U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES- BIOSIMILAR PRODUCT

NDA/BLA #:	BLA 125533
Supplement #:	Original.
Drug Name:	EP2006, biosimilar to reference product Neupogen
Indication(s):	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
Applicant:	Sandoz Biopharmaceuticals
Date(s):	Stamp Date: May 8, 2014
	BsUFA Goal Date: March 8, 2015
Review Priority:	Standard
Biometrics Division:	Division of Biometrics V
Statistical Reviewer:	Kyung Yul Lee, Ph.D.
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Keywords:

Link to keywords: biosimilar, non-inferiority, duration of severe neutropenia, febrile neutropenia, ANCOVA, , equivalence, no clinically meaningful difference

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1 EXECUTIVE SUMMARY

Sandoz submitted a biologics license application BLA125553 under section 351(k) of the Public Health Service Act (PHS Act) to support EP2006 as a biosimilar product to US-licensed Neupogen (filgrastim). Sandoz is seeking licensure of EP2006 for the same indications as currently approved for Neupogen: The indications are as follows:

1) to decrease the incidence of infections, 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;

2) for reducing the time to neutrophil recovery and the duration of fever, following induction or consolidation chemotherapy treatment of adults with AML;

3) 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 marrow transplantation;

4) for the mobilization of hematopoietic progenitor cells into the peripheral blood for collection by leukapheresis; and

5) for chronic administration 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.

To support a demonstration of biosimilarity, a stepwise approach was used following the FDA's scientific recommendation. The stepwise approach starts with structural and functional characterization of both the proposed biosimilar product and the reference product. Results of nonclinical and/or clinical studies follow to assess remaining questions with regards to potential residual uncertainty about biosimilarity.

This review is to evaluate the results of the clinical study, EP06-302 (PIONEER) which was a randomized, double-blind, parallel-group, multi-center study of EP2006 and Neupogen® in histologically proven breast cancer patients. Patients eligible for neoadjuvant or adjuvant treatment were treated with myelosuppressive TAC chemotherapy (Taxotere® [docetaxel 75 mg/m2] in combination with Adriamycin® [doxorubicin 50 mg/m2] and Cytoxan® [cyclophosphamide 500 mg/m2]), 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 Neupogen for Cycles, 2, 4, and 6; Group 3 Neupogen cycles 1, 3, and 5 and EP2006 for Cycles 2, 4, and 6; Group 4 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 Neupogen® (US-licensed) 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 0.5×10^9/L), during Cycle 1 of the neoadjuvant or adjuvant TAC regimen in breast cancer patients.

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 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 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 Neupogen, respectively. The 90% CI of the mean difference is (-0.21, 0.28). The analysis showed that EP2006 is equivalent to Neupogen in terms of efficacy as measured by the mean difference of DSN between EP2006 and Neupogen being less than 1 day for both the upper and lower bounds of the 90% CI

Our conclusion is consistent with the advisory committee's recommendation. The advisory committee meeting for oncology drug products was held on January 7, 2015 for this application. The advisory committee voted unanimously (14-0) that EP2006 should receive licensure as a biosimilar product for each of the five indications for which US-licensed Neupogen is currently approved.

2 INTRODUCTION

2.1 Overview

Granulocyte colony-stimulating factor (G-CSF) is a lineage-specific colony-stimulating factor which is produced by monocytes, fibroblasts, and endothelial cells. G-CSFs restore the number of neutrophils and keep the neutrophil count above the critical level at which febrile neutropenia (FN) can occur. The clinical use of recombinant human G-CSF (rhG-CSF) is to reduce the duration of neutropenia and the incidence of febrile neutropenia (FN) in patients with malignancies treated with myelosuppressive chemotherapy regimens as well as to reduce the duration of neutropenia in patients undergoing myeloablative therapy prior to bone marrow transplantation.

The first approved recombinant human G-CSF is Amgen's filgrastim (Neupogen®). The European Commission granted a marketing authorization valid throughout the EU for Ratiograstim® (a biosimilar filgrastim) to ratiopharm GmbH on September, 2008. The FDA and European Medicines Agency (EMA) approved in 2002 the first second-generation, recombinant methionyl form of human G-CSF (PEG-r-metHuG-CSF) that is pegylated under the INN pegfilgrastim.

In February 2009, EP2006 was approved by the European Medicines Agency (EMA) in the same indications as those of EU-approved Neupogen® and unrestricted renewal of the authorization has been granted by the EMA in the meantime.

Study EP06-302 was designed to demonstrate non-inferiority of EP2006 to US-licensed Neupogen® in the prevention of neutropenic complications in breast cancer patients treated with established myelosuppressive chemotherapy.

Table 1 : List of all studies included in analysis

	Phase and Design	Treatment Period	Follow-up Period	# of Subjects per Arm	Study Population
EP006-302	*Phase 3*	*18 weeks*	*6 weeks*	*192 (48/arm)*	*Breast cancer*

2.2 Data Sources

The study report and data were provided electronically; the location/names of study report, analysis datasets (ADAM) including STDM datasets and SAS programs are as follows;

Study Reports:
\\cdsesub1\bla\eCTD_Submissions\STN125553\0000\m5\53-clin-stud-rep\535-rep-effic-safety-stud\neutropenia-scn-pbpc-hiv\5351-stud-rep-conntr-sr-ep06-302
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Dataset
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Program
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3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

Reviewer reviewed the quality and integrity of the submitted data. Examples of relevant issues include the following:

- It is possible to reproduce the primary analysis dataset, and in particular the primary endpoint, from the original data source.
- The sponsor didn't provide subgroup analysis results at the initial BLA submission, so we requested subgroup results through information request.

