

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

125294Orig1s000

MEDICAL REVIEW(S)



MEMORANDUM

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

FROM: Thomas M. Herndon, Medical Officer, DHP
THROUGH: Albert Deisseroth, Team Leader, DHP
TO: File
SUBJECT: Addendum to Clinical Review of Response to CR
Submission BLA125294
SUBMIT DATE: February 29, 2012
PRODUCT: tbo-filgrastim (Neutroval, XM-02, (b) (4))
SPONSOR: Teva Pharmaceuticals
DATE: August 10, 2012

On November 30, 2009, TEVA Pharmaceuticals submitted BLA 125294 for tbo-filgrastim, a follow-on filgrastim which is a recombinant human N-methionyl granulocyte colony stimulating factor (C-CSF) to be reviewed through Section 351(a) of the PHS Act for the indication *reduction of the duration of severe neutropenia in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a clinically significant incidence of febrile neutropenia*. A Complete Response (CR) letter was issued on September 29, 2010. Teva submitted a Response to CR on February 29, 2012.

(b) (4)

(b) (4)

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Clinical Reviewer Recommendation

The clinical reviewer agrees with the CDRH Combination Products Human Factors Specialist and a human factors study is not required at this time.

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/s/

THOMAS M HERNDON
08/13/2012

ALBERT B DEISSEROTH
08/13/2012



MEMORANDUM

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

FROM: Thomas M. Herndon, Medical Officer, DHP
THROUGH: Albert Deisseroth, Team Leader, DHP
TO: File
SUBJECT: Clinical Review of Response to CR Submission
BLA125294
SUBMIT DATE: February 29, 2012
PRODUCT: Neutroval (XM-02, (b) (4))
SPONSOR: Teva Pharmaceuticals
DATE: July 23, 2012

On November 30, 2009, TEVA Pharmaceuticals submitted BLA 125294 for Neutroval (XM02), a follow-on filgrastim which is a recombinant human N-methionyl granulocyte colony stimulating factor (C-CSF) to be reviewed through Section 351(a) of the PHS Act for the indication *reduction of the duration of severe neutropenia in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a clinically significant incidence of febrile neutropenia*. A Complete Response (CR) letter was issued on September 29, 2010. Teva submitted a Response to CR on February 29, 2012.

As there were no issues with the clinical portion of the original BLA submission of November 30, 2009, the Response to CR contains no new clinical data. The Clinical Review for the original BLA remains the Clinical Review for the Response to CR.

At the present time, all issues raised in the response to CR have been adequately addressed by the Applicant. Of note, one of the deficiencies (Deficiency 1) in the Response to CR letter concerned the integrity of the clinical data. Based on the FDA inspection of the BioGeneriX AG facility (b) (4), there was a concern that the integrity of the database for Study XM02-2-INT, the pivotal trial submitted to support the efficacy of the product may have been compromised. After the initial database lock on January 2, 2006, and subsequent data unblinding, the data base was unlocked and the data were altered on at least two separate dates (January 17, 2006 and January 23, 2006). The FDA requested information about the quality control and/or quality assurance activities at each stage of data handling, from initial data entry into the data base through the final database lock that were undertaken to ensure the integrity of safety and efficacy data. In addition, the FDA asked TEVA to provide documentation, including justification and the audit trail for all changes made to the database after unblinding and a detailed analysis of the impact of all changes made to the data base after initial data lock and unblinding on the safety and efficacy data.

In the Applicant's response to this deficiency, TEVA states that two FDA investigators, Mr. James Kewley, and Mr. Jonathan Helfgott, re-inspected the Biogenex site (b) (4). In the December 16, 2011 report of that inspection, there were no concerns identified relating to the integrity of the data base used for Study XM02-02-INT. During this inspection, the quality control and quality assurance safeguards were physically demonstrated to the FDA inspectors and found to be satisfactory. Inspection of the audit trail at that visit also confirmed that no inappropriate changes were made to the data base. Following review of the data and reports from OSI and discussion with the OSI reviewer and the CDTL, this reviewer concludes that it is unlikely that the violations noted during the initial inspection impact the results of the data submitted as part of the BLA.

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signature.**

/s/

THOMAS M HERNDON
07/24/2012

ALBERT B DEISSEROTH
07/24/2012

Office Director Summary Review for Regulatory Action

Date	September 29, 2010
From	Richard Pazdur, MD <i>R Pazdur MD</i>
Subject	Office Director Summary Review
BLA #	STN BL 125294/0
Applicant Name	Teva Pharmaceuticals USA
Date of Submission	November 30, 2009
PDUFA Goal Date	September 30, 2010
Proprietary Name / Established (USAN) Name	Neutroval/Established name to be determined
Dosage Forms / Strength	Solution for subcutaneous injection in prefilled syringes with and without UltraSafe Passive® Needle Guard 300 mcg/0.5mL and 480 mcg/0.8 mL
Proposed Indication	"Neutroval® (b) (4) is indicated for the reduction in the duration of severe neutropenia and the incidence of febrile neutropenia in patients treated with established myelosuppressive chemotherapy."
Recommended Action for NME:	Complete Response

Material Reviewed/Consulted	Names of discipline reviewers
OND Action Package, including:	
Regulatory Project Manager Review	Danyal Chaudhry
Medical Officer Review	Thomas Herndon
Statistical Review	Hong (Laura) Lu
Statistical Team Leader Review	Kun He
NonClinical Pharmacology/Toxicology Review	Mary Jane Masson-Hinrichs
NonClinical Supervisory Pharm/Tox Review	Anne Pilaro
QT-IRT Consult	Suchitra Balakrishnan & Hao Zhu
CMC Review	Dov Pluznik and Jee Chung
Immunogenicity Review	Laura Salazar-Fontana
Clinical Pharmacology Review	Sarah Schreiber
Facilities Review (Drug Substance)	Anastasia Lolas
Facilities Review (Drug Product)	Kalavati Suvama
CDRH/DAGID/Hospital Devices Branch	William Burdick
DDMAC PI & Patient Labeling Reviews	Nisha Patel, Sheila Ryan, & Cynthia Collins
DSI Review	Lauren Iacono-Connors
CDTL Review	Suzanne Demko
OBP Carton/Container Review	Kimberly Rains
OSE/DMEPA Consult Review	Loretta Holmes
OSE/DRISK Patient Labeling Review	Steve L. Morin
SEALD Labeling Review	Elisabeth Piault-Louis

OND=Office of New Drugs
DDMAC=Division of Drug Marketing, Advertising and Communication
OSE= Office of Surveillance and Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DSI=Division of Scientific Investigations
DDRE= Division of Drug Risk Evaluation
DRISK=Division of Risk Management
CDTL=Cross-Discipline Team Leader

1. Introduction/Background

Neutroval®, a granulocyte colony stimulating factor (G-CSF) secreted by genetically-engineered bacteria containing the gene for human G-CSF, is seeking U.S. marketing approval under 351(a) of the Public Health Service (PHS) Act. The proposed indication is for the “reduction in the duration of severe neutropenia and the incidence of febrile neutropenia in patients treated with established myelosuppressive chemotherapy”. Neupogen® (filgrastim), currently marketed in the U.S., is also a human G-CSF product. Other related products marketed in the U.S., which work through the same or similar receptors on granulocytes for the proposed indication for Neutroval, are Neulasta® (pegfilgrastim) and Leukine® (sargramostim). Neutroval was approved in the EU under an abbreviated pathway for biosimilar products; however, at the time of BLA submission (November 30, 2009), there was no mechanism for abbreviated approval in the U.S. Subsequent to the BLA submission, the Patient Protection and Affordable Care Act (PPAC Act) was signed into law (March 23, 2010), which amended the PHS Act to create an abbreviated approval pathway for biological products.

2. Single Trial to Support Efficacy and Other Clinical Trials

Five trials were submitted in support of this BLA, which included two Phase 1 studies (XM02-01 and XM02-05) conducted in a total of 200 healthy volunteers, one study (XM02-02) designed to investigate efficacy and safety in 348 patients, and two additional safety studies (XM02-03, XM02-04) in 329 patients randomized 2:1 to XM02 versus Neupogen. A brief description of these studies are listed below.

1. **XM02-01-LT**, Comparative study of pharmacodynamic and pharmacokinetic parameters of XM02 and Neupogen when formulations are given to healthy volunteers
2. **XM02-05-DE**, Study on the bioequivalence of 5 µg/kg or 10 µg/kg of XM02 and Neupogen, each after intravenous or subcutaneous administration, in healthy female and male subjects. A multi-center, randomized, single dose, single blind, two-way crossover design
3. **XM02-02-INT, Efficacy and safety of XM02 compared to Neupogen in patients with breast cancer receiving chemotherapy, a multinational, multi-center, randomized, controlled study. The single trial conducted to establish the efficacy of XM02.**
4. **XM02-03-INT**, Safety and efficacy of XM02 in patients with small cell or non-small-cell lung cancer receiving platinum-based chemotherapy, a multi-national multi-center, randomized, controlled study
5. **XM02-04-INT**, Safety and efficacy of XM02 in patients with Non-Hodgkin's-Lymphoma receiving chemotherapy, a multi-national, multicenter, randomized, controlled study

Studies XM02-02, XM02-03, XM02-04 were conducted in patients with cancers who were scheduled to receive myelosuppressive chemotherapy. Studies XM02-03 and XM02-04 were randomized (1:1), double blind, active-controlled trials that enrolled 240 patients with lung cancer and 92 patients with NHL. These studies were designed to provide an assessment of comparative safety and activity of XM02 to an active control (EU-marketed Neupogen) to aid in the design of a definitive efficacy trial (XM02-02 INT).

A single trial, XM02-02, was conducted to establish the efficacy of XM02 for the proposed indication of reduction in the duration of severe neutropenia (DSN). Study XM02-02 is a multinational, multicenter, randomized (2:2:1), active- and placebo-controlled trial conducted in women with high-risk stage II, or with stage III or IV breast cancer receiving initial chemotherapy as adjuvant treatment or as treatment of metastatic disease. The trial included two planned comparisons of the effect on the duration of severe neutropenia following myelosuppressive therapy; these were reduction in the duration of severe neutropenia (DSN) in the Neutroval arm as compared to placebo arm and non-inferiority of the mean DSN in the Neutroval arm as compared to EU-marketed Neupogen.

A reduction in mean DSN has been accepted by FDA as a valid surrogate for reduction in the incidence of infection and febrile neutropenia when the duration of severe neutropenia in the absence of growth factors is approximately 4-5 days. The major efficacy trial reportedly shows both a significant reduction in the mean DSN and fell within pre-specified bounds set out in the protocol for determination of non-inferiority against an active comparator. FDA did not agree with the non-inferiority margin specified in the clinical protocol.

Treatment Plan

Study drug treatment with XM02/EU-Neupogen/Placebo was administered at a dose of 5 mcg/kg subcutaneously, daily for 5-14 days, beginning on study day 2. Treatment was to be continued until study day 15 or a post-nadir ANC of $\geq 2.0 \times 10^9/L$. Patients in the placebo arm were switched to XM02 during chemotherapy cycles 2-4. Concomitant chemotherapy consisted of doxorubicin 60 mg/m² and docetaxel 75 mg/m² on day 1 of a 21-day cycle for up to 4 cycles.

Analysis Plan

The primary efficacy endpoint was the duration of severe neutropenia (DSN) in cycle 1. There was no plan specified for testing of secondary endpoints in the protocol which adjusted for alpha spending. Based on this lack of a pre-specified plan for preservation of alpha, the FDA statistical reviewers identified all secondary endpoints as "exploratory".

A single planned interim analysis was planned after 50% of the patients had completed cycle 1 to assess the validity of the assumptions regarding variability, with a proposal for sample size re-estimation in the event that the variability in the DSN was underestimated. The proposal for the interim analysis was revised in protocol amendment 3 to limit the analyses to data from the two active treatment arms.

Results - Efficacy Analyses

Study XM02-02 registered and randomized 350 subjects at 52 centers in 10 countries. Results demonstrated that the mean duration of severe neutropenia was significantly shorter in XM02-treated patients compared to placebo-treated patients following docetaxel/doxorubicin chemotherapy in women receiving initial chemotherapy treatment for metastatic or high-risk localized breast cancer. After adjustments for "treatment", "country" and "adjuvant vs. metastatic therapy", and baseline ANC value, the mean duration of severe neutropenia in cycle 1 was 1.1 and 3.8 days ($p < 0.0001$, χ^2 test) in the XM02 and placebo arms, respectively, with a difference of -2.7 days (95% CI -3.2 days, -2.2 days).

Concerns regarding Teva's methods for imputation of missing data or "replacement" were noted in Dr. Lu's review where she conducted a series of sensitivity analyses to examine the robustness of the treatment effects of XM02 on the duration of severe neutropenia. Dr. Lu determined that the primary analysis conducted by Teva is robust and consistent with the results of the sensitivity analyses.

As noted in Section 2 of Dr. Keegan's summary review, Teva did not provide adequate justification for the non-inferiority margin of a 1-day difference in mean DSN between the XM02 and the active control arm. In addition, Teva did not provide adequate justification that a margin based on treatment effects with US-marketed Neupogen could be extrapolated to treatment effects with the EU-marketed product. Therefore, claims of non-inferiority to Neupogen will not be permitted, however the active-controlled data does provide supportive data for XM02.

Based on the results obtained in the full analysis set, the mean DSN for both XM02 and for EU-marketed Neupogen was 1.1 days. The difference in the mean DSN was 0.03 days and the 95% confidence intervals around this observed difference were -0.26 days and + 0.33 days.

3. Safety

The application contained safety data from five clinical trials; however, data from two pharmacokinetic/pharmacodynamic studies in which healthy volunteers received a single dose of XM02 are not included below in analyses of safety due to the limited exposure. Safety data are presented in this summary that includes 543 XM02-treated patients enrolled in three studies (XM02-03 (SCLC or NSCLC population), XM02-04 (NHL population) and XM02-02 (metastatic breast cancer population)). Of these 534 patients, 356 patients received only XM02 in combination with 4-6 cycles of chemotherapy. Protocols XM02-03 and XM02-04 had an active control for the first cycle only (n=115) and Protocol XM02-02 INT had a placebo-control for the first cycle only (72 patients) and an active control (134 patients) for the treatment cycles 1-4. Brief synopses of each of these three studies are provided below:

Across the 677 patients enrolled in these three studies, the median age of the safety population was 56 years (range: 20 years to 80 years) and 65% were female. Based on the known toxicity profile of other G-CSF products, Teva anticipated that bone pain would be the most common adverse reaction, and Teva developed a standardized medical query (SMQ) for bone pain. Across all three studies conducted in patients with cancer, the incidence of bone pain was 23.5% in the 534 XM02-treated patients. No patients discontinued the study drug due to bone pain. The safety database was also assessed for reports of adverse reactions identified with other G-CSF products. There were no cases of acute respiratory distress syndrome, sickle cell crisis, or splenic rupture in the XM02 integrated safety database.

The clinical program for XM02 was not adequate in design (placebo-controlled for only one cycle in one study) or size to rule out the possibility of the stimulation or promotion of malignancies involving the myeloid lineage. There were no reported cases of secondary myeloid cancers in the integrated safety database.

Immunogenicity

The results submitted and performed with the unvalidated assays showed that no patients had binding antibodies or neutralizing antibodies during the study treatment with XM02 during Study XM02-02 (N = 195). Please see Dr. Keegan's summary review for Immunogenicity results for Studies XM02-03 and XM02-04.

