CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125294Orig1s000

STATISTICAL REVIEW(S)

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

NDA/BLA #:	BLA 125-294/0033 (New BLA-Resubmission to CR)
Drug Name:	Neutroval (b) (4) Injection
Indication(s):	Reduction in the Duration of Severe Neutropenia
Applicant:	Teva Pharmaceuticals USA
Date(s):	Submitted 2/29/2012
Review Priority:	Standard
Biometrics Division:	Division of Biometrics V (HFD-711)
Statistical Reviewer:	Qing Xu, Ph.D
Concurring Reviewers:	Mark Rothmann, Ph.D, Team Leader
	Rajeshwari Sridhara, Ph.D, Division Director
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Clinical Team:	Thomas Herndon, M.D, Clinical Reviwer
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Project Manager:	Lara Akinsanya

Submission Backgroud

This submission contains sponsor's responses to the Complete Response (CR) letter that was issued on September 29, 2010. In this submission, Teva Pharmacetuicals is addressing all deficiencies and information requests identified by the Agency in the Complete Response (CR) letter. PDUFA goal date is August 20, 2012. There is no additional clinical study submitted in this resubmission.

Conclusions and Recommendation

As the submission does not contain any additional clinical study, there is no additional statistical comment provided for this resubmission. Please refer to the Dr. Lu's statistical report for the statistical comments for the original submission.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

QING XU
07/27/2012

MARK D ROTHMANN
07/27/2012

RAJESHWARI SRIDHARA
07/27/2012

U.S. Department of Health and Human Services
Food and Drug Administration
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STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES – TEAM LEADER'S MEMO

NDA/Serial Number:	BLA129254/0
Drug Name:	Neutroval ® (XM02)
Indication(s):	Reduction in the Duration of Severe Neutropenia
Applicant:	Teva Pharmaceuticals USA
Date(s):	Submitted 11/30/2009
	PDUFA date 9/30/2010
Review Priority:	Standard
Biometrics Division:	V (HFD-711)
Primary Reviewer:	Dr. Laura Lu, Ph.D
Secondary Reviewer:	Kun He, Team Leader
Concurring Reviewer:	Dr. Rajeshwari Sridhara, Ph.D, Acting Division Director
Medical Division:	Biological Oncology Products (HFD-107)
Clinical Team:	Dr. Thomas Herndon, MD, Medical Reviewer
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	Dr. Patricia Keegan, MD, Division Director
Project Manager:	Mr. Danyal Chaudhry, Project Manager

Keywords: superiority, equivalence, missing value, sensitivity analysis

The Applicant is seeking an approval of Neutroval (XM02) for the indication of reduction in duration of severe neutropenia (DSN) (b) (4) , and submitted one efficacy study XM02-02 and two safety studies XM02-03 and XM02-04.

Study XM02-02 was a randomized, international, controlled study in patients with high-risk stage II, or with stage III or IV breast cancer needing chemotherapy. XM02 was developed in Europe as a similar biological product to the innovator filgrastim (Neupogen). The primary objectives of Study XM02-02 were to confirm of assay sensitivity with respect to DSN by comparing XM02 versus placebo, and to demonstrate of equivalence of XM02 and filgrastim in the first cycle of chemotherapy. A total of 350 patients were randomized with a ratio of 2:2:1 to XM02, European-manufactured filgrastim and placebo. Patients were enrolled in 52 study centers in 10 countries from Europe, South America and South Africa. Among them, 348 patients were included in the full analysis (FA) dataset by excluding two patients erroneously randomized with screening failures.

The primary endpoint DSN was defined as Grade 4 neutropenia with an absolute neutrophil count (ANC) $<0.5 \times 10^9$/L. DSN was to be analyzed by ANCOVA including the factors "treatment", "country" and "adjuvant vs. metastatic therapy", and with the baseline ANC value as covariate. Missing ANC values were imputed mainly by linear interpolation. Assay sensitivity with respect to DSN in Cycle 1 was to be demonstrated by comparing XM02 versus placebo. If the difference was significant (two-sided $p \leq 0.05$ with shorter DSN for XM02), equivalence between XM02 and filgrastim was assessed. To show equivalence between XM02 and filgrastim, the two-sided 95% confidence interval (CI) for the difference in DSN in Cycle 1 had to lie entirely within the equivalence range of [-1 day, +1 day]. A difference of 1 day was considered to be the maximum clinically acceptable difference.

The Applicant's primary analysis demonstrated that XM02 was superior to placebo in DSN with statistically significant reduction in DSN (2.7 days reduction in DSN, $p<0.0001$), and XM02 was equivalent to European filgrastim with the 95% confidence interval (-0.26, 0.33) for mean difference in DSN lying within the 1 day margin.

The statistical issues in the Applicant's analyses are mainly in data replacement and data imputation. In Applicant's primary analysis for XM02 vs. placebo, the DNS value of 11 placebo patients who received therapeutic G-CSF treatment were replaced with the median DSN value of placebo patients who received no G-CSF treatment. This approach could underestimate the variability of DSN in placebo arm, and may exaggerate the statistical significance of the difference in DSN. Also, missing ANCs were mostly imputed by linear interpolation of the ANC values immediately before and after the missing value. The validity of this method is questionable by assuming an ANC value to be in-between the ANC values before and after.