3.2 Evaluation of Efficacy

3.2.1 Study Design and Endpoints

This study was a randomized, double-blind, parallel-group, multi-center study comparing the efficacy and safety of EP2006 and Neupogen® in histologically proven breast cancer patients treated with TAC combination chemotherapy (docetaxel 75 mg/m^2, doxorubicin 50 mg/m^2, and cyclophosphamide 500 mg/m^2). A total of 192 patients were randomized to either EP2006 or US-licensed Neupogen® in four groups (48/group) from 25 centers; 10 centers in Russia, 6 centers in Ukraine and 6 centers in Hungary, 1 center in Latvia, 1 center in Slovakia, and 1 center in Czech Republic. The four groups are as follows;

Table 2 : Planned Treatment Groups

Group	n	Cycle 1	Cycle 2	Cycle 3	Cycle 4	Cycle 5	Cycle 6
1 EP	48	EP2006	EP2006	EP2006	EP2006	EP2006	EP2006
2 EPNEU	48	EP2006	Neupogen	EP2006	Neupogen	EP2006	Neupogen
3 NEUEP	48	Neupogen	EP2006	Neupogen	EP2006	Neupogen	EP2006
4 NEU	48	Neupogen	Neupogen	Neupogen	Neupogen	Neupogen	Neupogen

The patients underwent TAC combination chemotherapy (docetaxel 75 mg/m^2, doxorubicin 50 mg/m^2, and cyclophosphamide 500 mg/m^2), administered intravenously on Day 1 of each chemotherapy cycle and given for six cycles with 3 weeks /cycle. Study drug (EP2006 or Neupogen®) was administered daily starting on Day 2 of each chemotherapy cycle (at least 24 hours after chemotherapy ended) and continued until the ANC recovered to 10×10^9/L after the nadir or up to a maximum of 14 days (whichever occurred first). EP2006 and Neupogen® were injected subcutaneously with a daily dose of 5 mcg/kg body weight.

The total study duration was up to 24 weeks, including up to three weeks screening, approximately 18 weeks of active treatment (6 TAC chemotherapy cycles), and a follow-up visit about six weeks after the start of the last cycle (approximately four weeks after the last study medication administration).

Patient's ANC, platelet values and hemoglobin values had to be above the defined limits (ANC $\geq 1.5 \times 10^9$/L, platelets $\geq 100 \times 10^9$/L, and Hemoglobin $\geq$ 10g/dL) at the Day 1 of Cycle 1.

In Cycle 1, blood samples for the determination of the ANC were taken on Day 1, daily until the ANC recovered to 10×10^9/L after the nadir or until Day 15, whichever occurred first.
In Cycles 2 to 6, blood samples were taken on Day 1 prior to chemotherapy and daily from Day 7 onwards until the ANC recovered to 10×10^9/L after the nadir or until Day 15, whichever occurred first.

Primary Endpoint:

The primary efficacy endpoint was the mean DSN in Cycle 1. The DSN was set to 0 in patients who did not experience severe neutropenia in Cycle 1. In patients who experienced several episodes of severe neutropenia, the number of days for each episode was summed up.

Secondary endpoints:

The key two secondary endpoints were the depth of ANC nadir and time to ANC recovery. The depth of ANC nadir was defined as the patient's lowest ANC in a chemotherapy cycle. Time to ANC recovery was defined as the time from ANC nadir day until the patient's ANC increases to $\geq 2 \times 10^9$/L day after the nadir in cycle 1.

The depth of ANC nadir was analyzed with descriptive statistics for Cycle 1 and for each cycle. A descriptive analysis was performed for the combined treatment groups 1 + 2, and 3 + 4 only. If the nadir was $\geq 2 \times 10^9$/L for all time points after administration of chemotherapy the time was set to 0 day.

The other secondary endpoints were the incidence of FN, the number of days of fever, the frequency of infections and duration of hospitalization due to FN.

The incidence of FN was calculated as the number of patients with at least one episode of FN divided by the number of patients at risk in a given time interval (in each cycle the period

between Day 2 to Day 15 was considered for the analysis). FN was defined as having both an oral temperature ≥ 38.3°C and an ANC < 0.5×10^9/L on the same day. The incidence of FN was analyzed separately for each cycle and over all cycles (overall incidences).

3.2.2 Statistical Methodologies

The following rules were pre-specified to treat missing data in assessing the primary endpoint.

- The ANC before and after the missing day was ≥ 0.5×10^9/L: the day could be ignored as a potential day of severe neutropenia.
- If at both neighboring days the ANCs were < 0.5×10^9/L, then the missing day was to be set to severe neutropenia.
- If the day before was < 0.5×10^9/L and the day after ≥ 0.5×10^9/L, then the missing day was to be set to severe neutropenia.
- If the day before was ≥ 0.5×10^9/L and the day after < 0.5×10^9/L, then the missing day was to be set to severe neutropenia.
- If any of the neighboring days were also missing, severe neutropenia could not be determined and the data remained missing.