The incidence of anti-XM02 antibody formation obtained in clinical studies is not considered reliable since it was not assessed using validated assay methods. The unvalidated immunogenicity assays yielded the following results: five of the 534 patients exposed to XM02 tested positive for binding antibodies during study treatment; 4 of these 5 patients also tested positive for neutralizing antibodies. No evidence of toxicity profile or clinical response was associated with binding antibody or neutralizing antibody development. The impact of immunogenicity on XM02 PK could not be assessed since XM02 PK data were not collected in patients who tested positive for binding or neutralizing antibodies. In order to characterize pharmacologic aspects of the product now and for assessment of planned or inadvertent changes to manufacturing that impact quality, development and characterization of the immunogenic properties with validated assays will be required as post-marketing required studies, if this product is approved in the future.

4. CMC/Device

The OBP reviewer and team leaders and the facilities reviewers for drug product and drug substance conclude that there are no outstanding CMC issues for Neutroval that would preclude approval.

OBP's recommendations on CMC characterization are based on their determination that the manufacturing process is well controlled and consistently produces pure and potent product and that the characterization of the

drug product and drug substance under stressed and non-stressed conditions. Inspections at DS manufacturing site (Vilnius, Lithuania) occurred May 31, 2010. The DP manufacturing facility inspection was waived. The manufacturing inspection was acceptable, with an exception noted by the CMC microbiology reviewer. However these issues do not preclude a finding that the product is safe, pure, and potent, therefore these issues will be addressed through agreed-upon post-marketing commitments.

I also concur with the conclusions reached by the OBP reviewer regarding the limitations of the current assay methods for assessment of immunogenicity. However, since the primary manifestation of clinically relevant anti-product antibody responses manifests as prolonged neutropenia, the clinical safety data obtained in the pivotal study and supportive safety studies were adequate to rule out that an immune response neutralizes the drug product based on the lack of unexpected or unusually prolonged neutropenia observed in clinical studies.

(b) (4)

I concur with Dr. Keegan, OBP and CDRH's conclusions.

5. Nonclinical Pharmacology/Toxicology

There is an outstanding pharm/tox issue that precludes approval. The application lacks a nonclinical assessment of developmental and reproductive toxicity of XM02 in DART studies conducted in at least one relevant animal species. Teva has not provided adequate scientific justification of why such studies would not be informative or infeasible. Teva has provided information from the published literature; however, since Teva is seeking approval for their product under 351(a) of the PHS Act, the application may not rely on data from other products to establish safety and effectiveness. The published data from other products in this class report abortifacient properties. Characterization of the extent and severity of these properties should be performed prior to approval and included in product labeling.

There were no genotoxicity or carcinogenicity studies performed with XM02 and none were required to support the BLS. The genotoxicity of large molecular weight proteins cannot be assessed using current assay methods and carcinogenicity assessments are not required given the proposed indication and intended patient population.

6. Clinical Pharmacology/Biopharmaceutics

There are no outstanding clinical pharmacology issues that preclude approval. The clinical pharmacology reviewer staff had determined that Teva must conduct an assessment of the impact of Neutroval on QT prolongation. This is based on the assessment of the submitted EKG data and is consistent with advice conveyed to Teva during the pre-IND/pre-BLA meeting.

Minimal dose-exploration was conducted with this product and there was no attempt to explore the dose-response or dose-toxicity relationships or to identify a maximum tolerated dose. The selection of the dose and dose regimen for the efficacy and safety trials were supported by pharmacokinetic and bioavailability studies (bulleted below) conducted in healthy volunteers at two doses and by two routes of administration along with an active comparator (n=176 subjects) and based on the evidence of similar pharmacokinetics and

pharmacodynamic activity to the doses of EU-marketed Neupogen (which are also the same as the recommended doses of the FDA-approved Neupogen®).

- XM02-01 LT was a randomized, dose-comparison, active-controlled, two-arm, two-period, cross-over study comparing the PK and pharmacodynamics (PD) of XM02 and EU-marketed Neupogen in healthy male volunteers.
- XM02-05 DE was a randomized, four-arm, dose- and schedule-comparison of the PK and PD parameters of XM02 and EU-marketed Neulasta. The study was intended to establish bioequivalence between XM02 and EU-marketed Neupogen and also characterized the bioavailability of subcutaneously administered XM02.

The pharmacokinetic profile of XM02 was also assessed in a subgroup of patients with cancer (XM02-02, XM02-03, XM02-04) in two active-controlled trials and in the three-arm, active- and placebo-controlled efficacy trial.

The median T_{max} was 6 hours and the median half-life ($t_{1/2}$) was 8.9 hours for the 5 mcg/kg dose in healthy volunteers. Increasing the dose of XM02 from 5 to 10 mcg/kg resulted in an approximately 3-fold increase in both C_{max} and AUC 0-48h. In patients with cancer receiving chemotherapy, the median T_{max} of XM02 ranged from 4 to 6 hours and the median $t_{1/2}$ ranged from 3.2 to 3.8 hours. Accumulation after repeated daily dosing was not observed. Based on this cross-study comparison, the pharmacology reviewer concluded that there were no interactions regarding dose adjustment based on the underlying cancer or chemotherapy regimen, across the limited numbers of cancer and chemotherapy regimens included in these studies.

No gender-related differences were observed in the pharmacokinetics of XM02 administered by the subcutaneous route of administration. No dose adjustment is recommended for mild renal impairment. The pharmacokinetic profile in patients with moderate and severe renal impairment has not been assessed. However, based on the safety margin of XM02 and the lack of relationship between the incidence of the major adverse event (bone pain) and degree of renal impairment, an XM02 dosage adjustment would not be clinically warranted. The pharmacokinetic profile in patients with hepatic impairment has not been studied.

7. Clinical Microbiology

The findings of the microbiology reviewer regarding sterility of drug substance and drug product are briefly discussed under the CMC section (section 4) above.

No clinical microbiology data were obtained in clinical trials submitted to this application.

8. Advisory Committee Meeting

This is the fourth product indicated for the prevention of severe neutropenia and febrile neutropenia in patients with cancer receiving myelosuppressive therapy and the third product which acts specifically on the G-CSF receptor. There were no unexpected clinical safety or efficacy issues requiring the advice of the Oncologic Drugs Advisory Committee.

9. Pediatrics

This BLA contained a request for deferral of pediatric studies and proposed to conduct a trial in pediatric patients as a required post-marketing commitment. The PeRC agreed with the Division to grant a partial waiver and the deferral for this product.

10. Other Relevant Regulatory Issues

DSI's audit of the Contract Research Organization responsible for oversight of the study and data analysis revealed that the database was unlocked and modified on two occasions following initial data lock. The reasons for the modifications to the database could not be provided during the audit and an information request was placed with Teva to identify all changes made, provide justification for each change, characterize the impact of the changes to the database on key safety and efficacy analyses.

This issue remains unresolved and precludes approval of this BLA.

11. Labeling

- The **proprietary name** was acceptable by DMEPA.
- The **proper name**, (b) (4), was found to not be acceptable by the Biosimilars Review Committee and Biologics Implementation Committee, (b) (4).

[REDACTED]

This is an unresolved issue that precludes approval.

- **Physician labeling**
Labeling negotiations were not initiated during this review cycle given the critical nature of the outstanding deficiencies, which precludes approval.
- **Carton and immediate container labels:** Requests for modification of carton and immediate container labels have been provided to Teva.
- **Patient labeling:** Teva submitted proposed patient labeling following the format recommended for Medication Guides. I concur with the findings of the clinical review team that there are no specific safety concerns that require a Medication Guide. I also concur that patient labeling in the form of a Patients' Instructions for Use (PIU) is appropriate, since other products approved for the same indication are self-administered or administered by caregivers who are not medically trained. The Division, CMC, CDRH, and OSE proposed modifications to Teva's submitted patient labeling that conform to a Patients' Instructions for Use (PIU) document.

12. Decision/Action/Risk Benefit Assessment

Regulatory Action: Complete Response. Multiple review disciplines have identified concerns with this application, resulting in recommendations that the application not be approved. There were no disagreements

within disciplines regarding these recommendations and I concur with the individual discipline recommendations as well with Dr. Keegan's recommendations. The issues surrounding a Complete Response action are:

1. Based on the FDA inspection of BioGeneriX AG (b) (4) there is concern that the integrity of the database for Study XM02-02-INT, the single trial submitted to support the efficacy of Neutroval, may have been compromised. Specifically, after the initial database lock on January 2, 2006, and subsequent data unblinding, the database was unlocked and the data were altered on at least two separate dates, i.e. January 17th and January 23rd, 2006.
2. (b) (4)
3. The sponsor has not provided adequate information concerning their device closure system. Based on FDA's assessment, the sponsor appears to be relying solely on the fill weight as the definitive property to decide if the correct amount of therapy is being delivered through the syringe. There are physical aspects of syringes and needles such as dead space/volume, bond strength between the syringe/needle, and spacing of volumetric graduation markings that can impact the performance of the device. Additionally, based on FDA's review of DMF (b) (4) (Drug Master File for (b) (4)), it appears that the syringes may not conform to current FDA consensus standards regarding syringes and needles.
4. The literature assessment of the potential reproductive toxicity of granulocyte colony stimulating factor(s) provided in support of BLA 125294 does not fulfill the regulatory requirements for nonclinical developmental and reproductive toxicity studies with Neutroval. This BLA submitted under section 351(a) of the PHS Act may not rely on published literature describing studies of other biological products, including studies regarding a licensed biological product, to fulfill this requirement for approval.
5. The proposed proper name for Neutroval, (b) (4) is not acceptable for this BLA submitted under section 351(a) of the PHS Act, (b) (4)

Also, outlined below are areas of product characterization that will require further assessment, either prior to approval or as post-marketing requirements if the five issues above are satisfactorily addressed:

- Characterization of the potential for binding and neutralizing anti-product antibody responses using validated assay methods.
- Further characterization of critical attributes and narrowing of specifications with increased manufacturing experience, including specifications for in-process testing to ensure microbial sterility of the final product.
- Assessment in pediatric patients as required under PREA. Teva plans to assess the pharmacokinetic [systemic exposure (AUC_{0-t})] and pharmacodynamic [absolute neutrophil counts (ANC)] comparability of Neutroval in 50 pediatric patients between the ages of 1 month and 16 yrs 11 months, in three cohorts defined by age with at least 8-10 children per age cohort.
- Characterization of the effects of Neutroval on the corrected QT interval as a predictor for arrhythmic potential in a thorough QT study.

Risk Benefit Assessment: Provided that the issues regarding data integrity can be satisfactorily addressed in the resubmission, the findings of a study XM02-02 demonstrate that the benefits of reduction in duration of febrile neutropenia, supported by the finding of a reduction in the incidence of febrile neutropenia, is clinically meaningful and outweigh the risks of transient bone pain which is both modest in severity and self-limited.

Recommendation for Postmarketing Risk Evaluation and Mitigation Strategies

Based on the safety data contained in the application, there are no safety signals that would require either a restricted distribution program or any component of a REMS in order to ensure safe and effective use. In addition, none of the other products in this class have safety signals which have led to a requirement for a REMS.

Recommendation for other Postmarketing Requirements and Commitments, if approved in future

- PMR for thorough QT study
- PMR to develop validated assays for detection of binding and neutralizing anti-product antibodies.
- PMR to characterize the rate of anti-product antibody formation in the indication population as determined by validated assays.
- PMC for additional product characterization and tightening of specifications as additional manufacturing experience is gained.

Summary Review for Regulatory Action

Date	September 27, 2010
From	Patricia Keegan, M.D.
Subject	Division Director Summary Review
BLA #	STN BL 125294/0
Applicant Name	Teva Pharmaceuticals USA
Date of Submission	November 30, 2009
PDUFA Goal Date	September 30, 2010
Proprietary Name / Established (USAN) Name	Neutroval/ To be determined
Dosage Forms / Strength	Solution for subcutaneous injection in prefilled syringes with and without UltraSafe Passive® Needle Guard 300 mcg/0.5mL and 480 mcg/0.8 mL
Proposed Indication	“Neutroval® (b) (4) is indicated for the reduction in the duration of severe neutropenia and the incidence of febrile neutropenia in patients treated with established myelosuppressive chemotherapy.”
Recommended Action for NME:	Complete Response

Material Reviewed/Consulted	Names of discipline reviewers
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Regulatory Project Manager Review	Danyal Chaudhry
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Statistical Review	Hong (Laura) Lu
Statistical Team Leader Review	Kun He
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DDMAC=Division of Drug Marketing, Advertising and Communication

OSE= Office of Surveillance and Epidemiology

DMEPA=Division of Medication Error Prevention and Analysis

DSI=Division of Scientific Investigations

DDRE= Division of Drug Risk Evaluation

DRISK=Division of Risk Management

CDTL=Cross-Discipline Team Leader

Division Director Summary Review

1. Introduction

The Biologics License Application (BLA) for Neutroval[®] seeks U.S. marketing approval under 351(a) of the Public Health Service (PHS) Act for a biologic product, granulocyte colony stimulating factor (G-CSF) secreted by genetically-engineered bacteria containing the gene for human G-CSF. This would be the second human G-CSF product to be marketed in the U.S.; the first product is Neupogen[®] (filgrastim), manufactured by Amgen, Inc. Related products, which work through the same or similar receptors on granulocytes, that are marketed in the U.S. for the proposed indication sought by Teva, are Neulasta[®] (pegfilgrastim) also marketed by Amgen, Inc, and Leukine[®] (sargramostim), marketed by Bayer Healthcare Pharmaceuticals. Neutroval was approved in the EU under an abbreviated pathway for biosimilar products; however at the time of submission of the BLA on November 30, 2009, there was no mechanism for abbreviated approval in the U.S.

The major efficacy data supporting this application are derived from the results of a single well-conducted, placebo- and active-controlled trial that included two planned comparisons of the effect on the duration of severe neutropenia following myelosuppressive therapy; these were reduction in the duration of severe neutropenia (DSN) in the Neutroval arm as compared to placebo arm and non-inferiority of the mean DSN in the Neutroval arm as compared to EU-marketed Neupogen. A reduction in mean DSN has been accepted by FDA as a valid surrogate for reduction in the incidence of infection and febrile neutropenia when the duration of severe neutropenia in the absence of growth factors is approximately 4-5 days. The major efficacy trial reportedly shows both a significant reduction in the mean DSN and fell within pre-specified bounds set out in the protocol for determination of non-inferiority against an active comparator. As will be discussed in Section 2 and 7 below, FDA did not agree that with the non-inferiority margin specified in the clinical protocol.

This review will briefly discuss the information provided in the application; issues relating to design of the major efficacy trial and adequacy of the trial results (assuming these are reliable) to support a marketing application; issues resulting in a recommendation that the application not be approved, which must be addressed in a resubmission responding to the Complete Response letter; and issues requiring further data that are not critical for a determination of product approval but that should be addressed either in a resubmission addressing the complete response letter or as post-marketing requirements.

All disciplines have completed review of the application and multiple review disciplines have identified unique concerns with this application, resulting in recommendations that the application not be approved. There were no disagreements within disciplines regarding these recommendations and I concur with the individual discipline recommendations. The issues which resulted in recommendations that the BLA not be approved are:

- Unresolved questions regarding data integrity for the major efficacy trial. An FDA audit of the BioGenerix AG, the firm that conducted the study, revealed that the database was altered on two occasions following database lock.
- [REDACTED] (b) (4)
- Insufficient information regarding the controls on and stability of the container closure system for the “to-be-marketed” presentation (prefilled syringe).
- Insufficient information to characterize the potential risks on fetal development in pregnant women exposed to Neutroval. The application did not contain data obtained from developmental and reproductive toxicology (DART) studies in a relevant animal species nor did it contain adequate scientific justification for the absence of such studies.
- Lack of an acceptable proper name. The applicant proposed a proper name, [REDACTED] (b) (4)
- [REDACTED] (b) (4)
- [REDACTED] (b) (4)
- [REDACTED]
- [REDACTED]
- [REDACTED]

A complete response letter will be issued requesting information and data that adequately addresses these issues.