To address the concerns above and to evaluate the robustness of the Applicant's results, following sensitivity analyses were performed by Dr. Laura Lu:

1. DSN results were based on intent-to-treat (ITT) data without replacing DSN values for placebo patients receiving therapeutic G-CSF treatment. The missing ANCs were

imputed by the method proposed by Dr. Laura Lu (please refer to Appendix A of statistical reviewer by Dr. Laura Lu for this application dated July ???, 2010). The sensitivity analyses demonstrated that XM02 was superior to placebo in DSN with statistically significant reduction in DSN (2.5 days reduction in DSN, $p<0.0001$), and XM02 was equivalent to European filgrastim with the 95% confidence interval (-0.26, 0.32) for mean difference in DSN lying within the 1 day margin.

2. DSN results were based on ITT data without replacing DSN values for placebo patients receiving therapeutic G-CSF treatment. Missing ANCs were treated as $<0.5 \times 10^9$/L (non-response). The sensitivity analyses demonstrated that XM02 was superior to placebo in DSN with statistically significant reduction in DSN (2.4 days reduction in DSN, $p<0.0001$), and XM02 was equivalent to European filgrastim with the 95% confidence interval (-0.33, 0.49) for mean difference in DSN lying within the 1 day margin.

3. DSN results were based on ITT data without replacing DSN values for placebo patients receiving therapeutic G-CSF treatment. Missing ANCs were treated as $<0.5 \times 10^9$/L in XM02 arm (response), but as $\geq 0.5 \times 10^9$/L in placebo arm (no response). This is the worst case analysis. The sensitivity analyses demonstrated that XM02 was superior to placebo in DSN with statistically significant reduction in DSN (2.2 days reduction in DSN, $p<0.0001$), and XM02 was equivalent to European filgrastim with the 95% confidence interval (-0.03, 0.67) for mean difference in DSN lying within the 1 day margin.

(b) (4) Although the data did demonstrate that the 95% confidence interval (-0.26, 0.33) for mean difference between XM02 and European filgrastim in DSN lay within the 1 day equivalence margin, an equivalence claim of XM02 vs. Neupogen (b) (4)

For further details regarding the design, data analyses, and results, please refer to the statistical review by Dr. Laura Lu for this application.

This Team Leader agrees with the primary statistical reviewer Dr. Laura Lu's recommendations and conclusions for this application.

This Team Leader's overall conclusion is that Study XM02-02 demonstrated that XM02 was superior to placebo in DSN with statistically significant reduction in DSN (2.7 days reduction in DSN, $p<0.0001$). Although the analyses demonstrated that XM02 was equivalent to European filgrastim with the 95% confidence interval (-0.26, 0.33) in DSN difference lying within the 1 day margin, (b) (4)

SIGNATURES/DISTRIBUTION LIST

Secondary Reviewer: _____
Kun He, Statistical Team Leader

Concurring Reviewer: _____
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Date: July 30, 2010

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STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/Serial Number:	BLA129254/0
Drug Name:	Neutroval (XM02)
Indication(s):	Reduction in the Duration of Severe Neutropenia
Applicant:	Teva Pharmaceuticals USA
Date(s):	Submitted 11/30/2009, PDUFA date 9/30/2010
Review Priority:	Standard
Biometrics Division:	Division of Biometrics V (HFD-711)
Statistical Reviewer:	Dr. Laura Lu, Ph.D
Concurring Reviewers:	Dr. Kun He, Ph.D, Team Leader
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	Dr. Patricia Keegan, MD, Division Director
Project Manager:	Mr. Danyal Chaudhry, Project Manager

Keywords: superiority, equivalence, missing value, sensitivity analysis

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1. EXECUTIVE SUMMARY

BLA129254/0 was submitted for the approval of Neutroval (XM02) with the indication of reduction in duration of severe neutropenia (DSN) (b) (4) XM02 was developed in Europe as a similar biological product to the innovator filgrastim (Neupogen). One efficacy Study XM02-02 and two safety studies XM02-03 and XM02-04 were submitted in this BLA in supporting the proposed indication. Study XM02-02 was conducted in Europe, South America and South Africa. In this study, XM02 was compared with placebo for essay sensitivity and compared with European-manufactured filgrastim (b) (4)

1.1 Conclusions and Recommendations

Study XM02-02 demonstrated that XM02 was superior to placebo in DSN with statistically significant reduction in DSN (2.7 days reduction in DSN, $p<0.0001$), and XM02 was equivalent to European filgrastim with the 95% confidence interval (-0.26, 0.33) in DSN difference lying within the 1 day margin. (b) (4)

1.2 Brief Overview of Clinical Studies

Study XM02-02 is the only efficacy study submitted in this BLA in supporting the proposed indication of reduction in the duration of DSN. Study XM02-02 is a multinational, multicenter, randomized, controlled Phase-III study in patients with high-risk stage II, or with stage III or IV breast cancer needing chemotherapy. A total of 350 patients were randomized with a ratio of 2:2:1 to XM02, European-manufactured filgrastim and placebo. Patients were enrolled from Europe, South America and South Africa. Among them, 348 patients were included in the primary analysis dataset (full analysis set) by excluding two patients erroneously randomized with screening failures. The primary endpoint of Study XM02-02 is DSN defined as Grade 4 neutropenia with an absolute neutrophil count (ANC) $<0.5 \times 10^9$/L. XM02 was compared with placebo for essay sensitivity and compared with European-manufactured filgrastim (b) (4) (b) (4)

1.3 Statistical Issues and Findings

The applicant's primary analysis on DSN demonstrated that XM02 was superior to placebo in DSN with statistically significant reduction in DSN (2.7 days reduction in DSN, $p<0.0001$), and XM02 was equivalent to European filgrastim with the 95% confidence interval (-0.26, 0.33) for mean difference in DSN lying within the 1 day margin.