The primary efficacy endpoint was analyzed using an analysis of co-variance (ANCOVA) with treatment group, kind of chemotherapy and baseline ANC value as a covariate.

The full analysis set (FAS) included all randomized patients who received at least one dose of study medication. The per protocol (PP) set is a subset of the FAS including those patients who completed the first chemotherapy cycle without major protocol deviations. The primary analysis population was the PP population. The primary endpoint was additionally analyzed based on the FAS as a sensitivity analysis to evaluate the robustness of the results.

A one-sided 97.5% Clopper-Pearson CI for the difference of overall FN incidence between the switched and un-switched (between EP2006 and Neupogen®) patients was calculated. Switching was to be considered non-inferior to not switching if the lower bound of the one-sided 97.5% CI was above the non-inferiority margin of -15%.

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 adequately small with a narrow confidence interval, one might conclude that the difference is immaterial.

The maximum daily temperature was analyzed with descriptive statistics separately for each cycle and over all cycles. Fever was defined as an oral temperature ≥ 38.3°C. The number of patients who had fever at least once was presented with counts and percentages for each cycle and over all cycles.

Sample Size Calculation
The sample size was calculated based on the non-inferiority of EP compared to Neupogen® concerning the DSN defined as days with ANC <0.5 x 10^9/L in cycle 1. The non-inferiority margin was set to 1 day and non-inferiority should be regarded as confirmed if the upper limit of the two-sided 95% CI for the difference of the expected DSN between EP and Neupogen® would be less than 1 day. Assuming the difference between EP and Neupogen® of 0.25 days in favor of Neupogen® and the standard deviation of about 1.5 days, the sample size should be at least 86 patients per treatment group assuring 90% power. Based on primary analysis population with per-protocol population, 10% of the randomized patients were expected to be excluded in the per-protocol population. The sample size of 192 patients (96/treatment group) was planned.

3.2.3 Patient Disposition, Demographic and Baseline Characteristics

A total of 258 patients were screened and 218 patients were randomized and 40 patients were excluded; 3 due to not meeting inclusion criteria, 2 due to meeting exclusion criteria, and 34 due to other reasons. The first patient enrolled date was on December 26, 2011 and the last patient entered on June 17, 2013.

Among 218 randomized patients, 54 patients were allocated to EP group, 55 patients were allocated to EPNEU group, 55 patients were allocated to NEUEP group and 54 patients were allocated to NEU group.

A total of 34 patients did not complete the study or discontinued study treatment prematurely; 29 patients did not complete the study drug treatment and 33 patients did not complete the study.

The primary reason for premature treatment and study discontinuations are summarized in Table 3.

Table 3 : Primary Reason for Premature Treatment and Study Discontinuations

Primary reason	EP N=54 n (%)	EPNEU N=55 n (%)	NEUEP N=55 n (%)	NEU N=54 n (%)	Total N=218 n (%)
Treatment Discontinuation					
Withdrawal	5 (9.3)	3 (5.5)	3 (5.5)	2 (3.7)	13 (6.0)
Lost to follow up	0	0	1 (1.8)	1 (1.9)	2 (0.9)
Death	1 (1.9)	0	0	0	1 (0.5)
Physician decision	1 (1.9)	1 (1.8)	3 (5.5)	0	5 (2.3)
Other	2 (3.7)	2 (3.6)	0	4 (7.4)	8 (3.7)
Withdrawal from the study					
Withdrawal	4 (7.4)	3 (5.5)	3 (5.5)	2 (3.7)	12 (5.5)
Lost follow up	1 (1.9)	1 (1.8)	2 (3.6)	1 (12.9)	5 (2.3)
Death	1 (1.9)	0	0	0	1 (0.5)
Other	6 (11.1)	3 (5.5)	3 (5.5)	3 (8.8)	15 (6.9)

A total of 29 patients discontinued the treatment. A total of 33 patients were withdrawn from the study. Among 218 randomized patients, 14 patients had major protocol deviations. The primary reasons for the protocol deviation were due to administration of commercial filgrastim (9 patients); and due to no study drug during the cycles (5 patients).

The sponsor's analysis population sets are summarized in Table 4.

Table 4 : Analysis Population Sets

	EP N=54 n (%)	EPNEU N=55 n (%)	NEUEP N=55 n (%)	NEU N=54 n (%)	Total N=218 n (%)
ITT	54	55	55	54	218
FAS	53	54	55	52	214
SAF	53	54	55	52	214
PP	50	51	52	51	204
PP-I	40	45	44	46	175

SAF = Safety (set); FAS = Full analysis set; PP = Per protocol (set); SAF-I = Safety interchangeability (set); PP-I = Per protocol interchangeability (set); sponsor's Table 11-1

Among 218 randomized patients, 214 patients were treated with study drug (full analysis set (FAS)) after excluding 4 patients who were not treated or only treated with commercial filgrastim. This is the same with the safety analysis population (SAF). The protocol deviations were 4 patients from EP; 4 patients EPNEU, 3 patients NEUEP and 3 patients from NEU. After excluding 14 protocol deviation patients from 218 randomized patients, the PP included 204 patients. There were 4 patients who were treated in the study, but did not receive the study drug after Cycle 1, 19 patients who did not complete all six cycles, and 16 patients who completed all six cycles, but had major protocol violations. After excluding all 39 patients from 214 PP populations, the PP-I included 175 patients. The analyses population for switched (Group 1 [EP] and 4 [NEU]) vs. un-switched (Group 2 [EPNEU] and 3 [NEUEP]) was PP-I.