Additional areas of product characterization that will require further assessment, either prior to approval or as post-marketing requirements if the five issues above are satisfactorily addressed, are:

- Characterization of the potential for binding and neutralizing anti-product antibody responses using validated assay methods.
- Further characterization of critical attributes and narrowing of specifications with increased manufacturing experience, including specifications for in-process testing to ensure microbial sterility of the final product.
- Assessment in pediatric patients as required under PREA. Teva plans to assess the pharmacokinetic [systemic exposure (AUC_{0-t})] and pharmacodynamic [absolute neutrophil counts (ANC)] comparability of Neutroval in 50 pediatric patients between the ages of 1 month and 16 yrs 11 months, in three cohorts defined by age with at least 8-10 children per age cohort.
- Characterization of the effects of Neutroval on the corrected QT interval as a predictor for arrhythmic potential in a thorough QT study.

2. Background

On April 26, 2004, BioGeneriX AG finalized protocol XM02-02-INT, titled “Efficacy and Safety of XM 02 compared to Filgrastim in patients with breast cancer receiving chemotherapy”, with the primary objective of “demonstration of equivalence of XM 02 and

Filgrastim (Neupogen – Amgen) in patients with breast cancer during the first cycle of chemotherapy with respect to the duration of severe neutropenia (DSN)”. The contract research organization responsible for the conduct of the study was (b) (4). As initially designed, the study was a 2-arm study comparing XM02 to EU-marketed Neupogen, however prior to initiation of patient accrual the protocol was amended (amendment 1, dated August 31, 2004) to include a placebo-arm, with randomization of 2:2:1 to XM02, EU-filgrastim, and placebo, respectively, and to include an additional co-primary study objective of “Confirmation of assay sensitivity with respect to DSN by comparing XM 02 versus placebo”.

Patients were accrued between December 30, 2004 and September 26, 2005.

During the conduct of the study, the protocol was amended twice. The January 28, 2005 amendment incorporated the following changes:

- Previous versions of the original protocol permitted “therapeutic” use of G-CSF during cycle 1; this amendment clarified that patients in the placebo arm who received G-CSF in cycle 1 would be considered ‘protocol violators’. Use of therapeutic G-CSF was discouraged and investigators were strongly advised to rely on systemically active antibiotics
- Modification stated that patients in the placebo arm who received “therapeutic” G-CSF would be excluded from the per-protocol (PP) analysis.
- Modification to remove the paragraph describing therapeutic G-CSF in patients with afebrile neutropenia >7 days removed.
- The primary analysis of the primary endpoint (DSN in the PP population) was revised to state that patients in the placebo arm receiving therapeutic G-CSF for febrile neutropenia would be excluded from the PP analysis. In other analyses, the DSN for such patients would be assumed to be the median DSN of all placebo patients not receiving therapeutic G-CSF

The third amendment, dated April 26, 2005, consisted on one modification:

- Modification to the planned interim analysis for re-estimation of the sample size. The interim analysis timing (after 50% of patients completed cycle 1) did not change, however the comparison will be limited to the two active treatment arms in accordance with the primary efficacy endpoint in Europe (assessment of bioequivalence between XM02 and the active control). If an adjustment to the sample size occurred, the randomization ratio would remain at 2:2:1.

The statistical analysis plan (SAP) was dated December 16, 2005, was finalized before data base lock. The SAP contained detailed descriptions of the statistical analyses to be performed.

The final study report was generated April 25, 2006, with an addendum to the report dated June 28, 2006 which contained the results of immunogenicity tested at study day 180 and a second addendum dated September 14, 2007 which contained the following selected additional exposure and safety data.

- Exposure data.
- Adverse Events (AEs) of special interest presented by each treatment cycle.
- Laboratory parameters of special interest presented by each treatment cycle.
- Antibody data (immunogenicity), after re-analysis with a new cut-off value.

In addition, the addendum contained an additional analysis of the primary endpoint using the Poisson regression model.

On July 29, 2008, Teva requested a pre-IND/pre-BLA meeting to discuss their intent to submit by the end of the fourth quarter of 2008 or early first quarter 2009, a Biologics License Application (BLA) for a recombinant N-methionyl human granulocyte colony-stimulating factor (r-metHuG-CSF, *E. coli*); in their pre-IND (pIND 103188) briefing package, Teva also referred to this product as TevaGrastim, XM02, and as filgrastim. Teva's product development program was designed in accordance with EU regulations and EMEA guidance for establishing that the Teva product is biosimilar to the product Neupogen (filgrastim) manufactured by Amgen Inc and approved for marketing in the EU. TevaGrastim was granted EU Marketing Authorization by EMEA on Sept 15, 2008, on the basis of safety and efficacy studies conducted outside the U.S. between 2003 and 2006.

Teva met with FDA on November 25, 2008 to obtain advice regarding the clinical, preclinical, and CMC data requirements to support the submission of a BLA (b) (4)

(b) (4)

(b) (4)

The application was to be supported by a completed clinical program composed of five studies: two dose-ranging, pharmacokinetic and pharmacodynamic studies (one single-dose, active-controlled, study in healthy volunteers comparing PK characteristics of Neutroval and EU Neupogen by the intravenous and subcutaneous routes of administration and one study in patients with solid tumors), one study designed to investigate efficacy and safety in 348 patients, and two additional safety studies in 329 patients randomized 2:1 to XMO2 versus Neupogen.

FDA noted that a recombinant N-methionyl human granulocyte colony-stimulating factor would be licensed under section 351 of the Public Health Service Act (PHS Act, 42 U.S.C. 262), rather than approved pursuant to a New Drug Application under section 505 of the Federal Food, Drug, and Cosmetic Act (FFD&C Act, 21 U.S.C. 355). At the time of the meeting, there was no abbreviated approval pathway analogous to that in section 505(b)(2) or 505(j) of the FFD&C Act for protein products licensed as biological products under section 351 of the PHS Act.

FDA noted that comments on Teva's development program, including the circumstances under which Neupogen may be used as an active control in clinical studies, reflected current law and regulations for submission of a BLA. FDA advised Teva to provide a complete and detailed description of the chemistry, manufacturing, and controls information. FDA noted that the nonclinical toxicology program FDA anticipates that the nonclinical data for XM02 will be sufficient to support the (b) (4) proposed indication, for which safety and efficacy would be established in the completed Phase 3 clinical trial. The BLA should also contain data to establish the pharmacological relevance of the animal test species, for example, XM02 binding to rodent or monkey G-CSF receptor.

FDA noted that Teva had completed a single study designed to look at efficacy (XM02-02-INT) and that the study design and statistical analysis plan were not discussed with FDA prior to initiation of the trial intended to support licensure. Further, the only efficacy endpoint that incorporated appropriate alpha adjustment was the duration of severe neutropenia endpoint (DSN) in Study XM02-02-INT and therefore, all other efficacy endpoints in the three studies were considered exploratory. FDA noted that following issues relevant to the clinical data supporting licensure would need to be addressed in the proposed BLA:

- a. The application should provide evidence that the clinical setting (average DSN in the placebo arm for the same patient population/chemotherapy regimen) in which XM02 was evaluated is one that requires growth factor support to avoid a clinically important risk of febrile neutropenia. Such evidence is necessary to support the proposed claim of a clinical benefit (reduction in incidence of febrile neutropenia) based on the surrogate of reduction in DSN.
- b. Discuss why replication of the treatment effect in multiple trials was not needed to establish product efficacy, since an initial approval ordinarily requires demonstration of efficacy in two adequate and well-controlled trials.
- c. For comparisons to an active control (EU-sourced Neupogen) to be considered, the following information should be provided in the BLA
 - 1) Data establishing the treatment effect size (i.e., difference in DSN between the placebo and Neupogen) in this clinical setting defined by the patient population and background chemotherapy regimen. Ordinarily, such evidence should be replicated across multiple studies.

- 2) Justification of the proposed non-inferiority margin; the fraction of the treatment effect for the active control that is to be established for XM02 should be sufficient to confer a clinical benefit.
 - 3) The comparisons should be performed in both the intent-to-treat and the per-protocol populations. A definition for the per-protocol population should be included in the statistical analysis plan. If substantial differences are observed between the two populations, this may be indicative of poor study conduct.
- d. In light of the absence of an abbreviated approval pathway under section 351 of the PHS Act, the study will not support claims based on comparability to Neupogen nor will it support claims based on extrapolation to other indications for which Neupogen is approved.

Furthermore, FDA informed Teva that the BLA should address the potential developmental and reproductive toxicity of XM02. If the nonclinical developmental and reproductive toxicity data were not provided as part of the initial registration package, their absence should be scientifically justified. Teva was also informed that they cannot rely upon proprietary nonclinical data submitted to another BLA to support the safety of XM02 without written authorization from the license holder of that BLA. FDA advised that if a BLA is submitted for an indication that would include treatment of patients at risk for reproductive or developmental toxicity, and if the BLA lacks sufficient information regarding developmental and reproductive toxicity following exposure to XM02, then full non-clinical reproductive and developmental toxicity testing in pharmacologically responsive species would be required.

BL STN 125294 was submitted to FDA on November 30, 2009. The application was filed on January 29, 2010 and was designated as standard review application. The BLA has been amended by submissions dated December 8, , December 21, December 23, 2009, January 11, January 22, February 1, February 12, March 26, April 5, April 23, April 30, May 7, May 12, June 3, June 11, June 15, June 24, June 30, July 8, July 12, July 14, July 20, July 30, and August 19, 2010; the majority of these amendments were made in response to FDA information requests during facilities audits, informal requests made by e-mail or phone or in letters.

Since submission of BL STN 125294/0, the Patient Protection and Affordable Care Act (PPAC Act) was signed into law on March 23, 2010. The PPAC amends the Public Health Service Act (PHS Act) to create an abbreviated approval pathway for biological products that are demonstrated to be “highly similar” (biosimilar) to or “interchangeable” with an FDA-approved biological product. These new statutory provisions also are also referred to as the Biologics Price Competition and Innovation Act of 2009 (BPCI Act). An abbreviated license application submitted under this provision would be approved under section 351(k) of the PHS Act.

3. CMC/Device

I concur with the conclusions reached by the OBP reviewer and team leaders, the OBP immunogenicity reviewer, and the facilities reviewers for drug product and drug substance that there are no outstanding CMC issues for Neutroval that preclude approval. I also concur with the conclusions reached by the CDRH consultant that there is one issue regarding product presentation that precludes approval. (b) (4)

[REDACTED]

I concur with the conclusions reached by the OBP reviewer and team leaders that application could be approved based on CMC characterization. This recommendation is based on their determination that the manufacturing process is well controlled and consistently produces pure and potent product and that the characterization of the drug product and drug substance under stressed and non-stressed conditions. Inspections at DS manufacturing site (Vilnius, Lithuania) occurred 31 May 2010. The DP manufacturing facility inspection was waived. The manufacturing inspection was acceptable, with the exception noted by the CMC microbiology reviewer, as discussed in the next paragraph. Stability testing supports an expiry for the drug substance of (b) (4) stored at (b) (4) and for the drug product of 36 months when stored at 5°C ± 3°C.

Both the OBP reviewer and the CMC microbiology and sterility assurance (DS) reviewer identified several issues that require further investigation. However these issues do not preclude a finding that the product is safe, pure, and potent, therefore these issues will be addressed through agreed-upon post-marketing commitments. These issues are listed in section 13 of this summary review.

I also concur with the conclusions reached by the OBP reviewer regarding the limitations of the current assay methods for assessment of immunogenicity. Since the primary manifestation of clinically relevant anti-product antibody responses manifests as prolonged neutropenia, the clinical safety data obtained in the pivotal study and supportive safety studies were adequate to rule out that an immune response that neutralizes the drug product based on the lack of unexpected or unusually prolonged neutropenia observed in clinical studies. However, in order to characterize pharmacologic aspects of the product now and for assessment of planned or inadvertent changes to manufacturing that impact quality, development and characterization of the immunogenic properties with validated assays will be required as post-marketing required studies.

I concur with the conclusions reached by William Burdick, the CDRH consultant, regarding the deficiencies (b) (4)

[REDACTED]

The final drug product will be supplied in a pre-filled syringe. The container closure system selected for the product is distributed by (b) (4). The container closure system includes the syringe barrel with fixed needle and needle shield, and plunger stopper; validation information for the syringe prior to filling with the final drug product is provided in a cross-referenced Master File. However, the application lacked verification, validation, and testing information related to the final, finished product. (b) (4)

4. Nonclinical Pharmacology/Toxicology

I concur with the conclusions reached by the pharmacology/toxicology reviewer that there is one outstanding pharm/tox issue that precludes approval. The application lacks a nonclinical assessment of developmental and reproductive toxicity of XM02 in DART studies conducted in at least one relevant animal species. Teva has not provided adequate scientific justification for as to why such studies would not be informative or infeasible ; Teva has provided information from the published literature. Since Teva is seeking approval for their product under 351(a) of the PHS Act, the application may not rely on data from other products to establish safety and effectiveness (literature references) and cannot rely on FDA's previous findings of safety and effectiveness for another product without appropriate right of reference. The review staff considered these data necessary to obtain prior to approval in order to ensure that it is accurately labeled. The published data from other products in this class (granulocyte colony stimulating factors) report abortifacient properties. Characterization of the extent and severity of these properties should be performed prior to approval and included in product labeling.

The nonclinical safety program for XM02 consisted of two GLP 26-week repeat dose toxicity studies with 4-week recovery periods in rats (0, 5, 50, and 500 mcg/kg/day) and monkeys (0, 5, 25, and 125 mcg/kg/day), and in a standard battery of GLP safety pharmacology studies. The rat was determined to be the most sensitive species, with a maximum tolerated dose (MTD) of XM02 of 50 mcg/kg/day, based on the observation of a 20% mortality (deaths in 12 of 60 rats) in the 125 mcg/kg/day dose cohort. Mortality in these animals was attributed to severe pain caused by enlarged, swollen joints in hind paws and limbs. The MTD was not reached in the monkey, with no adverse clinical signs at doses up to 125 mcg/kg/day.

The major toxicities associated with XM02 treatment in rats and monkeys resulted from the exaggerated pharmacology of G-CSF and consisted of bone marrow hypercellularity, enlarged spleens, increased alkaline phosphatase (ALP), and extramedullary hematopoiesis (rat)/granulocyte infiltrations (monkey). These effects were dose-dependent and reversible. There were no detectable effects on the respiratory or central nervous system in rats or the cardiovascular system in dogs after a single dose of 3500 mcg/kg XM02 in the GLP safety pharmacology studies.

There were no genotoxicity or carcinogenicity studies performed with XM02 and none were required to support the BLS. The genotoxicity of large molecular weight proteins cannot be assessed using current assay methods and carcinogenicity assessments are not required given the proposed indication and intended patient population.

5. Clinical Pharmacology/Biopharmaceutics

I concur with the conclusions reached by the clinical pharmacology/biopharmaceutics reviewer that there are no outstanding clinical pharmacology issues that preclude approval. The clinical pharmacology reviewer staff had determined that Teva must provide conduct an assessment of the impact of Neutroval on QT prolongation as discussed in Guidance for Industry and FDA: International Conference for Harmonization (ICH) E14 as a post-marketing requirement (PMR) under 505(o). This is based on the assessment of the submitted EKG data and is consistent with advice conveyed to Teva during the pre-IND/pre-BLA meeting “The potential effects of XM02 on the QT interval needs to be evaluated through ECG monitoring in clinical studies following the principles discussed in the ICH-E14 guidance document (www.fda.gov/cder/guidance/6922fnl.htm). Please provide all available ECG data from XM02 studies and a summary of findings in the BLA submission. The results will determine whether further QT evaluation is warranted.”