The statistical reviewer's concerns regarding applicant's analyses are mainly with applicant's method in data replacement and data imputation. In Applicant's primary analysis for XM02 vs. placebo, the DNS value of placebo patients who received therapeutic G-CSF treatment were replaced with the median DSN value of placebo patients who received no G-CSF treatment. This approach could underestimate the variability of DSN in placebo arm, and may exaggerate the statistical significance of the difference in DSN. Also, missing ANCs were mostly imputed by linear interpolation of the ANC values immediately before and after the missing value. The

validity of this method is questionable by assuming an ANC value to be in-between the ANC values before and after.

To address the concerns above and to evaluate the robustness of the applicant's results, following sensitivity analyses were performed:

1. DSN results were based on intent-to-treat (ITT) data without replacing DSN values for placebo patients receiving therapeutic G-CSF treatment. The missing ANCs were imputed by the method specified in Appendix A (mostly by linear interpolation).
2. DSN results were based on ITT data without replacing DSN values for placebo patients receiving therapeutic G-CSF treatment. Missing ANCs were treated as $<0.5 \times 10^9$/L (non-response).
3. DSN results were based on ITT data without replacing DSN values for placebo patients receiving therapeutic G-CSF treatment. Missing ANCs were treated as $<0.5 \times 10^9$/L in XM02 arm (response), but as $\geq 0.5 \times 10^9$/L in placebo arm (no response). This is the worst case analysis.

The results of the sensitivity analyses (see Tables 6 and 7 in Section 3.1.4) are consistent with that of the applicant's analysis. Therefore, the reviewer's analyses confirm the finding of the applicant's analysis.

(b) (4) Although the data did demonstrate that the 95% confidence interval (-0.26, 0.33) for mean difference between XM02 and European filgrastim in DSN lay within the 1 day equivalence margin, (b) (4)

2. INTRODUCTION

2.1 Overview

BLA129254/0 was submitted for the approval of XM02 with the indication of reduction in DSN (b) (4)

XM02 was developed in Europe as a similar biological product to the innovator filgrastim (Neupogen). One efficacy Study XM02-02 and two safety studies XM02-03 and XM02-04 were submitted in this BLA in supporting the proposed indication. This review will focus on the efficacy study.

XM02-02 is the only efficacy study submitted in this BLA in supporting the proposed indication of reduction in the duration of DSN. Study XM02-02 was a multinational, multicenter, randomized, controlled Phase-III study in patients with high-risk stage II, or with stage III or IV breast cancer needing chemotherapy. A total of 350 patients were randomized with a ratio of 2:2:1 to XM02, European-manufactured filgrastim and placebo. Patients were enrolled from Europe, South America and South Africa. Among them, 348 patients were included in the full analysis (FA) dataset by excluding two patients erroneously randomized with screening failures. The primary endpoint of Study XM02-02 is DSN defined as Grade 4 neutropenia with an absolute neutrophil count (ANC) $<0.5 \times 10^9$/L. XM02 was compared with placebo for essay

sensitivity and compared with European-manufactured filgrastim [redacted] (b) (4)

2.2 Data Sources

All datasets submitted for this BLA can be accessed at \\cbsap58\m\eCTD_Submissions\STN125294\0000\m5\datasets\xm02-02-int\analysis. Efficacy evaluation in this BLA was mainly based on three electronic datasets: 'arandom.xpt', a derived efficacy dataset including treatment information and randomization number; 'acycanc.xpt', a derived efficacy dataset including ANC values in each day of each treatment cycle; and 'acycdsn.xpt', a derived efficacy dataset including DSN values for each patient.

3. STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

3.1.1 Study Design and Endpoint

Study XM02-02 was a multinational, multicenter, randomized, controlled Phase-III study in patients with high-risk stage II, or with stage III or IV breast cancer needing chemotherapy. The primary objectives of Study XM02-02 were
1. demonstration of equivalence of XM02 and filgrastim in the first cycle of chemotherapy with DSN, defined as grade 4 neutropenia with an ANC<0.5 x 10^9/L; and
2. confirmation of assay sensitivity with respect to DSN by comparing XM02 versus placebo.

Study XM02-02 was conducted in 52 study centers in 10 countries (Belarus, Slovenia, South Africa, Brazil, Chile, Russia, Hungary, Lithuania, Romania, and Poland). Patients were randomized with 2:2:1 ratio to either XM02, European manufactured filgrastim or placebo with stratification factors country and type of chemotherapy (adjuvant vs. metastatic therapy). The patients underwent a maximum of 4 chemotherapy cycles (3 weeks per cycle), each cycle beginning with a day of chemotherapy with doxorubicin 60 mg/m2 and docetaxel 75 mg/m2. Patients of the placebo group switched to treatment with XM02 after completion of Cycle 1.