The patients' demographics are summarized in Table 5.

Table 5 : Demographic Characteristics: Randomized Population

	EP (N=109) n (%)	NEU (N=109) n (%)
Age		
Mean (SD) (years)	49.4 (11.5)	48.4 (10.9)
<65	100 (91.7)	98 (89.9)
≥65	9 (8.3)	11 (10.1)
Chemotherapy		
Adjuvant	64 (58.7)	62 (56.9)
Neo-adjuvant	45 (41.3)	47 (43.1)

Region		
Russia	81 (74.3)	87 (79.8)
Ukraine	17 (15.6)	16 (14.7)
Other	11 (10.1)	6 (5.5)

The demographic characteristics were similar between the two groups. Mean ages were 49 years in the EP2006 group and 48 years in the Neupogen group. Patients who had adjuvant therapy were 59% in the EP2006 group and 57% in the Neupogen group. The most patients were enrolled from Russia in both groups.

The disease characteristics are summarized in Table 6.

Table 6 : Disease Characteristics: Randomized Population

	EP (N=109) n (%)	NEU (N=109) n (%)
Stage		
I	7 (6.4)	8 (7.3)
II	57 (52.3)	55 (50.5)
III	45 (41.3)	46 (42.2)
Surgery		
Yes	86 (78.9)	83 (76.2)
No	23 (21.1)	26 (23.9)
Radio Therapy		
Yes	9 (8.3)	10 (9.2)
No	100 (91.7)	99 (90.8)
ECOG Status		
0	84 (77.1)	84 (77.1)
1	25 (22.9)	25 (22.9)
Months since first diagnosis (months)		
Mean (SD)#	2.8 (16.3)	1.2 (1.9)

The disease characteristics were similar between the two groups. Majority patients were with breast stage II or III, ECOG score 0, yes surgery, no radio therapy. The mean months since first diagnosis were 2.8 months in the EP006 group and 1.2 months in the Neupogen group. The difference was one outlier (171 months) in the EP2006 group. The median months since first diagnosis were both one month.

3.2.4 Results and Conclusions

The primary analysis is summarized in Table 7, which are the same as the sponsor's.

Table 7 : DSN in Cycle 1: PP population

	EP (N=101)		NEU (N=103)
DSN			
Mean (SD)	1.17 (1.11)		1.20 (1.02)
Difference *		-0.04	
95% CI		(-0.33, 0.26)	
90% CI		(-0.28, 0.21)	
DSN (days), n (%)			
0	37 (36.6)		32 (31.1)
1	23 (22.8)		30 (29.1)
2	32 (31.7)		30 (29.1)
3	5 (4.9)		10 (9.7)
4	4 (4.0)		1 (1.0)

Sponsor's Table 11-4

The mean DSN in Cycle 1 was 1.17 days and 1.20 days for EP2006 and Neupogen, respectively. The estimated mean difference of DSN was -0.04 days and the upper limit of 95% of 0.26 (95% CI: -0.33, 0.26) which is below 1 day of non-inferiority margin. The analysis showed that EP2006 is equivalent to Neupogen in terms of efficacy as measured by the difference of DSN between EP2006 and Neupogen being less than 1 day for both the upper and lower bounds of the 90% CI

Reviewer's comment:
We believe that the equivalence margin of 1 day is appropriate. Please refer to Dr. Gootenberg's clinical review in STN125031, dated Jan 31, 2002, for the basis for use of DSN as a surrogate for FN and the non-inferiority margin of 1 day in DSN was used. Dr. Gootenberg also stated " a 1-day difference in DSN would be anticipated to result in approximately a 10% difference in febrile neutropenia. This was felt to be a meaningful and practical difference to exclude when comparing Pegfilgrastim and Filgrastim".

Reviewer's sensitivity analyses

FDA's sensitivity analysis 1:

In a sensitivity analysis of the primary endpoint, DSN was defined as days of ANC <1× 10^9/L and the results are summarized in Table 8.

Table 8 : DSN with ANC <1x10^9/L in Cycle 1

	EP (N=101)		NEU (N=103)
DSN			
Mean (SD)	1.76 (1.23)		1.84 (1.25)
Difference *		-0.08	
95% CI		(-0.43, 0.26)	
90% CI		(-0.37, 0.21)	

DSN (days), n (%)		
0	22 (21.8)	22 (21.4)
1	17 (16.8)	11 (10.7)
2	33 (32.7)	40 (38.8)
3	21 (20.8)	23 (22.3)
≥ 4	8 (7.9)	7 (6.8)

FDA's sensitivity analysis 2:

This reviewer analyzed the DSN in cycle 1 based on FAS population and the results are summarized in Table 9.

Table 9 : DSN in Cycle 1: FAS population

	EP (N=107)	NEU (N=107)
DSN		
Mean (SD)	1.18 (1.12)	1.20 (1.02)
Difference *	-0.02	
95% CI	(-0.31, 0.27)	
90% CI	(-0.26, 0.22)	
DSN (days), n (%)		
0	37	32
1	23	30
≥ 2	41	41

The mean DSN in cycle 1 was 1.18 and1.20 days for EP and NEU, respectively. The estimated mean DSN difference between EP and NEU was -0.02 days (95% CI:-0.31, 0.27*). The results based on FAS population were also consistent to those of PP population.*

The sample size, based on an equivalence test with margin (-1, 1), was 45 patients with standard deviation of 1 and 90% power at 2-sided α=0.05. The sample size based on equivalence test with margin of (-0.74, 0.74) was 99 patients with standard deviation of 1.11 and 90% power at 2-sided α=0.05.