XM02 is non-glycosylated protein, produced by recombinant DNA technology in *E. coli*. XM02 contain the same amino acid sequence as the native human granulocyte colony stimulating factor (G-CSF) with the exception of an N-terminal methionine necessary for transcription in *E. coli*. Human G-CSF regulates the proliferation and differentiation of myeloid progenitor cells, resulting in an increase in the number of mature functional neutrophils in the peripheral blood. XM02 exerts its effects through the same specific, high-affinity receptor on the surface of myeloid progenitor cells and mature myeloid cells as human G-CSF.

Minimal dose-exploration was conducted with this product and there was no attempt to explore the dose-response or dose-toxicity relationships or to identify a maximum tolerated dose. The selection of the dose and dose regimen for the efficacy and safety trials were supported by pharmacokinetic and bioavailability studies conducted in healthy volunteers at two doses and by two routes of administration along with an active comparator (n=176 subjects) and (based on the evidence of similar pharmacokinetics and pharmacodynamic activity to the doses of EU-marketed Neupogen (which are also the same as the recommended doses of the FDA-approved Neupogen®).

- XM02-01 LT was a randomized, dose-comparison, active-controlled, two-arm, two-period, cross-over study comparing the PK and pharmacodynamics (PD) of XM02 and EU-marketed Neupogen in healthy male volunteers. All patients received a single subcutaneous dose of XM02 or Neupogen at either 5 mcg/kg or 10 mcg/kg, with a 96 hour observation period and 2-week washout prior to cross-over. Fifty-six patients were enrolled (28 to the 5 mcg/kg dose and 28 to the 10 mcg/kg dose); of these 24 and 26 patients, respectively, completed the study.
- Protocol XM02-05 DE was a randomized, four-arm, dose- and schedule-comparison of the PK and PD parameters of XM02 and EU-marketed Neulasta. The study was intended to establish bioequivalence between XM02 and EU-marketed Neupogen and also characterized the bioavailability of subcutaneously administered XM02. One hundred forty-four healthy male and female volunteers were randomized to 4 treatment arms; 36 subjects were

randomized to each arm. There was a 16-day observation period after the first dose with a 3-week washout period prior to cross-over. The four treatment arms and number of subjects completed planned treatment and observations are listed below

- 5 mcg/kg G-CSF intravenous (n=36)
- 10 mcg/kg G-CSF intravenous (n=35)
- 5 mcg/kg G-CSF subcutaneous (n=35)
- 10 mcg/kg G-CSF subcutaneous (n=34)

The pharmacokinetic profile of XM02 was also assessed in a subgroup of patients with cancer in two active-controlled trials and in the three-arm, active- and placebo-controlled efficacy trial. The following table summarizes the design characteristics of these trials.

Protocol	Objectives	Population	Design	Treatment arms	Analysis Populations
XM02-02 INT	• Equivalent efficacy (DSN) • Safety • PK (subgroup)	Metastatic breast cancer receiving docetaxel/doxorubicin x 4 cycles	Randomized, 3-arm, active- and placebo-controlled for cycle 1 only	XM02 vs. EU- Neupogen vs. placebo Placebo at 5 mcg/kg s.c. x 5-14 days (Cycle 1); all pts receive XM02 cycles 2-4	ITT/PP X:140/133 N:136/129 P: 72/58
XM02-03 INT	• Safety • Efficacy(DSN) • PK (subgroup)	Lung cancer receiving platinum-based chemotherapy x 6 cycles	Randomized, active-controlled for cycle 1 only	XM02 vs. EU Neupogen at mcg/kg x 5-14 days s.c. (cycle 1); all pts receive XM02 cycles 2-6	Safety/PP X:158/148 N: 79/ 77
XM02-04-INT	Safety - Efficacy (DSN) - PK (subgroup)	Non-Hodgkin lymphoma receiving CHOP	Randomized, active-controlled for cycle 1 only	XM02 vs. EU Neupogen at mcg/kg x 5-14 days s.c. (cycle 1); all pts receive XM02 cycles 2-6	Safety/PP X: 63/55 N 29/29

The pharmacokinetics (PK) and pharmacodynamic effects, as determined by changes in absolute neutrophil counts, of Neutroval were assessed in healthy subjects and in patients with metastatic breast cancer, metastatic or advanced lung cancer, or non-Hodgkin's lymphoma receiving concurrent myelosuppressive chemotherapy.

Healthy subjects were assigned to receive single dose of Neutroval and a single dose of EU-marketed Neupogen at either 5 mcg/kg or 10 mcg/kg administered subcutaneously (XM02-01-LT) or by either the intravenous or subcutaneous route of administration (XM02-05-DE). The clinical pharmacology reviewer noted that "[T]he absolute bioavailability of 5 and 10 µg/kg SC Neutroval was 33% and 45%, respectively." The pharmacokinetic profile of the 5 mcg/kg dose administered subcutaneously in 33 healthy volunteers is summarized in the table below.

Pharmacokinetic data were also obtained in a subset of patients (12 patients in each of three protocols, listed in the table above) with breast or lung cancer or NHL, receiving myelosuppressive chemotherapy. Across all protocols, XM02 was administered at a dose of 5 mcg/kg subcutaneous beginning 24 hours after the completion of chemotherapy until absolute neutrophil count reached 10×10^9 cells/L following the nadir or after 14 days of XM02 dosing, whichever occurred first. Pharmacokinetic data for XM02 obtained during the first chemotherapy cycle are summarized below.

Protocol	Cancer/chemotherapy	geometric mean of serum C_{max} (CV%)	geometric mean of AUC_{0-24h} (CV%)
XM02-02-INT	Breast/docetaxel + doxorubicin	36 ng/mL (41%)	305 ng*h/mL (35%)
XM02-03-INT	Lung/ platinum-based	25 ng/mL (60%)	273 ng*h/mL (61%)
XM02-04-INT	NHL/ CHOP	20 ng/mL (24%)	184 ng*h/mL (23%)
XM02-01-LT* XM02-05-DE*	Healthy volunteers	18 ng/mL (41%)	158 ng*h/mL (37%)

* 5 mg/kg as a single subcutaneous dose

The median T_{max} was 6 hours and the median half-life ($t_{1/2}$) was 8.9 hours for the 5 mcg/kg dose in healthy volunteers. Increasing the dose of XM02 from 5 to 10 mcg/kg resulted in an approximately 3-fold increase in both C_{max} and AUC_{0-48h} . In patients with cancer receiving chemotherapy, the median T_{max} of XM02 ranged from 4 to 6 hours and the median $t_{1/2}$ ranged from 3.2 to 3.8 hours. Accumulation after repeated daily dosing was not observed. Based on this cross-study comparison, the pharmacology reviewer concluded that there were no interactions regarding dose adjustment based on the underlying cancer or chemotherapy regimen, across the limited numbers of cancer and chemotherapy regimens included in these studies.

No gender-related differences were observed in the pharmacokinetics of XM02 administered by the subcutaneous route of administration. Mild renal impairment (creatinine clearance 60–89 mL/min; N=11) had no clinical meaningful effect on XM02 pharmacokinetics. No dose adjustment is recommended for mild renal impairment. The pharmacokinetic profile in patients with moderate and severe renal impairment has not been assessed. However, based on the safety margin of XM02 and the lack of relationship between the incidence of the major adverse event (bone pain) and degree of renal impairment, an XM02 dosage adjustment would not be clinically warranted. The pharmacokinetic profile in patients with hepatic impairment has not been studied.

The data provided in the application were ECG's obtained at baseline and following two daily doses of XM02 at 5 mcg/kg/day subcutaneously in 102 patients with cancer receiving chemotherapy. These data were determined to be inadequate to establish the potential effects of XM02 on the QTc interval because ECGs were not obtained during the were not adequately evaluated in clinical trials because the post-baseline ECGs were obtained at times when XM02 was cleared from systemic circulation. Based on clinical observations, there is no evidence of arrhythmias with this product in the five clinical trials contained in the submission; there was a single case of syncope and no cases of sudden death in the post-marketing surveillance data obtained in Europe through March 31, 2010, representing (b) (4) daily XM02 doses. This data has been determined to be sufficient to support approval however a post-marketing requirement to conduct a thorough QT study will be required at the time of approval to more fully characterize treatment effects on QTc and arrhythmic potential. This will be requested since detection of a signal may be limited by the relatively limited post-marketing experience and the likelihood that any signals detected will be confounded by co-morbid medical conditions and concomitant medication.

6. Clinical Microbiology

The findings of the microbiology reviewer regarding sterility of drug substance and drug product are discussed under the CMC section (section 3) above.

No clinical microbiology data were obtained in clinical trials submitted to this application.

7. Clinical/Statistical-Efficacy

Five trials were submitted in support of this BLA. Two studies compared the pharmacodynamic and pharmacokinetic properties of XM02 to EU-Neupogen in healthy volunteers (XM02-01 and XM02-05) and the results were limited to assessment of pharmacokinetics and the safety of single doses at 5 or 10 mcg/kg/day by the intravenous or subcutaneous route of administration. The designs of these trials are summarized in section 5 of this summary review.

Three studies were conducted in patients with cancers who were scheduled to receive myelosuppressive chemotherapy. Two of these trials were randomized (1:1), double blind, active-controlled trials, XM02-03 and XM02-04 that enrolled 240 patients with lung cancer and 92 patients with NHL, respectively. Study XM02-03 and Study XM02-04 were designed to provide an assessment of comparative safety and activity of XM02 to an active control (EU-marketed Neupogen) to aid in the design of a definitive efficacy trial (XM02-02 INT). The design of these trials and results of pharmacokinetic data are summarized in section 5 and the safety information from these trials is included in the integrated safety data discussed in section 8 of this summary review.

There was a single trial, XM02-02-INT, conducted to establish the efficacy of XM02 for the proposed indication of reduction in the duration of severe neutropenia (DSN). Study XM02-02 is a multinational, multicenter, randomized (2:2:1), active- and placebo-controlled trial conducted in women with high-risk stage II, or with stage III or IV breast cancer receiving initial chemotherapy as adjuvant treatment or as treatment of metastatic disease. Due to the protocol-specified body-weight dosing (5 mcg/kg body weight) of study drug and the different fill volumes of the XM02 and EU-Neupogen syringes, the drug administrator and the pharmacist were not blinded to study drug treatment.

The co-primary objectives of Study XM02-02 were to confirm assay sensitivity with respect to duration of severe neutropenia (DSN) by comparing XM 02 versus placebo and to demonstrate the equivalence of XM02 and EU-marketed Neupogen during the first cycle of chemotherapy with respect to DSN. DSN was defined as the number of days with an absolute neutrophil count (ANC) of less than or equal to 0.5×10^9 neutrophils/L. As discussed below, these endpoints were tested hierarchically.

Additional study objectives were

- Incidence of febrile neutropenia per cycle and across all cycles (febrile neutropenia defined as body temperature of $> 38.5^{\circ}\text{C}$ for more than one hour, axillary measurement with a calibrated standard device, and absolute neutrophil count (ANC) $< 0.5 \times 10^9/\text{L}$)
- DSN in cycles 2 to 4
- Depth of ANC nadir in cycles 1 to 4
- Times to ANC recovery in cycles 1 to 4
- Mortality
- Incidence of adverse events AEs
- Changes of safety laboratory parameters
- Immunogenicity (development of antibodies against XM 02 and EU-Neupogen)

Treatment Plan

Study drug treatment with XM02/EU-Neupogen/Placebo was administered at a dose of 5 mcg/kg subcutaneously, daily for 5-14 days, beginning on study day 2. Treatment was to be continued until study day 15 or a post-nadir ANC of $\geq 2.0 \times 10^9/\text{L}$. Patients in the placebo arm were switched to XM02 during chemotherapy cycles 2-4.

Concomitant chemotherapy consisted of doxorubicin 60 mg/m² and docetaxel 75 mg/m² on day 1 of a 21-day cycle for up to 4 cycles. Appropriate dose modifications for chemotherapy-related toxicity were included in the protocol. Treatment could be delayed up to 14 days to allow recover from myelosuppression, defined as ANC $\geq 1.5 \times 10^9/\text{L}$ and platelets $\geq 100 \times 10^9/\text{L}$.

Study Monitoring Plan

Study monitoring during cycle 1, included measurement of ANC within 24 hours prior to chemotherapy, then daily until study day 15 or an ANC of $\geq 2.0 \times 10^9/\text{L}$, whichever was longer. In cycles 2, 3, and 4, ANC was assessed within 24 hours before chemotherapy and then daily starting on Day 5 until Day 15, or longer until ANC reached $\geq 2.0 \times 10^9/\text{L}$. In each cycle, body temperature (axillary) was measured daily until Day 15, or longer until ANC reached $\geq 2.0 \times 10^9/\text{L}$. Safety assessments (laboratory parameters, antibody sampling, physical examination, vital signs) were performed at screening, within 24 hours before chemotherapy in each cycle (Day 1), and at the end of study visit. Patients were monitored for adverse events (AEs) and concomitant medication throughout the study.

Three weeks after the last chemotherapy infusion (Day 85 ± 1), end of study assessments were performed. On Day 180 ± 5 , there was an additional assessment for determination of antibodies against XM 02 or EU-Neupogen.

Analysis Plan

The primary efficacy endpoint was the duration of severe neutropenia (DSN) in cycle 1. There was one planned interim analysis for re-estimation of sample size in the event that the assumptions regarding

The analysis was to be conducted in two stages, with the efficacy comparison (bioequivalence) to be conducted only if the assumptions regarding assay sensitivity with respect to the DSN

were confirmed. The first comparison was of DSN in cycle 1 between the XM02 and placebo arms. If this comparison demonstrated a statistically significant difference on DSN (ANCOVA, $p < 0.05$, two-sided), in favor of the XM02 arm, then the analysis for equivalence in DSN in cycle 1 between the XM02 and the EU-marketed Neupogen arms could be conducted. Due to this hierarchical testing procedure, no adjustment of the significance was required.

Based on the analysis plan, the two products (XM 02 and EU-marketed Neupogen) would be determined to be equivalent if the two-sided 95% confidence interval for the difference in DSN between the two arms excluded 1 day.

There was no plan specified for testing of secondary endpoints in the protocol which adjusted for alpha spending. Based on this lack of a pre-specified plan for preservation of alpha, the FDA statistical reviewers identified all secondary endpoints as “exploratory”.

The study sample size of 140 patients per active treatment arm was based on the following assumptions.

- 109 patients per active treatment arm will be required to reject the null hypothesis (that the difference in the mean DSN between the treatment and active control arm is greater than 1.0 days) with 90% power, based on the assumption that the observed difference in mean DSN will be less than 0.25 days and that the standard deviation is 1.7 days.
- 20% of the patients registered and randomized will not be eligible for per-protocol analysis. A single planned interim analysis was planned after 50% of the patients had completed cycle 1 to assess the validity of the assumptions regarding variability, with a proposal for sample size re-estimation in the event that the variability in the DSN was underestimated. The proposal for the interim analysis was revised in amendment 3 to the protocol to limit the analyses to data from the two active treatment arms.