One day after chemotherapy, XM02 or Filgrastim (5 µg/kg/day based on actual body weight) or placebo were injected for at least 5 days and a maximum of 14 days. Study drug had to be stopped earlier when an ANC of ≥10 x 10^9/L after nadir was reached. In Cycle 1, blood samples for the determination of the ANC were taken within 24 hours before chemotherapy and then daily from Day 2 until Day 15, or longer until ANC reached ≥2.0 x 10^9/L. In Cycles 2, 3, and 4, ANC were measured within 24 hours before chemotherapy and then daily starting on Day 5 until Day 15, or longer until ANC reached ≥2.0 x 10^9/L. In every cycle, body temperature (axillary) was measured daily until Day 15, or longer until ANC reached ≥2.0 x 10^9/L.

The primary efficacy endpoint was DSN in Cycle 1, defined as the number of days with grade 4 neutropenia with an ANC <0.5 x 10^9/L. Secondary efficacy endpoints were incidence of febrile neutropenia (observed febrile neutropenia (FN) defined as body temperature of >38.5°C for more than 1 hour, measured axillary with a calibrated standard device, and ANC <0.5 x 10^9/L, both measured on the same day) and of protocol defined FN (intake of systemic antibiotics) by cycle

and across all cycles, DSN in Cycles 2 to 4, depth of ANC nadir in Cycles 1 to 4, times to ANC recovery in Cycles 1 to 4 and mortality. DSN was to be analyzed by ANCOVA including the factors "treatment", "country" and "adjuvant vs. metastatic therapy", and with the baseline ANC value as covariate. Missing ANC values were imputed mainly by linear interpolation. The detailed methods for missing value imputation are described in Appendix A. No comparative analyses for secondary endpoints were planned. All results of secondary endpoints were considered as descriptive/exploratory.

Assay sensitivity with respect to DSN in Cycle 1 was to be demonstrated by comparing XM02 versus placebo. If the difference was significant (two-sided $p \leq 0.05$ with shorter DSN for XM02), equivalence between XM02 and filgrastim was assessed. To show equivalence between XM02 and filgrastim, the two-sided 95% confidence interval (CI) for the difference in DSN in Cycle 1 had to lie entirely within the equivalence range of [-1 day, +1 day]. A difference of 1 day was considered to be the maximum clinically acceptable difference. The per protocol (PP) set was the primary analysis set for the efficacy comparison of XM02 versus filgrastim. The comparison of XM02 versus placebo was based primarily on the FA set including all patients randomized. However, for patients with placebo receiving therapeutic G-CSF treatment, the DSN values in Cycle 1 were to be replaced with the median DSN value of patients with placebo who received no G-CSF treatment.

Assuming that the expected difference in mean DSN is <0.25 days and the common standard deviation is 1.7 days, a sample size of 109 patients per active treatment group is to demonstrate the equivalence of XM02 and filgrastim (95% confidence interval of mean difference in DSN lies within a 1 day margin) with 90% power and a 2-sided Type I error rate of 0.05. Taking into account that about 20% of the patients would not be eligible for per-protocol analysis regarding the primary endpoint, 140 patients were to be randomized into each active treatment groups. Assuming a larger standard deviation of 5 days in the placebo arm and a 2 days difference in DSN, 70 patients are needed to demonstrate the superiority of XM02 to placebo with a 90% power and a 2-sided 5% Type I error rate.

An interim analysis was planned and conducted after 50% of patients had completed Cycle 1, to evaluate the assumption about the standard deviation of the primary endpoint and to make a decision about whether to increase the sample size. Since the calculated standard deviation was not larger than the assumed value of 1.7, no adaptation of the sample size was necessary. No α level was spent on this interim analysis.

3.1.2. Patient Disposition

A total of 350 patients were randomized. Among these, 348 patients were included in the full analysis set by excluding two patients erroneously randomized with screening failures. The patient disposition of the full analysis set is presented in Table 1 below. Most patients completed study protocol. The 'Withdrawn due to other reasons' category is primarily due to withdrawal of consent.

Table 1. Patient Disposition

	XM02 (N=140)		Filgrastim (N=136)		Placebo (N=72)	
Disposition	n	%	n	%	n	%
Completed protocol	135	96	130	96	68	94
Withdrawn due to AE related to study drug	0	0	0	0	1	1
Withdrawn due to AE related to chemotherapy	1	1	1	1	1	1
Death	1	1	0	0	2	3
Withdrawn due to other reasons	3	2	5	4	0	0

The amount of missing ANC values ranges from 0 to 5.5% from Day 1 to Day 15 in Cycle 1 as displayed in Table 2.