FDA's sensitivity analysis 3:

In the site 703, 75% patients had commercial filgrastim, the reviewer analyzed the sensitivity analysis for DSN in cycle 1 excluding patients in the site 703 and patients who had commercial filgrastim. The results are summarized in Table 10.

Table 10: DSN in Cycle 1: FAS population Excluding Subjects with Exposure of Commercial Drug and Subjects in Site 703

	EP (N=92)	NEU (N=89)
DSN		
Mean (SD)	1.15 (1.12)	1.13 (1.02)
Difference *	0.01	
95% CI	(-0.30, 0.33)	
90% CI	(-0.25, 0.28)	
DSN (days), n (%)		
0	35	30
1	20	27
≥ 2	37	32

The results were similar to the primary analysis results.

FDA's Sensitivity analysis 4:
There are missing ANC values from Day 10 to Day 15 in the Cycle 1. We did not impute missing DSN days in the control group but imputed 0.1(sensitivity 1), 0.2 (sensitivity 2) days in the missing DSN in the EP2006 group for sensitivity analyses. These sensitivity analyses results are summarized in Table 11.

Table 11: Results for sensitivity analyses for DSN in Cycle 1

	EP	NEU	Differences (95% CI)
Sponsor's results (PP)	N=101	N=103	
Mean (SD)	1.17 (1.11)	1.20 (1.02)	-0.04 (-0.33, 0.26)
Reviewer's results (FAS)	N=107	N=107	
Mean (SD)	1.18 (1.12)	1.20 (1.02)	-0.02 (-0.31, 0.27)
Sensitivity 1 (EP 0.1)	N=107	N=107	
Mean (SD)	1.64 (1.07)	1.20 (1.02)	0.46 (0.18, 0.75)
Sensitivity 2 (EP 0.2)	N=107	N=107	
Mean (SD)	2.10 (1.03)	1.20 (1.02)	0.90 (0.63, 1.18)

The sensitivity analysis results were robust except sensitivity analysis number 2. The missing data mostly occurred after the ANC recovery and we normally assume ANC should be above $.5\times 10^9$ /L.

FDA's sensitivity analysis 5:

The assumption of normality of ANCOVA analysis does not hold, so the reviewer used negative binomial distribution assumption with Genmod based on PP population. The difference (NEU-EP2006) and 95% CI and 90% CI are as follows;

Difference (EP2006-NEU) (95% CI): -0.03 (-0.28, 0.22)

Difference (EP2006-NEU) (90% CI): -0.03 (-0.24, 0.18)

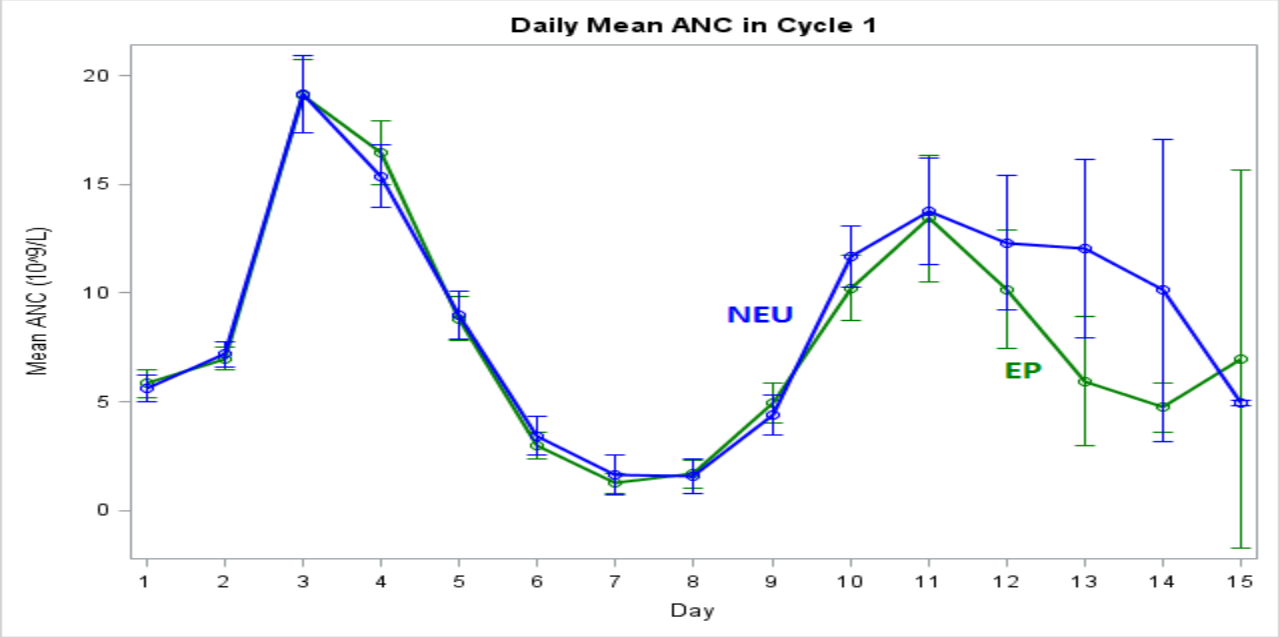
The results were similar to that of ANCOVA. In addition, we analyzed the data using Poisson regression and bootstrap method, the results were similar.