The statistical analysis plan identified three patient populations for data analysis:

- **Full analysis set:** The full analysis set comprises all randomized patients
- **Safety set:** The safety set comprises all patients of the full analysis set who received at least one dose of study treatment.
- **Per protocol set:** The per protocol set comprises all patients of the full analysis set, who received at least one cycle of chemotherapy, who received their study treatment (XM 02 or Filgrastim) for at least one cycle and who did not have any major protocol violations including violations of inclusion and exclusion criteria.

Demographic and baseline characteristics were to be evaluated for the full analysis set and for the per-protocol set.

The efficacy analyses were to be conducted in the per-protocol set (primary efficacy analysis) and for the full analysis set (supportive analyses).

Results

Study XM02-02 registered and randomized 350 at 52 centers in 10 countries (Belarus, Slovenia, South Africa, Brazil, Chile, Russia, Hungary, Lithuania, Romania, and Poland). The

full analysis population excluded two patients who were randomized but did not meet eligibility criteria for the study (screening failures). The demographics of the full analysis population are presented in the following table, taken from Dr. Herndon's review.

Patient Demographics (Full Analysis Set) for Study XM02-02 for Cycle 1

	XM02 (N=140) N (%)	EU-Neupogen (N=136) N (%)	Placebo (N=72) N (%)
Age (years) median range	51 25 - 75	51 28 - 74	48 28 - 74
Gender Female	139 (99)	135 (99)	72 (100)
Race Black Hispanic White Other	1 (1) 10 (7) 120 (86) 9 (6)	5 (4) 10 (7) 118 (87) 3 (2)	2 (3) 6 (8) 62 (86) 2 (3)
Stage High-Risk Stage II Stage III Stage IV	23 (16) 79 (56) 38 (27)	36 (26) 69 (51) 31 (23)	15 (21) 38 (53) 19 (26)

The following table from Dr. Herndon's review provides a summary of the disposition of patients. More than 95% of patients completed the study. The category titled "Withdrawn due to other reasons" primarily consists of patients who withdrew consent.

Patient Disposition (Full Analysis Set)

DISPOSTION	XM02 N=140	EU-Neupogen N=136	Placebo N=72
Complete Protocol	96%	96%	94
Withdrawn due to Adverse Event Attributed to Study Drug	0	0	1%
Withdrawn due to Adverse Event Attributed to Chemotherapy	1%	1%	1%
Died	1%	0	3%
Other	2%	4%	0

Efficacy Analyses

Study XM02-02 demonstrated that the mean duration of severe neutropenia was significantly shorter in XM02-treated patients compared to placebo-treated patients following docetaxel/doxorubicin chemotherapy in women receiving initial chemotherapy treatment for metastatic or high-risk localized breast cancer. After adjustments for “treatment”, “country” and “adjuvant vs. metastatic therapy”, and baseline ANC value, the mean duration of severe neutropenia in cycle 1 was 1.1 and 3.8 days ($p < 0.0001$, χ^2 test) in the XM02 and placebo arms, respectively, with a difference of -2.7 days (95% CI -3.2 days, -2.2 days).

As noted in Dr. Lu’s review, due to her concerns regarding Teva’s methods for imputation of missing data or “replacement”, she conducted a series of sensitivity analyses to examine the robustness of the treatment effects of XM02 on the duration of severe neutropenia. There were two specific imputation methods that concerned Dr. Lu. First, in Teva’s primary analysis comparing with XM02 arm with the placebo arm, the observed DSN for placebo patients who received therapeutic G-CSF treatment was replaced with the median DSN for all placebo patients who received no G-CSF treatment. Dr. Lu noted that this approach could underestimate the variability of DSN in placebo arm and exaggerate the statistical significance of the difference in DSN. Second, Dr. Lu raised concerns regarding imputing values for missing ANC’s, based on linear interpolation using the ANC values immediately before and after the missing value. Dr. Lu raised questions regarding the validity of this method since it assumes an ANC value to be in-between the ANC values before and after. Based on the results of the sensitivity analyses (summarized in Tables 6 and 7 in Section 3.1.4 of Dr. Lu’s review), Dr. Lu determined that the primary analysis conducted by Teva is robust and consistent with the results of the sensitivity analyses.

The mean duration of severe neutropenia observed in the placebo-control arm is lower than anticipated based on historical controls. Thus the inclusion of a placebo-arm, as recommended by the EU regulatory authorities to confirm assay sensitivity, was warranted. Historical data available at the time of the approval of Neulasta showed that, in the absence of growth factor support, chemotherapy regimens similar to the one used in XM02-02 (i.e., doxorubicin 60 mg/m² and docetaxel 75 mg/m² administered every three weeks) resulted in a 100% incidence of severe neutropenia with a mean duration of severe neutropenia of 5-7 days and incidence of febrile neutropenia of 30-40%. Only with chemotherapeutic regimens that have a prolonged duration of severe neutropenia (5-7 days) is a reduction in mean duration of severe neutropenia a valid surrogate for reduction in febrile neutropenia. Due to the inclusion of a placebo control, confirmation that the surrogate was valid was possible.

Febrile neutropenia was defined as body temperature of $>38.5^{\circ}\text{C}$ for more than one hour, and $\text{ANC} < 0.5 \times 10^9/\text{L}$, occurring on the same day. In addition, patients receiving systemic antibiotics in a cycle were considered as having FN in this cycle. If these two conditions (temperature $>38.5^{\circ}\text{C}$ for >1 hour and $\text{ANC} < 0.5 \times 10^9/\text{L}$) were met, regardless of whether systemic antibiotics were administered, this was categorized as “observed FN”. If systemic antibiotics were given, regardless of whether the two “threshold conditions” were met, this was categorized as “protocol defined FN”. The majority of the events were defined by administration of systemic antibiotics in all three arms (see Dr. Lu’s review for details). The incidence of observed or of protocol-defined febrile neutropenia was lower in the Neutroval arm compared to the placebo arm (12.1% vs. 36.1%). Since the protocol did not prospectively specify the method for adjustment of secondary

endpoints, comparative claims for the reduction in the incidence of febrile neutropenia in the package insert or promotional labeling should not include p-values. However, FDA finds this comparison compelling because it confirms that the surrogacy of reduction for DSN for reduction in febrile neutropenia is present even with the shorter than anticipated DSN in the placebo-arm.

As noted in Section 2 of this summary review, Teva did not provide adequate justification for the non-inferiority margin of a 1-day difference in mean DSN between the XM02 and the active control arm. In addition, Teva did not provide adequate justification that a margin based on treatment effects with US-marketed Neupogen could be extrapolated to treatment effects with the EU-marketed product. Therefore, claims of non-inferiority to Neupogen will not be permitted, however the active-controlled data does provide supportive data for XM02.

Based on the results obtained in the full analysis set, the mean DSN for both XM02 and for EU-marketed Neupogen was 1.1 days. The difference in the mean DSN was 0.03 days and the 95% confidence intervals around this observed difference were -0.26 days and + 0.33 days. The results in the per-protocol set were essentially the same.

8. Safety

The application contained safety data from five clinical trials. The size of the safety database and duration of exposure is sufficient for characterization of treatment-emergent signals although data are somewhat limited by the use of active-controlled study designs and limited amount of controlled data beyond chemotherapy cycle 1, as will be discuss further in this section of the review. (b) (4)

. This will be discussed at the end of this section.

Data from two pharmacokinetic/pharmacodynamic studies in which healthy volunteers received a single dose of XM02 are not included below in analyses of safety due to the limited exposure. Safety data are presented in this summary that includes 541 XM02-treated patients enrolled in three studies conducted in patients with cancer, Studies XM02-03, XM02-04 and XM02-02. Of these 541 patients, 356 patients received only XM02 in combination with 4-6 cycles of chemotherapy. Analyses of safety conducted by Dr. Herndon evaluated results within individual studies and pooled analyses across all studies conducted in patients with cancer. The dose and duration of exposure was adequate to assess safety for the intended use. The safety data in this application is limited by the availability of internally-controlled data to cycle 1 in two of the three studies and availability of a placebo-control for only one study, which is also limited to the first cycle. The design of these studies limits the ability to detect safety signals, since it is contingent on detection of signals that occur at higher rates than the active control. Protocols XM02-03 and XM02-04 had an active control for the first cycle only (n=115) and Protocol XM02-02 INT had a placebo-control for the first cycle only (72 patients) and an active control (136 patients) for the treatment cycles 1-4. Brief synopses of each of these three studies are provided below:

- Study XM02-03: There were 240 patients with small cell lung cancer (SCLC) or advanced non-small cell lung cancer (NSCLC) who were previously untreated or had received only one prior chemotherapy regimen enrolled in this trial, of these 237 received at least one dose of study drug in following chemotherapy. Concomitant chemotherapy consisted of platinum-based chemotherapy administered in 3- or 4-week cycles for up to 6 cycles. Patients were randomized (2:1) to receive XM02 (n=158) or EU-marketed Neupogen (n=79) during cycle 1; in all subsequent chemotherapy cycles, patients received open-label XM02. The dose of XM02 was 5 mcg/kg/day subcutaneously administered following chemotherapy for 14 days or until evidence of neutrophil recovery.
- Study XM02-04: There were 92 patients with previously untreated aggressive NHL enrolled in this randomized, active-controlled trial enrolled in this trial; all patients received at least one dose of study drug in following chemotherapy. Concomitant chemotherapy consisted of CHOP (cyclophosphamide IV 750 mg/m², doxorubicin IV 50 mg/m², and vincristine IV 1.4 mg/m² on day 1 of each treatment cycle and prednisolone 100 mg/day days 1-5 of each cycle) for up to 6 21-day cycles. Patients were randomized (2:1) to receive XM02 (n=63) or EU-marketed Neupogen (n=29) during chemotherapy cycle 1; in all subsequent chemotherapy cycles, patients received open-label XM02. The dose of XM02 was 5 mcg/kg/day subcutaneously administered following non-steroid chemotherapy for 14 days or until evidence of neutrophil recovery.
- Study XM02-02: There were 350 patients with high-risk stage II or metastatic breast cancer who had received no previous systemic treatment for breast cancer, enrolled in this trial; of these 350 patients, 348 received at least one dose of study drug in following chemotherapy. Concomitant chemotherapy consisted of docetaxel 75 mg/m² and doxorubicin 60 mg/m² in 3-week cycles for up to 4 cycles. Patients were randomized (2:2:1) to receive XM02 (n=140), EU-marketed Neupogen (n= 136), or placebo (n= 72) during cycle 1; in all subsequent chemotherapy cycles, patients randomized to placebo received XM02. . The dose of XM02 was 5 mcg/kg/day subcutaneously administered following chemotherapy for 14 days or until evidence of neutrophil recovery.

Across the 541 XM02-treated patients enrolled in these three studies, the median age of the safety population was 55 years (range: 20 years to 80 years) and 58% were female. A more detailed breakdown of the demographics for the safety analysis population is provided in the following table, abstracted from Dr. Herndon's review.

Demographics for Pooled Safety Dataset

	XM02 only¹ N=356 N (%)	EU- Neupogen only² N=136 N (%)	EU- Neupogen/ XM02³ N=115 N (%)	Placebo/ XM02⁴ N=72 N (%)	Any XM02 N=541 N (%)	Overall N=677 N (%)
Age (years)						
Median	55	51	57	48	55	54
Range	18-83	28-75	33-83	28-74	18-83	18-83
Age Categories						
≥ 65 years	71 (20%)	19 (14%)	32 (28%)	9 (13%)	11 (21%)	131 (19%)
Gender						
Female	199 (56%)	129 (96%)	39 (34%)	72 (100%)	308 (58%)	439 (65%)
Race						
Caucasian	319 (90%)	116 (87%)	109 (95%)	62 (86%)	488 (90%)	606 (90%)

¹ XM02 arms of Studies XM02-02, XM02-03, and XM02-04

² Active control arm of Study XM02-02

³ Active control arm of Studies XM02-03 and XM02-04

⁴ Placebo-control arm of Study XM02-02

Based on the known toxicity profile of other G-CSF products, Teva anticipated that bone pain would be the most common adverse reaction, Teva developed a standardized medical query (SMQ) for bone pain that included the MedDRA preferred terms: arthralgia, back pain, bone pain, musculoskeletal pain, neck pain, pain in extremity, pain in jaw, pelvic pain, and sacral pain. Using this SMQ, an analysis of data from cycle 1 of Study XM02-02, the only placebo-controlled findings, demonstrated that bone pain was the most frequent treatment-emergent adverse reaction that occurred at a higher incidence in patients treated with Neutroval compared with patients treated (14.2% vs. 9.7% in cycle 1). Across all three studies conducted in patients with cancer, the incidence of bone pain was 23.5% in the 541 XM02-treated patients. No patients discontinued the study drug due to bone pain.

The safety database was also assessed for reports of adverse reactions identified with other G-CSF products. There were no cases of acute respiratory distress syndrome, sickle cell crisis, or splenic rupture in the XM02 integrated safety database.

The clinical program for XM02 was not adequate in design (placebo-controlled for only one cycle in one study) or size to rule out the possibility of the stimulation or promotion of malignancies involving the myeloid lineage. There were no reported cases of secondary myeloid cancers in the integrated safety database.

The evaluation of anti-product antibody formation (immunogenicity) is limited by two specific factors: (1) the assay methods used to assess for binding and neutralizing antibodies were not validated for acceptable performance and (2) given the cross-over from active control to XM02 after cycle 1 in trials XM02-03 and XM02-04, data from patients randomized to the control arm are not interpretable as the patients received more than one G-CSF product.

Of the available information from Protocol XM02-02, the following data are reproduced from

Teva's addendum to the study report. The report notes that no patient experience neutralizing antibodies in Protocol XM02-02. There was a higher than expected incidence of patients who were positive prior to treatment in all study arms. There did not appear to be differences in the proportion of patients who developed binding antibodies, keeping in mind that all patients in the placebo arm received XM02-02 from cycle 2 to the end of study.

	XM02 (N=140)		Filgrastim (N=136)		Placebo/XM02 (N=72)		Overall (N=348)		XM02 vs. Filgrastim
	N	%	N	%	N	%	N	%	
Screening									
Exposed to study drug	140	100.0	136	100.0	72	100.0	348	100.0	
Missing	1	0.7	0	0.0	2	2.8	3	0.9	
Positive	5	3.6	3	2.2	2	2.8	10	2.9	
Negative	132	94.3	133	97.8	68	94.4	333	95.7	
Questionable (equivocal)	2	1.4	0	0.0	0	0.0	2	0.6	p= 0.5016
Before cycle 1									
Exposed to study drug	140	100.0	136	100.0	72	100.0	348	100.0	
Missing	2	1.4	0	0.0	0	0.0	2	0.6	
Positive	5	3.6	4	2.9	1	1.4	10	2.9	
Negative	132	94.3	131	96.3	71	98.6	334	96.0	
Questionable (equivocal)	1	0.7	1	0.7	0	0.0	2	0.6	p= 1.0000
Before cycle 2									
Exposed to study drug	140	100.0	136	100.0	72	100.0	348	100.0	
Missing	5	3.6	5	3.7	5	6.9	15	4.3	
Positive	4	2.9	2	1.5	1	1.4	7	2.0	
Negative	131	93.6	128	94.1	66	91.7	325	93.4	
Questionable (equivocal)	0	0.0	1	0.7	0	0.0	1	0.3	p= 0.5620
Before cycle 3									
Exposed to study drug	137	100.0	131	100.0	70	100.0	338	100.0	
Missing	1	0.7	2	1.5	1	1.4	4	1.2	
Positive	2	1.5	5	3.8	1	1.4	8	2.4	
Negative	133	97.1	123	93.9	68	97.1	324	95.9	
Questionable (equivocal)	1	0.7	1	0.8	0	0.0	2	0.6	p= 0.6344
Before cycle 4									
Exposed to study drug	136	100.0	131	100.0	69	100.0	336	100.0	
Missing	2	1.5	1	0.8	0	0.0	3	0.9	
Positive	2	1.5	3	2.3	0	0.0	5	1.5	
Negative	132	97.1	127	96.9	69	100.0	328	97.6	
Questionable (equivocal)	0	0.0	0	0.0	0	0.0	0	0.0	p= 0.6804
End of Study									
Exposed to study drug	140	100.0	136	100.0	72	100.0	348	100.0	
Missing	2	1.4	5	3.7	3	4.2	10	2.9	
Positive	2	1.4	2	1.5	1	1.4	5	1.4	
Negative	136	97.1	129	94.9	68	94.4	333	95.7	
Questionable (equivocal)	0	0.0	0	0.0	0	0.0	0	0.0	p= 1.0000
Antibody follow-up									
Exposed to study drug	140	100.0	136	100.0	72	100.0	348	100.0	
Missing	14	10.0	17	12.5	10	13.9	41	11.8	
Positive	4	2.9	7	5.1	3	4.2	14	4.0	
Negative	122	87.1	112	82.4	59	81.9	293	84.2	
Questionable (equivocal)	0	0.0	0	0.0	0	0.0	0	0.0	p= 0.3652

N = number of patients, % = 100 * (N affected / N exposed)

Placebo/XM02: patients of this group were randomised to placebo in cycle 1 and switched to XM02 afterwards

p: 2-sided p-value of Fisher's exact test excluding missing records.