Table 2. Number and Percent of Patient with Missing ANC Value in Cycle 1

Study Day	All subjects N=348	Placebo N = 72	XM02 N = 140	Filgrastim N=136
1	0 (0.0%)	0 (0.0)	0 (0.0%)	0 (0.0%)
2	2 (0.6%)	1 (1.4)	0 (0.0%)	1 (0.7%)
3	3 (0.9%)	1 (1.4)	2 (1.4%)	0 (0.0%)
4	3 (0.9%)	1 (1.4)	1 (0.7%)	1 (0.7%)
5	2 (0.6%)	0 (0.0)	1 (0.7%)	1 (0.7%)
6	4 (1.1%)	1 (1.4)	2 (1.4%)	1 (0.7%)
7	3 (0.9%)	0 (0.0)	1 (0.7%)	2 (1.5%)
8	5 (1.4%)	1 (1.4)	2 (1.4%)	2 (1.5%)
9	6 (1.7%)	1 (1.4)	2 (1.4%)	3 (2.2%)
10	5 (1.4%)	1 (1.4)	1 (0.7%)	3 (2.2%)
11	8 (2.3%)	1 (1.4)	2 (1.4%)	5 (3.7%)
12	8 (2.3%)	1 (1.4)	3 (2.1%)	4 (2.9%)
13	9 (2.6%)	1 (1.4)	3 (2.1%)	5 (3.7%)
14	15 (4.3%)	2 (2.8)	7 (5.0%)	6 (4.4%)
15	19 (5.5%)	3 (4.2)	11 (7.9%)	5 (3.7%)

3.1.3 Patient Demographics

Patient demographics are generally balanced between the three treatment arms. The patient population is mostly female. The information for gender, age, race, cancer stage and type of chemotherapy among the treatment arms are summarized in Table 3 below.

Table 3. Patients Demographics

	XM02 (N=140)	Filgrastim (N=136)	Placebo (N=72)
Age mean (min;max)	51 (25;75)	51 (28;74)	50 (28;74)
Gender (n, %)			
Female	139 (99%)	135 (99%)	72 (100%)
Male	1 (1%)	1 (1%)	0
Race (n, %)			
Black	1 (1%)	5 (4%)	2 (3%)
Hispanic	10 (7%)	10 (7%)	6 (8%)
White	120 (86%)	118 (87%)	62 (86%)
Other	9 (6%)	3 (2%)	2 (3%)
Cancer Stage (n, %)			
Stage II	23 (16%)	36 (26%)	15 (21%)
Stage III	79 (56%)	69 (51%)	38 (53%)
Stage IV	38 (27%)	31 (23%)	19 (26%)
Therapy (n, %)			
Adjuvant	96 (69%)	96 (71%)	47 (65%)
Metastatic	44 (31%)	40 (29%)	25 (34%)

3.1.4. Efficacy Results

Primary endpoint: DSN

The results for DSN in FA population are presented in Table 4. After adjusted by "treatment", "country" and "adjuvant vs. metastatic therapy", and baseline ANC value, the mean difference (LSMEAN difference) between XM02 and placebo is -2.7 days with $p < 0.0001$. The mean difference between XM02 and filgrastim is -0.03 day with a 95% confidence interval (-0.32, 0.26) and $p < 0.0001$. As presented in Table 5, the results in PP population are consistent to that in the FA population.

Table 4. DSN Results in FA population

	PL	XM02	filgrastim
N	72	140	136
Mean (day)	3.8	1.1	1.1
Difference from XM02 in LSMEAN (95% CI)	2.7 (2.2, 3.2)		-0.03 (-0.32, 0.26)
P-value (χ^2)	<0.0001		0.85

Table 5. DSN Results in PP population

	PL	XM02	filgrastim
N	58	133	129
Mean (day)	3.9	1.1	1.1
Difference from XM02 in LSMEAN (95% CI)	2.7 (2.1, 3.4)		-0.03 (-0.33, 0.26)
P-value (χ^2)	<0.0001		0.83

Reviewer's comments regarding results in DSN:

1. Comments regarding data replacement and data imputation

In Applicant's primary analysis for XM02 vs. placebo, the DNS value of placebo patients who received therapeutic G-CSF treatment were replaced with the median DSN value of placebo patients who received no G-CSF treatment. This approach could underestimate the variability of DSN in placebo arm, and may exaggerate the statistical significance of the difference in DSN. Also, missing ANCs were mostly imputed by linear interpolation of the ANC values immediately before and after the missing value. The validity of this method is questionable by assuming an ANC value to be in-between the ANC values before and after.

To address the concerns above and to evaluate the robustness of the applicant's results, following sensitivity analyses were performed:

1). DSN results were based on ITT data without replacing DSN values for placebo patients receiving therapeutic G-CSF treatment. The missing ANCs were imputed by the method specified in Appendix A (mostly by linear interpolation).

2). DSN results were based on ITT data without replacing DSN values for placebo patients receiving therapeutic G-CSF treatment. Missing ANCs were treated as $<0.5 \times 10^9$ /L (non-response).

3). DSN results were based on ITT data without replacing DSN values for placebo patients receiving therapeutic G-CSF treatment. Missing ANCs were treated as $<0.5 \times 10^9$ /L in XM02 arm (response), but as $>=0.5 \times 10^9$ /L in placebo arm (no response). This is the worst case analysis.

Results of the three sensitivity analyses were compared with the applicant's results in Tables 6 and 7 below.

Table 6. Results of Sensitivity Analyses for XM02 vs. Placebo

	Difference in LSMEAN	95% CI	P-value
Applicant's analysis	-2.7	(-3.2, -2.2)	<0.0001
Sensitivity analysis 1	-2.5	(-3.0, -2.0)	<0.0001
Sensitivity analysis 2	-2.4	(-2.9, -1.9)	<0.0001
Worst-case analysis	-2.2	(-2.7, -1.6)	<0.0001

Table 7. Results of Sensitivity Analyses for XM02 vs. Filgrastim

	Difference in LSMEAN	95% CI
Applicant's analysis	0.03	(-0.26, 0.33)
Sensitivity analysis 1	0.03	(-0.26, 0.32)
Sensitivity analysis 2	0.08	(-0.33, 0.49)
Worst-case analysis	0.32	(-0.03, 0.67)

Results in Tables 6 and 7 conformed that of the applicant's analysis.

