITTMENTS:

PMC #1 Description: To re-adjust the [redacted] bioburden limit [redacted] based on process capability from 20 batches of product.

PMC Schedule Milestones:
Final Protocol Submission: _____
Study/Trial Completion: _____
Final Report Submission: _____
Other: N/A _____

During application review, explain why this issue is appropriate for a PMC instead of a pre-approval requirement. Check reason below and describe. ☐ Need for drug (unmet need/life-threatening condition) X Long-term data needed (e.g., stability data) ☐ Only feasible to conduct post-approval ☐ Improvements to methods (e.g., stability data) ☐ Theoretical concern ☐ Manufacturing process analysis ☐ Other

As detailed below in item 2, the Sponsor is requested to perform an analysis to reevaluate the allowable bioburden level for EP2006 drug product [redacted]. The current limit of [redacted] is based on deviations noted for manufacture of two EP2006 DP lots, and is [redacted] than the current industry practice limit of ≤ 100 CFU/100 mL. The [redacted] bioburden levels of at least 20 commercial EP2006 batches will be examined to allow for setting of a [redacted] bioburden limit. This readjustmen can only be conducted post-approval.

Describe the particular review issue and the goal of the study.

BLA 125553 proposes (b) (4) bioburden limit (b) (4) for EP2006 drug product (b) (4). This limit is based on deviations recorded for two EP2006 batches (b) (4) for batch V3021, (b) (4) for batch V3030) and is (b) (4) than the current industry practice limit of ≤ 100 CFU/100 mL. The (b) (4) should be (b) (4) to be consistent with process capabilities.

11. LABELING: Labelling is currently under negotiation between the FDA and the Applicant.

12. REGULATORY RECOMMENDATION: This secondary (TL) reviewer recommends approval of EP2006 as a biosimilar to US-licensed Neupogen for all 5 indications for which Neupogen is currently licensed.

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/s/

ALBERT B DEISSEROTH
02/09/2015