Source: CSR XM02-02-App.16.2.10-Addendum01-App.3 Table 2.1

The impact of anti-product antibodies responses on the pharmacokinetics of XM02 could not be assessed since pharmacokinetic data were not collected in patients who tested positive for binding or neutralizing antibodies.

The CDRH consultant reviewed information regarding the product presentation in a (b) (4)

(b) (4) This syringe was developed several decades ago and does not conform with current ISO standards. (b) (4)

9. Advisory Committee Meeting

This is the fourth product indicated for the prevention of severe neutropenia and febrile neutropenia in patients with cancer receiving myelosuppressive therapy and the third product which acts specifically on the G-CSF receptor. The primary endpoint, a reduction in the duration of severe neutropenia following myelosuppressive chemotherapy, is an accepted surrogate for febrile neutropenia when the duration of severe neutropenia in the absence of a neutrophil growth factor is at least 4-5 days but less than 14 days (i.e., not prolonged as is the case with induction chemotherapy for acute leukemia or following hematopoietic progenitor cell transplantation). There were no unexpected clinical safety or efficacy issues requiring the advice of the Oncologic Drugs Advisory Committee.

10. Pediatrics

I concur with the CDTL and the PeRC's recommendations regarding Teva's plans to conduct of pediatric studies required under PREA. The BLA contained a request for deferral of pediatric studies and proposed to conduct trial in pediatric patients as required post-marketing commitment. Specifically, Teva requested a partial waiver of pediatric studies under PREA for neonates up to 1 month of age, deferral of studies in children between the ages of 1 month to (b) (4) years and provided a proposed plan for assessing the comparability of Neutroval pharmacokinetics and pharmacodynamics between adults and children as deferred studies. This request was evaluated by the clinical review team and reviewed by the PeRC PREA Subcommittee on August 11, 2010. The PeRC agreed with the Division to grant a partial waiver and the deferral for this product.

I do not concur with the PeRC's premise which underlies their recommendation that Teva be required to conduct a study to establish a safe and effective dose in pediatric patients if the 5 mcg/kg/day dose does not result in "similar responses as compared to adults". There is no way to determine a safe and effective dose based on pharmacokinetic comparability since the exposure-response relationship for this product has not been established. Further, the exposure-response relationship is particularly difficult for this product due to age-related

differences in marrow cellularity and the unique receptor-mediated clearance of this product. Therefore, an efficacy study will be required to establish a safe and effective dose for pediatric patients for purposes of describing a recommended dose for pediatric patients/subpopulations in product labeling. Regardless of the outcome of the PK/PD study, efficacy studies will be required to support a specific claim for pediatric patients or subpopulations of pediatric patients.

11. Other Relevant Regulatory Issues

A major unresolved issue that precludes approval was identified during the FDA's Division of Scientific Investigations audit of BioGenerix AG. Non-clinical and clinical development of XM02 was conducted by BioGenerix AG, (b) (4). Under a license agreement between BioGenerix AG and Sicor Biotech UAB in Lithuania, XM02 was brought to market in the European Union as a biosimilar product (to the EU-marketed reference product, Neupogen®). Sicor Biotech UAB is an indirect wholly-owned subsidiary of Teva Pharmaceuticals USA, Inc. BioGenerix AG was the commercial sponsor at the time of Protocol XM02-02-INT was conducted and was responsible for the contract with a CRO, (b) (4) for the conduct and oversight of the protocol and data analysis for Protocol XM02-02-INT. Although the two highest accruing clinical sites were inspected, site 2513 enrolling 26 patients and site 2519 enrolling 21 patients, no single clinical study site contributed a substantial proportion of study subjects and thus no single site or limited number of sites would have had substantial impact on the study results. There interim classifications for these sites were VAI and NAI, respectively. FDA also chose to inspect BioGenerix AG, and a CRO, (b) (4), in accordance with the CDER Sponsor/Monitor/CRO Inspection using the Bioresearch Monitoring Compliance Program (CP 7348.810). The findings of this audit revealed that the database was unlocked and modified on two occasions following initial data lock. The reasons for the modifications to the database could not be provided during the audit and an information request was placed with Teva to address the following

- Identify all changes made
- Provide justification for each change
- Characterize the impact of the changes to the database on key safety and efficacy analyses.

12. Labeling

- Proprietary name: I concur with the recommendations of the DMEPA consultant that the proposed proprietary name is acceptable. The proprietary name review conducted by the Division of Medication Error and Prevention on March 19, 2010 evaluated the proposed name, Neutroval, from a safety and promotional perspective based on the product characteristics provided by the Applicant. This evaluation did not identify concerns that would render the name unacceptable based on the product characteristics and safety profile known at the time of the review and DMEPA found the proposed proprietary name, Neutroval, conditionally acceptable for this product.

- Proper name: I concur with the recommendations of the Biosimilars Review Committee and Biologics Implementation Committee that the proposed proper name, (b) (4), is not acceptable. (b) (4)
 (b) (4)
 (b) (4)
 (b) (4)
- Physician labeling
 Labeling negotiations were not initiated during this review cycle given the critical nature of the outstanding deficiencies, which may preclude approval.
- Carton and immediate container labels: Requests for modification of carton and immediate container labels have been provided to Teva.
- Patient labeling: Teva submitted proposed patient labeling following the format recommended for Medication Guides. I concur with the findings of the clinical review team that there are no specific safety concerns that require a Medication Guide. I also concur that patient labeling in the form of a Patients' Instructions for Use (PIU) is appropriate, since other products approved for the same indication are self-administered or administered by caregivers who are not medically trained. The clinical review team, with input from the CMC review staff, CDRH and OSE consultants, proposed modifications to Teva's submitted patient labeling that conform to a Patients' Instructions for Use (PIU) document. In addition, modifications were proposed for clarity of instructions and for "command" language.

13. Decision/Action/Risk Benefit Assessment

- Regulatory Action: Complete Response
- Risk Benefit Assessment
 Provided that the issues regarding data integrity can be satisfactorily addressed in the resubmission, the findings of a study XM02-02 demonstrate that the benefits of reduction in duration of febrile neutropenia, supported by the finding of a reduction in the incidence of febrile neutropenia, is clinically meaningful and outweigh the risks of transient bone pain which is both modest in severity and self-limited. This conclusion is based solely on the comparison of the XM02 and placebo arms in Study XM02-02.

During the July 28, 2009 pre-BLA meeting with Teva, and as summarized in greater detail of section 2 of this summary review, FDA informed Teva that in order to consider claims based on comparisons to the active control, the following information should be provided in the BLA

- Data establishing the treatment effect size (i.e., difference in DSN between the placebo and Neupogen) in this clinical setting defined by the patient population and

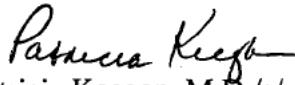
background chemotherapy regimen. Ordinarily, such evidence should be replicated across multiple studies.

- Justification of the proposed non-inferiority margin; the fraction of the treatment effect for the active control that is to be established for XM02 should be sufficient to confer a clinical benefit.
- The comparisons should be performed in both the intent-to-treat and the per-protocol populations. A definition for the per-protocol population should be included in the statistical analysis plan. If substantial differences are observed between the two populations, this may be indicative of poor study conduct.

Teva's application did not adequately address either the first or the second bullet point. Therefore, the comparison of XM02 efficacy to an active control provides additional information that supports product activity but cannot be used to establish efficacy. With regard to first bullet, Teva alluded to the basis for the effect size through reliance on data obtained with the US-manufactured Neupogen, however Teva did not support their assertions that [REDACTED] (b) (4)

[REDACTED] With regard to the second bullet, Teva failed to provide data that supports the difference of 1-day as a difference sufficient to preserve treatment effect on the true endpoint (febrile neutropenia). Teva states that the chosen margin of 1-day is appropriate because a difference of 1 day is considered to be the maximum clinically acceptable difference. However, Teva did not provide data that a difference of up to 1 day will exclude clinically meaningful differences in the incidence of febrile neutropenia, taking into account the duration of severe neutropenia demonstrated in the control arm.

- Recommendation for Postmarketing Risk Evaluation and Mitigation Strategies
Neither the review team nor I recommend a REMS for this product. Based on the safety data contained in the application, there are no safety signals that would require either a restricted distribution program or any component of a REMS in order to ensure safe and effective use. In addition, none of the other products in this class have safety signals which have led to a requirement for a REMS.
- Recommendation for other Postmarketing Requirements and Commitments
 - PMR for thorough QT study
 - PMR to develop validated assays for detection of binding and neutralizing anti-product antibodies.
 - PMR to characterize the rate of anti-product antibody formation in the indication population as determined by validated assays.
 - PMC for additional product characterization and tightening of specifications as additional manufacturing experience is gained.


/Patricia Keegan, M.D./s/ 9/27/2010
Director, Division of Biologic Oncology Products

September 27, 2010

Cross-Discipline Team Leader Review

Date	September 22, 2010
From	Suzanne Demko
Subject	Cross-Discipline Team Leader Review
BLA #	125294
Supplement #	0
Applicant	Teva Pharmaceuticals, USA
Date of Submission	November 30, 2009
PDUFA Goal Date	September 30, 2010
Proprietary Name / Proper Name	Neuroval/ Pending
Dosage forms / Strength	300 mcg/0.5 ml and 480 mcg/0.8 ml in single-use, prefilled syringes
Proposed Indication(s)	Reduction in the duration of severe neutropenia and the incidence of febrile neutropenia in patients treated with established myelosuppressive chemotherapy for cancer
Recommended:	Complete Response Letter

1. Introduction

A Biologic License Application (BLA) for XM02 (Neuroval®) was submitted to the Food and Drug Administration (FDA) by Teva Pharmaceuticals, USA (Teva) on November 30, 2009. XM02 is a non-glycosylated r-metHuG-CSF expressed in *Escherichia coli*. Non-clinical and clinical development of XM02 was conducted by BioGeneriX AG, (b) (4)

(b) (4) Under a license agreement between BioGeneriX AG and Sicor Biotech UAB in Lithuania, an indirect wholly-owned subsidiary of Teva, the clinical development program for XM02 was designed to support a filing for Marketing Authorization as a biosimilar product in the European Union (EU). XM02 was approved in the EU as Tevagrastim in September, 2008 with EU-approved filgrastim (EU-filgrastim) as the referenced product. (b) (4) formulations of XM02 are registered under the following trade names: BiograstimCI, Filgrastim-Mepha, Filgrastim ratiopharm, and RatiograstimCI, and are marketed in Europe by BioGenerix AG, RatioPharm, or Teva.

This application was submitted to FDA under the Public Health Service Act (PHS Act, 42 U.S.C. 262), section 351 (a), Licensure of Biological Establishments and Products. Subsequent to this filing, passage of the Patient Protection and Affordable Care (PPAC) Act created an abbreviated pathway for approval of biologic products which is described under a subtitle of the PPAC Act, the Biologics Price Competition and Innovation (BPCI) Act of 2009. Under the BPCI Act, an applicant may seek approval for a "biosimilar" product under the requirements of a new section of the PHS Act, section 351 (k).

The proposed indication for XM02 is a reduction in the duration of severe neutropenia and the incidence of febrile neutropenia in patients with cancer treated with myelosuppressive chemotherapy (b) (4)

Submitted in support of the application were the results of a single efficacy trial, Study XM02-02, conducted in patients with breast cancer who required chemotherapy. Also submitted in support of the application were two safety studies conducted in patients with lung cancer and non-Hodgkin lymphoma who were randomized to EU-filgrastim or XM02, and two pharmacokinetic/pharmacodynamic trials conducted in healthy volunteers.

The trial submitted to support efficacy, Study XM02-02, was a multinational, controlled, randomized (2:2:1) trial in which 350 patients with high-risk stage II, or stages III or IV breast cancer received XM02 (n=140), EU-filgrastim (n=136), or placebo (n=72). The statistical design of the trial included a planned non-inferiority analysis comparing XM02 to EU-filgrastim, as well as a planned analysis comparing XM02 to placebo for assay sensitivity. The primary efficacy endpoint was duration of severe neutropenia (DSN) during cycle 1 of chemotherapy (doxorubicin 60 mg/m² IV bolus and docetaxel 75 mg/m² IV). Study treatments were initiated at doses of 5 µg/kg/day subcutaneously the day after the end of chemotherapy (CTX), and discontinued when an absolute neutrophil count of $\geq 0 \times 10^9/L$ after nadir was reached.

The choice of a non-US-approved active comparator, EU-filgrastim, for the non-inferiority design aspect of the efficacy trial would be appropriate to support a non-inferiority claim for a BLA filed under section 351 (a) of the PHS Act if justification for the non-inferiority margin is supported by establishing the effect size of EU-filgrastim. No such justification was submitted by the applicant.

The two additional studies conducted in patients with cancer, XM02-03 and XM02-04, were designed to support safety, but included a DSN endpoint. XM02-03 was a multinational, randomized (2:1), controlled trial of 240 patients (XM02 = 160, EU-filgrastim = 80) with lung cancer (SCLC or advanced NSCLC with no more than 1 prior chemotherapy cycle) who received myelosuppressive platinum-based chemotherapy. Patients randomized to receive EU-filgrastim in cycle 1 received XM02 in subsequent cycles. XM02-04 was a multinational, randomized (2:1), controlled trial of 92 patients (XM02 = 63 and EU-filgrastim = 29) with chemotherapy naive aggressive NHL (permissible subtypes: diffuse large B-cell lymphoma, mediastinal large B-cell lymphoma, follicular lymphoma grade 3, anaplastic large cell lymphoma) requiring chemotherapy who received cyclophosphamide 750 mg/m² IV, doxorubicin 50 mg/m² IV, vincristine 1.4 mg/m² IV on Day 1 of each cycle, and prednisolone 100 mg/day orally from Day 1 to Day 5. Additionally, some subjects enrolled had received rituximab. Patients randomized to receive EU-filgrastim in cycle 1 received XM02 in subsequent cycles. Although both of these trials included efficacy endpoints and analyses, these analyses were exploratory and were not considered in the primary analyses of efficacy for this application.