2. Comments regarding equivalence between XM02 and Neupogen

Based on data from a phase 3 trial of Neupogen versus placebo in subjects undergoing chemotherapy for small-cell lung cancer (Blackwell and Crawford, 1994), logistic regression analysis applied to both treatment groups showed that each day of grade 4 neutropenia during Cycle 1 was associated with a 10% increase in the rate of FN. Based this relationship, a 1 day difference in DSN would be anticipated to result in approximately a 10% difference in FN. This was selected as a meaningful and practical difference in treatment outcome on which to be based for the equivalence margin.

Based on the 1 day margin in mean difference of DSN, results in Table 7 demonstrated that XM02 is equivalent to European filgrastim with the 95% confidence interval of (-0.26, 0.33) in mean difference in DSN. (b) (4) [redacted].

Secondary Endpoints

Analyses for secondary endpoints are exploratory. Due to the clinical meaningfulness, results for febrile neutropenia (FN) in Cycle 1 are presented in Table 8 below.

Table 8. Results for Febrile Neutropenia in Cycle 1.

Type of FN	XM02 N = 140		Filgrastim N = 136		Placebo/XM02 N = 72	
	n*	(%), [95% CI]	n	(%), [95% CI]	n	(%), [95% CI]
Observed FN**	1	(0.7%) [0.1%,3.9%]	0	(0.0%) [0.0%,2.7%]	4	(5.6%) [2.2%,13.4%]
Systemic antibiotics without observed FN	16	(11.4%) [7.2%,17.8%]	17	(12.5%) [8.0%,19.1%]	22	(30.6%) [21.1%,42.0%]
Observed or protocol defined FN	17	(12.1%) [7.7%,18.6%]	17	(12.5%) [8.0%,19.1%]	26	(36.1%) [26.0%,47.6%]

There were 3 deaths during the treatment period (1 in XM02 arm and 2 in placebo/XM02 arm) and 1 after treatment period in XM02 arm. Descriptive results for depth of ANC nadir and times to ANC recovery in Cycle 1 are presented in Tables b.1 and b.2 of Appendix B.

3.2 Evaluation of Safety

Please see the medical officer Dr. Tom Herndon's review in regards of safety evaluation.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race and Age

Subgroup results on DSN were analyzed by age and race. Subgroup analysis by gender was not conducted since the population was almost entirely women (99.4%). The subgroup results are generally consistent with that of the primary analyses, except that XM02 appears to have a longer DSN than filgrastim in the Hispanic group. Detailed results are presented in Figures 1 and 2 below.