Secondary Endpoints

1. Depth of ANC Nadir

The key secondary endpoint was the depth of ANC nadir and time to recovery of the ANC nadir in cycle 1. The daily mean ANC in Cycle 1 is plotted in Figure 1.

Figure 1 : Daily Mean ANC in Cycle 1: FAS population

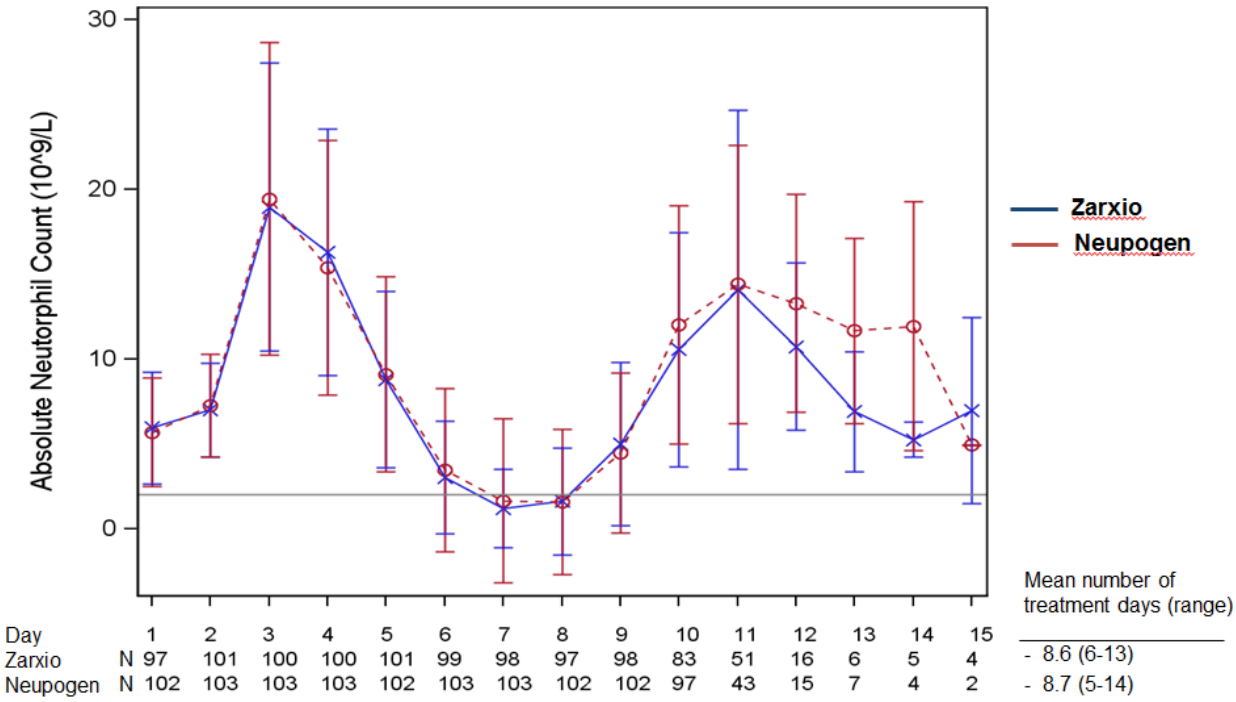


N															
	EP	101	101	101	101	101	101	101	99	98	87	56	25	16	15	14
	NEU	103	103	103	103	103	103	103	102	102	98	45	17	9	6	4

The daily means ANC in Cycle 1 between EP and NEU were similar until Day 10, a time when AND recovery was observed.

During the ODAC meeting of January 7, 2015, the FDA presented a similar graph of ANC profile in the PP set (Figure 1), which was found different from the sponsor's graph (Figure 2) in the same PP set.

Figure 2 : Sponsor's Time course of ANC in Cycle 1 (PP set)



Below, we list the sources of the discrepancies of those two graphs, Figure 1 and Figure 2.

1) If a subject's ANC value is missing (but this subject is still being monitored) at any day, this subject is not counted in the sample size on that day in the sponsor's graph but is counted in FDA's graph.

2) While the sponsor plotted mean+/- standard deviation, the FDA plotted mean with 95% confidence limits for each day.

3) While the sponsor plotted ANC from day 1 to day 21 (with no data from day 16-day 20), the FDA plotted up to day 15.

Both graphs are reasonable, but have different display preferences. Other than these minor differences, the two graphs are the same.

The results for ANC depth and time occurred ANC nadir based on PP population are summarized in Table 12.

Table 12: Sponsor's Depth and Time Occurred ANC nadir in Cycle 1: PP population

	EP (N=101)	NEU (N=103)
Mean (SD)	0.73 (1.14)	0.76 (1.31)
ANC nadir at Day, n (%)		
Mean(SD)	7.27 (1.31)	7.45 (1.45)
1-5	4 (4.0)	2 (1.9)
6	2 (2.0)	2 (1.9)
7	60 (59.4)	58 (56.3)
8	31 (30.7)	37 (35.9)
9	3 (3.0)	1 (1.0)
10-15	1 (1.0)	3 (2.9)

The mean depth of ANC nadir was 0.73 in the EP2006 group and 0.76 in the Neupogen group. The mean time occurred ANC nadir was 7.27 days in the EP2006 group and 7.35 days in the Neupogen group. The mean depth and the mean time of ANC nadir occurred were similar between the two groups in Cycle 1.