The efficacy data upon which this application relies were obtained from 348 patients (out of 350 randomized) included in the primary analysis dataset (two patients were excluded after

randomization because they failed screening). The primary endpoint, DSN, was defined as National Cancer Institute, Common Terminology Criteria for Adverse Events (NCI CTCAE) Grade 4 neutropenia with an absolute neutrophil count (ANC) $<0.5 \times 10^9/L$. XM02 was compared to placebo for assay sensitivity and compared to EU-filgrastim for an equivalence claim between XM02 and US-approved Neupogen® with respect to the primary endpoint. The statistical analysis plan for DSN included an analysis of covariance (ANCOVA) to incorporating the factors "treatment", "country" and "adjuvant vs. metastatic therapy", with the baseline ANC as covariate. Missing ANC values were imputed by linear interpolation. Assay sensitivity with respect to DSN in Cycle 1 was to be demonstrated by comparing XM02 to placebo. If the difference was statistically significant in favor of XM02, non-inferiority between XM02 and EU-filgrastim was assessed. To demonstrate non-inferiority, the two-sided 95% confidence interval (CI) for the difference in DSN in Cycle 1 had to lie entirely within the range of (- 1 day, + 1 day). This 1 day difference was considered to be the maximum clinically acceptable difference.

The primary analysis of the efficacy data demonstrated that XM02 was superior to placebo with a highly statistically significant reduction in DSN (2.7 days reduction, $p < 0.0001$), and XM02 was non-inferior to EU-filgrastim with the 95% confidence interval (-0.26, 0.33) for mean difference in DSN lying within the 1 day margin. The data were robust, and the results were consistent with the primary analysis which confirmed the Applicant's findings. With regard to the Applicant's equivalence claim to US-approved Neupogen, although the data demonstrated that the 95% confidence interval (-0.26, 0.33) for the mean difference between XM02 and EU-filgrastim in DSN was within the 1 day non-inferiority margin, an equivalence claim for XM02 vs. US-approved Neupogen was not established because of the lack of comparative results between US-filgrastim and EU-filgrastim.

Safety data for this application were obtained from 877 subjects (200 healthy volunteers, 677 patients with cancer) who received at least one dose of XM02. The primary safety review focused on analyses of the data obtained from the three trials enrolling 677 patients with cancer who received XM02 at the dose proposed for labeling, 5µg daily administered subcutaneously. The incidences of adverse events were evaluated individually, and pooled analyses were also performed. The primary clinical reviewer also evaluated the safety database for adverse events known to be associated with marketed G-CSF products. The safety profile of XM02 compared favorably with the active comparator (EU-filgrastim) in all three trials. Bone pain was the most common adverse event, reported in 24% of patients receiving XM02 compared to 31% of patients receiving EU-filgrastim (pooled analysis, all cycles of therapy). Searches of the safety database for evidence of toxicities known to be associated with marketed G-CSF products, i.e., splenic rupture, allergic reactions, and acute respiratory distress syndrome, resulted in identification of only one case of an allergic reaction.

Although the efficacy and safety data submitted with this application would otherwise support approval, deficiencies identified by other review Divisions preclude a recommendation for approval. It is recommended that the applicant receive a Complete Response Letter. Following are brief discussions of the major deficiencies:

1. Database Integrity for Study XM02-02: Based on the findings from the Division of Scientific Investigations (DSI) inspection of the Applicant (the actual Inspection took place at (b) (4)), there are unresolved questions with regard to the integrity of the database containing all data for the single efficacy trial conducted and submitted in support of this application. DSI submitted an information request (IR) to the Applicant on August 17, 2010 requesting the details of the Applicant's standard operating procedures with regard to the management, oversight, quality control, and security of the database since the initial data lock up to the present. A response to the IR was received on September 2, 2010. As a result of the complexity and magnitude of information, the response will not be reviewed during this review cycle. In addition, the Applicant must submit a detailed analysis of the impact of their findings on the evaluation of the efficacy and safety data for all database changes made after initial database lock and unblinding.

(b) (4)

3. Inadequate Information on Analyses of the Device Closure System: A consultant review performed by the Center for Devices and Radiologic Health (CDRH) identified inadequate information in the application pertaining to analyses of the device closure system. The Applicant is relying solely on the fill weight of the syringe as the definitive property to decide if the correct amount of XM02 is being delivered through the syringe. There are physical aspects of syringes and needles such as dead space/volume that can affect the amount delivered. In addition, based on a review of DME (b) (4) (Drug Master File for (b) (4)), the syringes may not conform to current FDA consensus standards regarding syringes and needles.

4. Lack of Reproductive Toxicology Studies: Applications filed under section 351 (a) of the PHS Act require assessments of the nonclinical developmental and reproductive risks associated with the product. In general, an embryo-fetal toxicology study in a single species is required. However in the past, for certain agents that are well characterized with regard to their effect on nonclinical developmental and reproductive risk, FDA has relied upon class effects to inform risk communication in labeling. In lieu of an embryo-fetal toxicology study, the Applicant provided a review of the scientific literature to support their contention that embryo-fetal toxicology studies are not necessary for this application and to demonstrate the class effects of G-CSF products. A review of the literature assessment by the Division's nonclinical review team concluded that the developmental and reproductive toxicities associated with recombinant G-CSF products, primarily an abortifacient effect, were well-characterized and consistent within the scientific class. A class labeling approach to communicate the developmental and reproductive risks of XM02 would be acceptable to the nonclinical review team. However, the Division was advised by the Office of Regulatory Policy (ORP), the Office of Chief Counsel (OCC), the Biosimilar Review Committee, and the Biosimilar Implementation Committee that the literature assessment of the potential reproductive toxicity

of XM02 does not fulfill the regulatory requirements for assessing nonclinical developmental and reproductive toxicity under section 351(a) of the PHS Act. An application filed under this section may not rely on published literature describing studies of other biological products, including licensed products, to fulfill the requirement. Therefore, the nonclinical team is recommending that this application receive a CR Letter, and that results from the complete battery of fertility, embryo-fetal and pre/post natal nonclinical development toxicity studies will be required

5. Microbial Control for Drug Substance Manufacturing Process: Inspection of the drug substance manufacturing site revealed there were no routine in-process tests for bioburden and endotoxin control (b) (4)

Routine monitoring for bioburden and bacterial endotoxins should be conducted since several batches with high counts were identified and the (b) (4) produces high amounts of endotoxin in the process. The applicant has proposed several changes to the filgrastim drug substance manufacturing process to address the issues identified at inspection and improve microbial control. However, the proposed changes and validation for these changes will not be complete until after the PDUFA action date for this application.

6. Unacceptable Proper Name, (b) (4): The proper name submitted by the applicant, (b) (4), is not acceptable (b) (4)

2. Background

Granulocyte colony-stimulating factor (G-CSF) is a hematopoietic cytokine and an endogenous growth factor that regulates the proliferation and differentiation of progenitor cells within the bone marrow and the release of mature neutrophils into the peripheral blood. G-CSF is a positive regulator of granulopoiesis, acting at different stages of myeloid cell development. G-CSF enhances the effector functions of normal mature neutrophils, including chemotaxis, phagocytosis and oxidative metabolism. It exerts its effects via a high-affinity G-CSF-specific receptor mechanism, accounting for its selective action as compared with many other cytokines. The endogenous, human form of G-CSF is a glycoprotein composed of a single polypeptide chain of (b) (4) amino acids. A bacterially synthesized, non-glycosylated commercial recombinant methionyl human G-CSF (r-metHuG-CSF) was approved by FDA in 1991 under the proper name filgrastim (Neupogen®). Neupogen is indicated to decrease the incidence of infection, as manifested by febrile neutropenia (FN), in patients with nonmyeloid malignancies receiving myelosuppressive chemotherapy (CTX), and for reducing the time to neutrophil recovery and the duration of fever following induction or consolidation chemotherapy treatment of adults with AML. Neupogen is also indicated for reducing the duration of neutropenia in patients undergoing myeloablative therapy followed by bone marrow transplantation, and for the mobilization of autologous peripheral blood stem cells as monotherapy or after myelosuppressive CTX. Finally, Neupogen is indicated in long-term treatment of severe congenital, cyclical or idiopathic neutropenia.

Intensive cytotoxic chemotherapy for the treatment of cancer often results in profound neutropenia, which may lead to hospitalization for treatment of fever or to potentially fatal infections. The most widely accepted definition of neutropenia is an absolute neutrophil count (ANC) <500 cells/ μL or $<1,000$ cells/ μL with a predicted nadir of <500 cells/ μL . There is an increased risk of occult infection in patients with an ANC $<1,000$ cells/ μL , and the risk of infection increases as the ANC decreases. Fever in a neutropenic patient is usually defined as a single temperature of $>38.3^{\circ}\text{C}$ (101°F), or a sustained temperature $>38^{\circ}\text{C}$ (100.4°F) for more than one hour. Patients who are neutropenic may not exhibit fever as their presenting symptom despite the presence of infection. This occurs more often in elderly patients or patients receiving corticosteroids or other anti-pyretics.

Factors contributing to the pathogenesis of febrile neutropenia include the direct effects of chemotherapy on mucosal barriers and immune deficits related to the underlying malignancy. Chemotherapy-induced mucositis followed by seeding of the blood stream with endogenous flora from the entire GI tract is believed to explain a majority of febrile neutropenic episodes. Obstruction of the lymphatics, biliary tract, bronchial, gastrointestinal or urinary systems by tumors, or as a result of surgical procedures, or infections related to indwelling catheters are also common causes of infections. Immune defects related to underlying malignancies also put patients at higher risk for infections.

Colony Stimulating Factors (CSFs) have been evaluated for prophylactic use following the administration of chemotherapy when neutropenia is anticipated ("primary prophylaxis"), during retreatment after a previous cycle of chemotherapy causing febrile neutropenia ("secondary prophylaxis"), and to shorten the duration of severe chemotherapy-induced neutropenia without fever ("afebrile neutropenia"). CSFs have also been evaluated as an adjunct to other therapies in patients with febrile neutropenia. The likelihood of developing febrile neutropenia is the primary factor determining whether or not prophylactic CSFs are indicated. The incidence of febrile neutropenia following treatment is influenced by the intensity of chemotherapy, the degree of injury to the gastrointestinal mucosa, the presence of underlying damage to the patient's hematopoietic stem cells, the concurrent use of radiation, and the overall clinical status of the patient. Current American Society of Clinical Oncology guidelines recommend prophylactic treatment with CSFs when the expected incidence of febrile neutropenia is over 20 percent. Treatment is suggested to reduce the need for hospitalizations for antibiotic therapy. If the incidence of febrile neutropenia is expected to be less than 10 percent following chemotherapy, CSFs are not recommended for routine primary prophylaxis. CSFs can also be used to maintain dose-dense or dose-intense chemotherapy strategies having survival benefits, or in settings where reductions in chemotherapy dose-intensity or dose-density are known to be associated with a poorer prognosis. When the risk of febrile neutropenia would prevent the administration of full doses of potentially curative chemotherapy, administration of CSFs is recommended for secondary prophylaxis in lieu of dose reduction. In patients with established afebrile neutropenia, CSFs are not recommended.

In the United States, in addition to filgrastim (Neupogen), the other currently approved G-CSF product is pegfilgrastim (Neulasta). Pegfilgrastim received regular approval in 2002. Current labeled indications are to decrease the incidence of infection, as manifested by febrile

neutropenia, in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a clinically significant incidence of febrile neutropenia.

The proposed indication for XM02 is a reduction in the duration of severe neutropenia and the incidence of febrile neutropenia in patients with cancer treated with myelosuppressive chemotherapy. The formulation of XM02 has the same excipients as EU-filgrastim (the active comparator in the single efficacy trial), (b) (4). (b) (4).

The IND under which this product was originally filed, IND 103188, was the subject of a pre-IND/Pre-BLA meeting held on November 25, 2008. The Applicant informed FDA of their intention to submit a BLA for XM02, which had received Marketing Authorization approval as a biosimilar product by the European Agency for the Evaluation of Medicinal Products (EMA) on September 15, 2008. EMA approval was based upon safety and efficacy studies conducted outside of the United States from 2003 – 2006. **The completed clinical program included two Phase I studies conducted in a total of 200 healthy volunteers, one study designed to investigate efficacy and safety in 348 patients, and two additional safety studies in 329 patients randomized 2:1 to XM02 versus Neupogen. The studies were as follows:**

1. XM02-01-LT, Comparative study of pharmacodynamic and pharmacokinetic parameters of XM02 and Neupogen when formulations are given to healthy volunteers
2. XM02-05-DE, Study on the bioequivalence of 5 µg/kg or 10 µg/kg of XM02 and Neupogen, each after intravenous or subcutaneous administration, in healthy female and male subjects. A multi-center, randomized, single dose, single blind, two-way crossover design
3. XM02-02-INT, Efficacy and safety of XM02 compared to Neupogen in patients with breast cancer receiving chemotherapy, a multinational, multi-center, randomized, controlled study
4. XM02-03-INT, Safety and efficacy of XM02 in patients with small cell or non-small-cell lung cancer receiving platinum-based chemotherapy, a multi-national multi-center, randomized, controlled study
5. XM02-04-INT, Safety and efficacy of XM02 in patients with Non-Hodgkin's-Lymphoma receiving chemotherapy, a multi-national, multicenter, randomized, controlled study

In draft responses to the Applicant's questions for the pre-IND meeting, FDA noted with regard to the XM02 development program:

"The only efficacy endpoint that incorporated appropriate alpha adjustment was the duration of severe neutropenia endpoint (DSN) in Study XM02-02-INT. All other efficacy endpoints in the three studies were exploratory analyses.

The study design and statistical analysis plan were not discussed with FDA prior to initiation. We have the following comments that would need to be addressed in order to file the proposed license application:

- a. Based on historical information, a clinically important incidence of febrile neutropenia is present only when the duration of severe neutropenia is 5 or more days in the absence of prophylactic antibiotics. The application should provide evidence that the clinical setting (average DSN in the placebo arm for the same patient population/chemotherapy regimen) in which XM02 was evaluated is one that requires growth factor support to avoid a clinically important risk of febrile neutropenia. Such evidence is necessary to support the proposed claim of a clinical benefit (reduction in incidence of febrile neutropenia) based on the surrogate of reduction in DSN.
- b. Replication of the treatment effect in multiple trials. Ordinarily, a minimum of two adequate and well-controlled trials are required.
- c. For comparisons to an active control (Neupogen) to be considered, the following information should be provided in the BLA
 - 1) Data establishing the treatment affect size (i.e., difference in DSN between the placebo and Neupogen) in this clinical setting defined by the patient population and background chemotherapy regimen. Ordinarily, such evidence should be replicated across multiple studies.
 - 2) Justification of the proposed non-inferiority margin; the fraction of the treatment effect for the active control that is to be established for XM02 should be sufficient to confer a clinical benefit.
 - 3) The comparisons should be performed in both the intent-to-treat and the per-protocol populations. A definition for the per-protocol population should be included in the statistical analysis plan. If substantial differences are observed between the two populations, this may be indicative of poor study conduct.
- d. In light of the absence of an abbreviated approval pathway under section 351 of the PHS Act, this study will not support claims based on comparability to Neupogen nor will it support claims based on extrapolation to other indications for which Neupogen is approved.”

The application for XM02 was submitted under the Public Health Service Act (PHS Act, 42 U.S.C. 262), section 351 (a), Licensure of Biological Establishments and Products. Subsequent to the filing, passage of the Patient Protection and Affordable Care (PPAC) Act created an abbreviated pathway for approval of biologic products which is described under a subtitle of the PPAC Act, the Biologics Price Competition and Innovation (BPCI) Act of 2009. Under the BPCI Act, an applicant may seek approval for a “biosimilar” product under the requirements of a new section of the PHS Act, section 351 (k). A thorough understanding of the regulatory requirements governing each potential approval pathway is essential to understanding several of the issues raised during the review of this application.