Figure 1. Subgroup Analyses for XM02 vs. Placebo

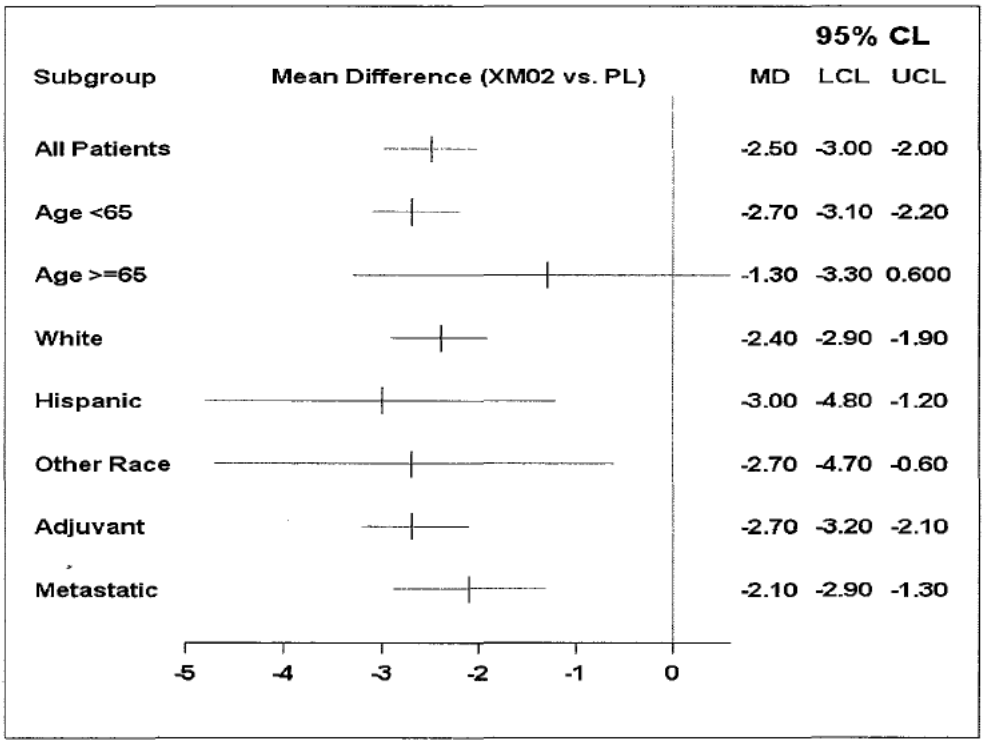
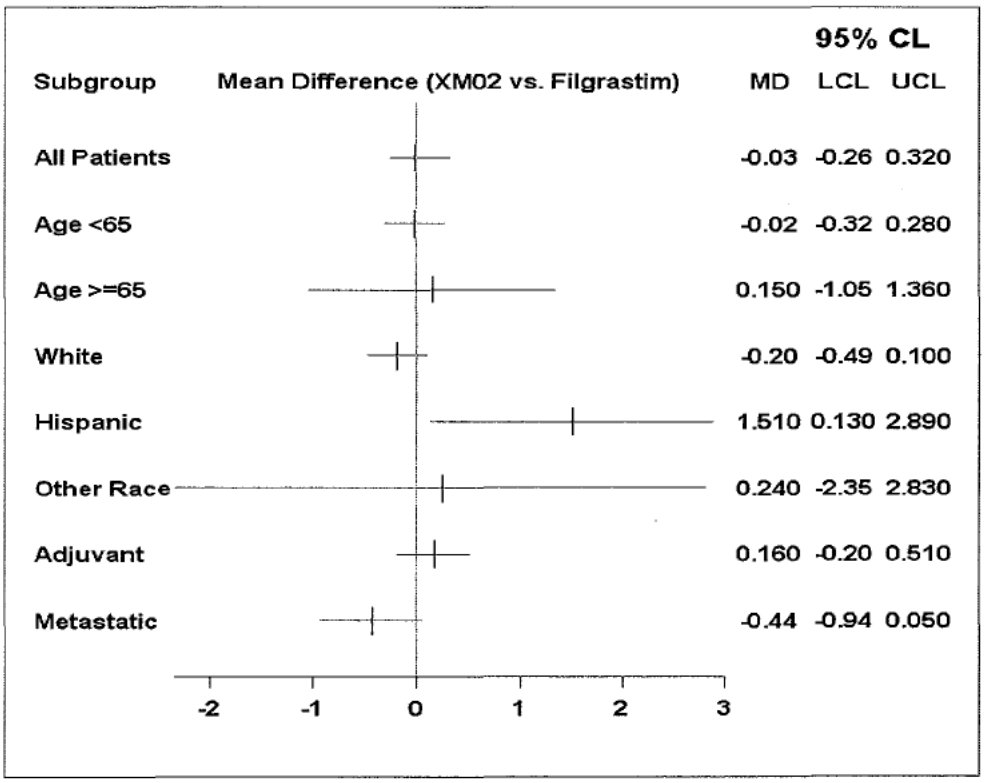


Figure 2. Subgroup Analyses for XM02 vs. Filgrastim



4.2 Other Special/Subgroup Populations

Results of subgroup analyses on DSN by type of chemotherapy (adjuvant vs. metastatic) were also performed. The results are consistent with that of the primary analyses and are presented in Figures 1 and 2 above.

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

Study XM02-02 is the only Phase-III efficacy trial submitted by the Applicant in supporting the indication of reduction in the duration of severe neutropenia when treated by with XM02 (b) (4) . In this study, the applicant's primary analysis on DSN demonstrated that XM02 was superior to placebo in DSN with statistically significant reduction in DSN (2.7 days reduction in DSN, $p<0.0001$), and XM02 was equivalent to European filgrastim with the 95% confidence interval (-0.26, 0.33) for mean difference in DSN lying within the 1 day margin.

The statistical reviewer's concerns regarding applicant's analyses are mainly with applicant's method in data replacement and data imputation. In Applicant's primary analysis for XM02 vs. placebo, the DNS value of placebo patients who received therapeutic G-CSF treatment were replaced with the median DSN value of placebo patients who received no G-CSF treatment. This approach could underestimate the variability of DSN in placebo arm, and may exaggerate the statistical significance of the difference in DSN. Also, missing ANCs were mostly imputed by linear interpolation of the ANC values immediately before and after the missing value. The validity of this method is questionable by assuming an ANC value to be in-between the ANC values before and after.

To address the concerns above and to evaluate the robustness of the applicant's results, following sensitivity analyses were performed:

1. DSN results were based on intent-to-treat (ITT) data without replacing DSN values for placebo patients receiving therapeutic G-CSF treatment. The missing ANCs were imputed by the method specified in Appendix A (mostly by linear interpolation).
2. DSN results were based on ITT data without replacing DSN values for placebo patients receiving therapeutic G-CSF treatment. Missing ANCs were treated as $<0.5 \times 10^9$ /L (non-response).
3. DSN results were based on ITT data without replacing DSN values for placebo patients receiving therapeutic G-CSF treatment. Missing ANCs were treated as $<0.5 \times 10^9$ /L in XM02 arm (response), but as $\geq 0.5 \times 10^9$ /L in placebo arm (no response). This is the worst case analysis.

The results of the sensitivity analyses (see Tables 6 and 7 in Section 3.1.4) are consistent with that of the applicant's analysis. Therefore, the reviewer's analyses confirm the finding of the applicant's analysis.