2. Time to Recovery of ANC Nadir

The results of time to ANC recovery in Cycle 1 based on PP population are summarized in Table 13.

Table 13: Sponsor's Time to ANC Recovery in Cycle 1: PP population

ANC Recovery Day	EP (N=101)	NEU (N=103)
Mean (SD)	1.79 (0.97)	1.68 (0.81)
Difference*	0.13	
95% CI*	-0.14, 0.36	

*:Difference and 95% CI were estimated using ANCOVA with treatment group and type of chemotherapy and a baseline ANC as a covariate

The mean times to recovery from ANC nadir were 1.79 days and 1.68 days, for EP2006 and Neupogen, respectively. The mean times to ANC nadir recovery were similar. The estimated mean differences in time to recovery ANC nadir was 0.13 days with 95% CI of (-0.14, 0.36). The results were the same with that of sponsor's.

3. Incidence of FN

The FN was defined as oral temperature ≥ 38.3°C while having an ANC < 0.5×10^9/L (both measured on the same day). The sponsor's results for incidence of FN are summarized in Table 14, confirmed by the reviewer.

Table 14: Sponsor's Incidence of FN in Cycle 1: PP population

	EP (N=101) n (%)	NEU (N=103) n (%)
FN		
Number of FN	4 (4.0)	2 (1.9)
Exact 95 % CI	(1.1, 9.8)	(0.0, 5.3)
Days of FN		
1	4 (4.0)	1 (1.0)
2	0	1 (1.0)
Missing	1 (1.0)	

Four patients in the EP group (4%) and 2 patients (1.9%) in the NEU group had FN cases. There were no clinically meaningful differences in the incidence of FN between the two groups.

Reviewer's additional analysis
The results for incidence of FN based on FAS population in Cycle 1 are summarized in Table 15.

Table 15: Incidence of FN in Cycle 1: FAS population

	EP (N=107)	NEU (N=107)
FN	N=106	N=107
Number of FN	5 (4.7)	1 (0.9)
Exact 95% CI	(1.5, 10.6)	(0.0, 5.1)
Days of FN		
1	5	1
2	0	1
Missing	1	

Five patients in the EP group (4.7%) and one patient (0.9%) in the NEU group had FN cases. These results were similar to that of PP population.

4. Number of Days of Fever

Fever was defined as an oral temperature ≥ 38.3°C. One patient's temperature was not available. The sponsor's mean fever days in Cycle 1 are summarized in Table 16, confirmed by the reviewer.

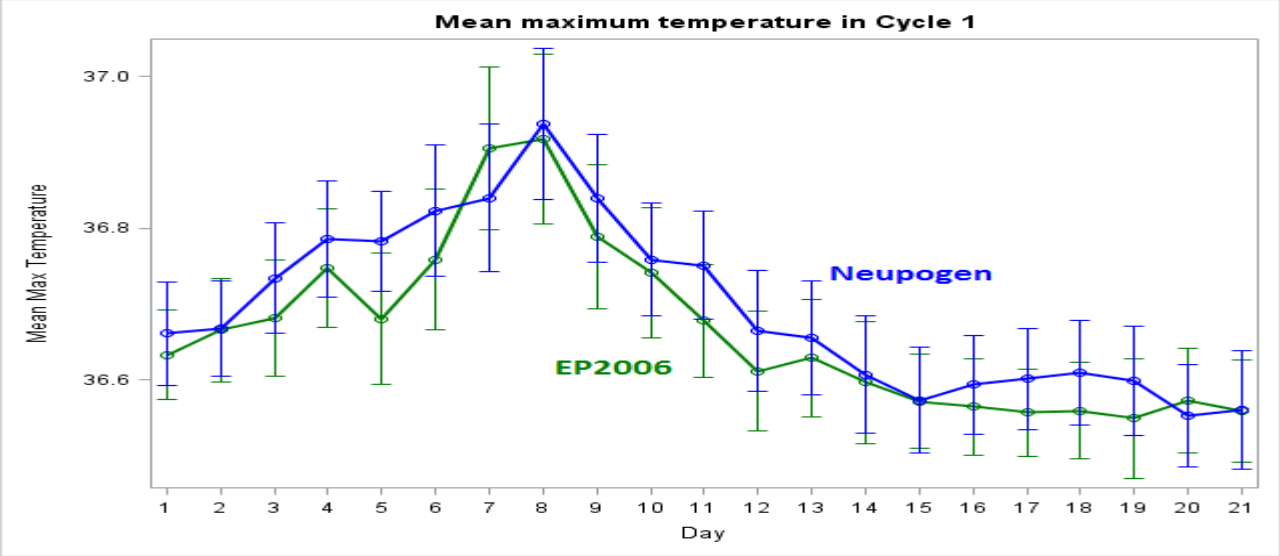
Table 16: Sponsor's Number of days in fever in Cycle 1: PP population

	EP (N=101) n (%)	NEU (N=103) n (%)
Number of days in fever		
Mean (SD)	0.07 (0.29)	0.04 (0.24)

The mean number of days of fever in Cycle 1 was 0.07 days in the EP group and 0.04 days in the NEU group. There were no differences between the two groups in number of fever days.