(b) (4). Although the data did demonstrate that the 95% confidence interval (-0.26, 0.33) for mean difference between XM02 and European filgrastim in DSN lay within the 1 day equivalence margin, (b) (4)

5.2 Conclusions and Recommendations

Study XM02-02 demonstrated that XM02 was superior to placebo in DSN with statistically significant reduction in DSN (2.7 days reduction in DSN, $p<0.0001$), and XM02 was equivalent to European filgrastim with the 95% confidence interval (-0.26, 0.33) in DSN difference lying within the 1 day margin. (b) (4)

SIGNATURES/DISTRIBUTION LIST

Primary Statistical Reviewer: Dr. Laura Lu
Date: 7/29/2010

Concurring Reviewers:

Statistical Team Leader: Dr. Kun He 7/29/2010

Acting Biometrics Division Director: Dr. Rajeshwari Sridhara 7/29/2010

cc:
HFD-107/Mr. Chaudhry, Dr. Herndon, Dr. Demko, Dr. Summer, Dr. Keegan
HFD-711/Dr. Lu, Dr. He, Dr. Sridhara, Ms. Patrician
HFD-711/Chron

Appendix A. Methods for Missing Value Imputation

Imputation of missing ANC values at Day 1 of Cycles 1 to 4 and at End of Study:

For all patients of the FA set, missing ANC values at Day 1 of Cycle 1 will be imputed with the screening ANC, and missing ANC values at Day 1 of Cycle 2 to 4 will be replaced with the (possibly imputed) ANC value at Day 1 of the previous cycle. Missing ANC values at End of Study will be replaced with the (possibly imputed) ANC value at Day 1 of Cycle 4. These imputations will also be done for drop-outs, e.g. if a patient terminated the study after Cycle 1, the ANC values at Day 1 of Cycles 2 to 4 and at End of Study should still be imputed.

Imputation of missing ANC values at Days 2 to 21 of Cycles 1 to 4:

If at least one ANC value after Day 6 is available in the given cycle, then missing ANC values of this cycle will be replaced with linear interpolation between the following two values:
(i) last available ANC value before the missing value, using also the (possibly imputed) ANC value at Day 1 of the given cycle, if necessary, but using no values of previous cycles,
(ii) first available ANC value after the missing value, using also the (possibly imputed) ANC value of Day 1 of the next cycle, if necessary, but using no later ANC values; if missing values occur at the end of cycle 4, then the (possibly imputed) ANC value at End of Study will be used.

If no ANC value after Day 6 is available in the given cycle, then the above interpolation will not be done for this cycle, and the missing ANC values of this cycle will not be replaced.

Appendix B. Results of Secondary Endpoints

Table b1. ANC Nadir in Cycle 1

	XM02	Filgrastim	Placebo
N	140	136	72
MEAN	0.655	0.651	0.163
SD	0.813	0.778	0.222
MIN	0.00	0.00	0.00
25th Percentile	0.100	0.100	0.000
MEDIAN	0.300	0.300	0.100
75th Percentile	1.000	0.900	0.300
MAX	4.50	3.60	1.10

Table b2. Times to ANC recovery in Cycle 1

	XM02	Filgrastim	Placebo
N	140	136	72
MEAN	8.0	7.8	14.0
SD	2.6	2.8	3.8
MIN	0	0	3
25th Percentile	8.0	8.0	13.0
MEDIAN	8.0	8.0	15.0
75th Percentile	9.0	9.0	16.0
MAX	20	17	20

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

NDA Number: 125085 (b) (4) **Applicant: Amgen** **Stamp Date: 11/17/09**

Drug Name: Avastin **NDA/BLA Type: sBLA**

On **initial** overview of the NDA/BLA application for RTF:

	Content Parameter	Yes	No	NA	Comments
1	Index is sufficient to locate necessary reports, tables, data, etc.	x			
2	ISS, ISE, and complete study reports are available (including original protocols, subsequent amendments, etc.)	x			
3	Safety and efficacy were investigated for gender, racial, and geriatric subgroups investigated (if applicable).	x			
4	Data sets in EDR are accessible and do they conform to applicable guidances (e.g., existence of define.pdf file for data sets).	x			

IS THE STATISTICAL SECTION OF THE APPLICATION FILEABLE? _Yes_____

Comments and requests:

For Study XM02, subgroup analyses should be conducted for Age (>65 and <=65) and Race (Caucasian, Black, Hispanic and other). Analysis results should include mean in each treatment group, mean differences (tevagrastim vs. placebo, tevagrastim vs. filgrastim, filgrastim vs. placebo), and standard errors for the mean differences. FDA acknowledges that subgroup analyses may not be powered to demonstrated efficacy, but are necessary for assessing consistency among different patient populations.

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Content Parameter (possible review concerns for 74-day letter)	**Yes**	**No**	**NA**	**Comment**
Designs utilized are appropriate for the indications requested.	x			
Endpoints and methods of analysis are specified in the protocols/statistical analysis plans.	x			
Interim analyses (if present) were pre-specified in the protocol and appropriate adjustments in significance level made. DSMB meeting minutes and data are available.			x	
Appropriate references for novel statistical methodology (if present) are included.			x	
Safety data organized to permit analyses across clinical trials in the NDA/BLA.				To be checked
Investigation of effect of dropouts on statistical analyses as described by applicant appears adequate.				To be checked

Reviewing Statistician — Date 1/26/10

Supervisor/Team Leader — Date 1/26/10

File name: 5_Statistics Filing Checklist for a New NDA_BLA110207