The mean daily maximum temperatures in Cycle 1 are plotted based on FAS population in Figure 3, confirmed by the reviewer.

Figure 3 : Mean Daily Maximum Temperatures in Cycle 1: FAS Population



N EP	106	106	106	106	105	105	105	105	105	105	101	100	100	99	99	99	99	99	99	96	94
NEU	106	107	107	107	107	107	107	107	107	107	104	100	99	99	98	98	98	98	97	97	93

The daily mean maximum temperatures seem little higher in Neupogen group compared to EP2006 group, but the daily mean maximum temperatures were between 36.5-36.9 ° C.

3.3 Evaluation of Safety

For a detailed summary of the evaluation of safety refer to the review by Dr. Donna Przepiorka.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race, Age, and Geographic Region

The reviewer conducted subgroup analyses for age groups (<65 years versus ≥ 65 years) and geographic region (Russia vs. Ukraine vs. Other) of the primary endpoint of DSN using difference and 90% CI are summarized in Table 17.

Table 17: Subgroup Analyses of DSN: Age and Region (90% CI): PP population

	EP (N=101)		NEU (N=103)		
	N	Mean (SD)	N	Mean (SD)	Difference (90% CI)
Age					
< 65	92	1.17 (1.12)	92	1.16 (1.02)	0.01 (-0.25, 0.28)
≥ 65	9	1.11 (0.93)	11	1.55 (1.04)	-0.44 (-1.24, 0.36)
Geographic Region					
Russia	74	1.18 (1.05)	82	1.26 (1.03)	-0.08 (-0.36, 0.19)
Ukraine	17	1.24 (1.43)	16	0.75 (0.86)	0.44 (-0.27, 1.15)
Other	10	1.00 (0.94)	5	1.80 (1.10)	-1.02 (-1.86, -0.18)

The mean DSN was 0.01 days shorter in the NEU group than the EP group in age < 65 group. The mean DSN were 1.11 days in the EP group and 1.55 days in the NEU group in age ≥ 65 group. However, there were only 20 patients in age ≥ 65 group. The results are generally consistent with the whole population except results obtained in subgroups with small sample size.

4.2 Other Special/Subgroup Populations

The reviewer also performed subgroup analyses of the primary endpoint by disease characteristics and summarized results in Table 18.

Table 18: Subgroup Analyses for DSN: Baseline Disease Characteristics (90% CI): PP population

	EP (N=101)		NEU (N=103)		
	N	Mean (SD)	N	Mean (SD)	Difference (90% CI)
Therapy					
Adjuvant	58	1.24 (1.20)	58	1.17 (1.11)	0.08 (-0.28, 0.43)
Neo-adjuvant	43	1.07 (0.96)	45	1.24 (0.91)	-0.17 (-0.50, 0.16)
Stage					
I	6	1.67 (1.63)	8	1.13 (1.13)	0.92 (-0.66, 2.50)
II	56	1.11 (1.11)	50	1.14 (1.05)	-0.02 (-0.37, 0.33)
III	39	1.18 (1.02)	45	1.29 (0.99)	-0.09 (-0.46, 0.28)
Surgery					
Yes	79	1.23 (1.15)	77	1.19 (1.04)	0.04 (-0.26, 0.33)
No	22	0.95 (0.90)	26	1.23 (0.99)	-0.26 (-0.71, 0.19)
Radio Therapy					
Yes	9	1.44 (1.24)	8	1.13 (0.64)	0.17 (-0.76, 1.09)
No	92	1.14 (1.10)	95	1.21 (1.05)	-0.07 (-0.33, 0.19)

ECOG					
0	79	1.18 (1.16)	81	1.20 (1.02)	-0.01 (-0.29, 0.28)
1	22	1.09 (0.92)	22	1.23 (1.07)	-0.08 (-0.61, 0.44)

The mean DSN difference between the two groups and the 90% CI has the upper and lower bound less than 1 day except subgroups with small sample size:

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and collective Evidence

The primary endpoint of mean DSN in Cycle 1 was 1.17 days and 1.20 days for EP and NEU, respectively. The 95% CI (-0.33, 0.26) and 90% CI (-0.28, 0.21) were within (-1, 1).

For secondary endpoints, the mean depth of ANC nadir was 0.73 in the EP2006 group and 0.76 in the Neupogen group. The mean time to ANC nadir recovery was 1.79 days in the EP2006 group and 1.68 days in the Neupogen group. The difference of mean time to recovery of ANC nadir was 0.13 days with 95% CI of (-0.14, 0.36). The mean depth and the mean time to ANC nadir recovery were similar between the two groups in Cycle 1.

For the incidence of FN, 4 patients in the EP group (4%) and 2 patients (1.9%) in the NEU group had FN cases.
The mean number of days of fever in Cycle 1 was 0.07 days in the EP group and 0.04 days in the NEU group. There were no clinically meaningful differences in the incidence of FN between the two groups.

5.2 Conclusions and Recommendations

The analyses of both the primary endpoint (DSN) as well as secondary endpoints in Cycle 1 of study EP06-302 support the conclusion that there was no clinically meaningful difference with respect to efficacy between EP2006 group and US-licensed Neupogen group in Cycle 1.

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/s/

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