3. CMC/Device

Product Manufacturing: *The following excerpts and summary, revised for this review, are based on the review provided by the Division of Therapeutic Proteins, Office of Biotechnology Products, OPS.*

The Division of Therapeutic Proteins, Office of Biotechnology Products, OPS recommends approval for Neuroval. The data submitted in the application are adequate to support the conclusion that the manufacture of Neuroval is well controlled, and leads to a product that is safe, pure and potent. It is recommended that this product be approved for human use under conditions specified in the package insert.

The Applicant has appropriately characterized the XM02 molecule through a series of characterization studies using both stressed and unstressed molecules. The Applicant used these studies, in addition to data from their manufacturing history and clinical trial material, to support the release and stability specifications for XM02. The release and stability specifications appropriately control product variants that are the result of the manufacturing process (e.g., host cell DNA) and long-term storage (e.g., methionine oxidation and deamidation).

The manufacturing process is well controlled and consistently produces pure and potent XM02. The Applicant demonstrated manufacturing consistency for the drug substance through process validation and 69 commercial scale (b) (4) lots produced at the cGMP facility in Lithuania. The manufacturing consistency for the drug product was demonstrated through process validation studies conducted with two full-scale drug product batches. The two drug product batches represent the 300 µg/0.5 ml and 480 µg/0.8 ml strengths. In addition, The Applicant included in-process data as well as batch analysis data from four drug product batches manufactured at a pilot scale, and provided data demonstrating comparability between the manufacturing scale and pilot scale lots of the drug product.

The proposed storage conditions and expiration dates are supported by stability data. (b) (4)

XM02 drug substance is stable when stored at (b) (4) for up to (b) (4) and the drug product is stable when stored at 5°C ± 3°C for up to 36 months.

The Applicant will be required to address immunogenicity issues related to their antibody assay by means of a Postmarketing Requirement (PMR). This is not an approvability issue because immunogenicity-related adverse events such as extended neutropenia or loss of efficacy were not observed in the XM02 clinical trials. In the absence of safety or loss-of-efficacy signals that could be attributed to anti-drug antibodies, it is acceptable to address the lack of immunogenicity data through post-marketing studies. At the same time, it is critical that the data be obtained so that the safety profile of the drug can be more fully understood. In addition, these assays should be available in the post-marketing environment to allow for the rapid evaluation of serum samples from patients with adverse events that might be attributable to the presence of anti-drug antibodies.

The PMR will assess the induction of anti-GCSF antibodies in serum from treated patients using validated assays. The Applicant will:

- a. establish validated screening, confirmatory and neutralizing assays to assess the immunogenicity of Neuroval in patient samples.
- b. establish validated assays to assess the ability of anti-Neuroval antibodies to cross-react with native human GCSF.
- c. analyze patient serum samples from the Neuroval phase 3 studies for the presence of anti-Neuroval and anti-native human GCSF antibodies using validated screening, confirmatory and neutralizing assays.

Facilities Review/Inspection: *The following excerpts and summaries, revised for this review, are based on the reviews provided by the Biotech Manufacturing Team, Office of Compliance.*

Drug Substance:

The application is not recommended for approval because of one microbiology deficiency regarding microbial control of the drug substance manufacturing process. The inspection of the drug substance manufacturing site revealed there were no routine in-process tests for bioburden and endotoxin control (b) (4)

Routine monitoring for bioburden and bacterial endotoxins should be conducted as there have been several batches with high counts and as the (b) (4) produces high amounts of endotoxin in the process. Endotoxins are defined as process-related impurities.

The Applicant has proposed several changes to the drug substance manufacturing process to address the issues identified at inspection and improve microbial control. However, the proposed changes and validation for these changes will not be complete until after the action date for this application. The applicant should submit data from these studies prior to reconsideration of this application for approval. Specifically, the following data should be submitted for review:

- a. In-process and final XM-02 bioburden and endotoxin data for the (b) (4) following the proposed changes.
- b. Microbial control data for storage (b) (4)
- c. Any other changes and data that could affect microbial process control (for example, changes in hold times).

Drug substance and drug product manufacturing facilities at SICOR Biotech, Vilnius Lithuania and TEVA Pharmaceutical Industries, Ltd., Kfar Saba, Israel, respectively, were inspected.

The drug substance is manufactured by SICOR Biotech UAB in Vilnius, Lithuania (FEI 3008110727). The site has never been inspected by FDA. A pre-license inspection was

conducted May 31-June 4, 2010. Several recommendations were made to the firm but there were no 483 observations. Initial classification is NAI.

Drug Product: The submission was reviewed from a CMC microbiology and sterility assurance perspective and is recommended for approval with post-marketing commitments to address the following issues:

- **Shipping Qualification:** Assessment of plunger movement, container closure integrity and package integrity after shipping of the filgrastim drug product from Kfar Saba, Israel to the US distribution site should be performed in a shipping qualification study. The data derived from the shipping qualification studies using worst case conditions (temperature, duration, shock impact) with minimum and maximum loads should be submitted in a CBE-30 supplement by a date to be provided by the Applicant.
- (b) (4) Data on (b) (4) accumulated after manufacture of 30 commercial batches and any changes to currently proposed (b) (4) action limits of (b) (4) prior to (b) (4) should be obtained. The data should be submitted in a CBE-30 supplement by a date to be provided by Applicant.

Device: *The following excerpts and summary, revised for this review, are based on the consult review provided by the Center for Devices and Radiologic Health.*

(b) (4)

The Applicant is relying solely on the fill weight of the syringe as the definitive property to decide if the correct amount of XM02 is being delivered through the syringe. There are physical aspects of syringes and needles such as dead space/volume that can affect the amount delivered. In addition, there have been several complaints from the medical community regarding the (b) (4), and the ability for users to manipulate them. Additionally, based on a review of DMF (b) (4) (Drug Master File for (b) (4)), the syringes may not conform to current FDA consensus standards regarding syringes and needles. (b) (4)

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4. Nonclinical Pharmacology/Toxicology

The following excerpts and summary, revised for this review, are based on the review provided by Mary Jane Masson Hinrichs, Ph.D., Division of Biologic Oncology Products.

Among the regulatory requirements to support approval of a BLA under section 351 (a) of the PHS Act are assessments of the nonclinical developmental and reproductive risks associated with the product. In general, an embryo-fetal toxicology study in a single species is required. However, class effects of certain agents that are well characterized with regard to their effect on nonclinical developmental and reproductive risks have been relied upon to support risk communication in labeling in the past. These effects have been demonstrated by an assessment of the scientific literature. The Applicant in this case has not performed an embryo-fetal toxicology study, but instead has provided a literature assessment of the developmental and reproductive risks. During the review cycle, the Division was advised by the Office of Regulatory Policy (ORP), the Office of Chief Counsel (OCC), the Biosimilar Review Committee, and the Biosimilar Implementation Committee that a literature assessment of the potential reproductive toxicity of XM02 does not fulfill the regulatory requirements for assessing nonclinical developmental and reproductive toxicity under section 351(a) of the PHS Act. An application filed under this section may not rely on published literature describing studies of other biological products, including licensed products, to fulfill the requirement. As a result, the nonclinical team recommends that this application receive a CR Letter which notifies the Applicant that a full battery of reproductive toxicology studies is required.

Nonclinical safety of XM02 was assessed in two Good Laboratory Practices (GLP) 26-week repeat dose toxicity studies with 4-week recovery periods in rats (doses of 0, 5, 50, and 500 µg/kg/day) and monkeys (doses of 0, 5, 25, and 125 µg/kg/day), as well as a standard battery of GLP safety pharmacology studies. From the repeat dose toxicity studies, the rat was determined to be the most sensitive species because of a significant number of animal mortality (20%) in the high dose group. As a result, 50 µg/kg/day was determined to be the maximum tolerated dose (MTD) of XM02 in the rat. In contrast, there were no deaths or adverse clinical signs in the monkey repeat dose toxicity study at doses of XM02 up to 125 µg/kg/day. The major toxicities associated with XM02 treatment in both species, i.e., bone marrow hypercellularity, enlarged spleens, increased alkaline phosphatase (ALP), extramedullary hematopoiesis (rat), and granulocyte infiltrations (monkey), were dose-dependent, related to the exaggerated pharmacology of G-CSF, and reversible in recovery animals. Similarly, the bone (joint) findings of painful, swollen hind limbs that led to the premature euthanization of a number of the animals in the high dose group in the rat repeat dose toxicity study, were dose-dependent, reversible, and also likely related to the exaggerated pharmacology of G-CSF since there were histological findings of hyperostosis and granulocytic infiltrates in articular surfaces and surrounding soft tissue of the bone. There were no detectable effects on the respiratory or central nervous system in rats or the cardiovascular system in dogs after a single dose of 3500 µg/kg XM02 in the GLP safety pharmacology studies.

There were no specific genotoxicity or carcinogenicity studies performed with XM02 since genotoxicity studies are not appropriate for large molecular weight proteins and a carcinogenicity assessment is not warranted for the intended patient population.

There were no developmental and reproductive toxicology studies conducted with XM02. The Applicant's proposed justification for the absence of these studies was based on the clinical indication, which limits use of XM02 to cancer patients receiving concomitant therapy with

anti-cancer agents with known reproductive and developmental risks. Upon review of this justification by the nonclinical review team, it was determined that it would be unethical to not communicate the potential reproductive and developmental risks associated with XM02 to patients and prescribers since there are currently two US-licensed recombinant G-CSF products that are labeled with this information. As a result, the Applicant was requested to provide an assessment of the potential reproductive toxicity of XM02 as an amendment to the BLA. In response to this request, the Applicant submitted a literature-based assessment of the reproductive toxicities associated with other G-CSF receptor agonists to support a 'class-labeling' approach. Upon review of the submitted literature, it was determined by the Pharmacology/Toxicology primary and secondary reviewers that the developmental and reproductive toxicities associated with recombinant G-CSF products, primarily an abortifacient effect, were well-characterized and consistent within the scientific class. A class labeling approach to communicate the developmental and reproductive risks of XM02 was deemed acceptable from the nonclinical perspective. However, as noted previously, during the review cycle the Division was advised by ORP, OCC, the Biosimilar Review Committee, and the Biosimilar Implementation Committee that a literature assessment of the potential reproductive toxicity of XM02 does not fulfill the regulatory requirements for assessing nonclinical developmental and reproductive toxicity under section 351(a) of the PHS Act. As a result, the nonclinical team has amended their review to recommend that this application receive a CR Letter which notifies the Applicant that a full battery of reproductive toxicology studies is required.

5. Clinical Pharmacology/Biopharmaceutics

The following excerpt, revised for this review, is based on the review provided by Sarah Schrieber, Pharm.D., Division of Clinical Pharmacology 5

XM02, Neutroval, is a recombinant methionyl human granulocyte colony-stimulating factor (G-CSF) produced by recombinant DNA technology using the bacterial strain *Escherichia coli* K802. It has a molecular weight of 18,799 Dalton and is composed of 175 amino acids. Neutroval is not glycosylated and contains a methionine residue at its amino (NH₂)-terminal end that is not present on endogenous human G-CSF. Neutroval is a sterile, clear, colorless, preservative-free solution containing (b) (4), glacial acetic acid, sorbitol, polysorbate 80, and Water for Injection.

The selection of dose and dose regimen for the efficacy and safety trials were based on data obtained in the phase 1 trials and historical clinical use with an FDA-approved product, Neupogen® (Amgen). To support this application, two phase 1 PK/PD trials in healthy volunteers (N=176) and three phase 3 trials in patients with breast cancer, lung cancer, or non-Hodgkin lymphoma (NHL) (N=348, 240, and 92, respectively) were conducted.

The pharmacokinetics (PK) and pharmacodynamics (PD) of XM02 were studied in healthy subjects and patients with cancer.

Pharmacokinetics Findings:

Healthy Subjects: Subjects in the phase 1 trials were assigned to receive single 5 µg/kg or 10 µg/kg IV or SC doses of Neutroval or European Neupogen (EU Neupogen). The absolute bioavailability of these doses were 33% and 45%, respectively. After single dose SC

administration of 5 $\mu\text{g/kg}$ Neutroval (N=33), the geometric mean (CV%) of serum C_{max} was 18 ng/mL (41%) and of $\text{AUC}_{0-48\text{h}}$ was 158 ng $\cdot$ h/mL (37%). The median T_{max} was 6 hours and the median half-life ($t_{1/2}$) was 8.9 hours. Increasing the dose of Neutroval from 5 to 10 $\mu\text{g/kg}$ resulted in an approximately 3-fold increase in both C_{max} and $\text{AUC}_{0-48\text{h}}$.

Cancer Patients: PK data were obtained from patients with breast cancer, lung cancer and NHL (N=12 per group) who received SC Neutroval 5 $\mu\text{g/kg/day}$. Following the 1st Neutroval dose in cycle 1, the geometric mean (CV%) of serum C_{max} and $\text{AUC}_{0-24\text{h}}$ were 36 ng/mL (41%) and 305 ng $\cdot$ h/mL (35%) in breast cancer, 25 ng/mL (60%) and 273 ng $\cdot$ h/mL in lung cancer (61%), and 20 ng/mL (24%) and 184 ng $\cdot$ h/mL (23%) in NHL, respectively. For the 3 groups combined, the median T_{max} was between 4 to 6 hours and the median $t_{1/2}$ was between 3.2 to 3.8 hours. The terminal half-life was calculated from serum levels measured up to 24 hours as compared to up to 48 hours in the healthy subjects. Accumulation after repeated dosing was not observed. No dose adjustment based on cancer type is warranted.

No gender-related differences were observed in the PK of Neutroval following SC administration. The PK profile in patients with renal or hepatic impairment has not been assessed.

Pharmacodynamic Findings:

Healthy Subjects: In healthy subjects who received a single SC Neutroval dose of 5 or 10 $\mu\text{g/kg}$, a transient decrease in the ANC occurred during the first hour, followed by an increase in ANC. Following subcutaneous 5 $\mu\text{g/kg}$ (N=61), the mean maximum ANC was $22 \times 10^9/\text{L}$; the median time to peak ANC was 12 hours. After subcutaneous 10 $\mu\text{g/kg}$ (N=58), the mean maximum ANC was $26 \times 10^9/\text{L}$; the median time to peak ANC was between 14 to 18 hours. The ANC returned to baseline by 4 days post-dose.

Cancer Patients: In cancer patients receiving various chemotherapies (N=361), SC Neutroval 5 $\mu\text{g/kg}$ was administered daily starting 24 hours after the completion of chemotherapy until an ANC of $10 \times 10^9/\text{L}$ after a nadir was reached or after 14 days of Neutroval dosing, whichever occurred first. During cycle 1, the time to maximum mean ANC was between 3 to 5 days, and then ANC decreased to a nadir by 7 to 11 days following chemotherapy. Mean ANC values returned to baseline by 21 days following completion of chemotherapy. The ANC profile was similar in subsequent chemotherapy cycles.

In a phase 1 study, XM02-05-DE it was determined that the absolute bioavailability of SC XM02 was 33% and 45% for the 5 $\mu\text{g/kg}$ and 10 $\mu\text{g/kg}$ dose, respectively. Intravenous pharmacokinetic data are available in humans; however, an indication for IV administration will not be granted for this application.

No drug distribution study and no drug metabolism study were conducted for XM02. These studies are not generally performed for biologic products because they are proteins which are degraded into amino acids that then recycled into other proteins.

Data from 124 healthy volunteers in trial XM02-05-DE demonstrated that gender did not alter the PK or PD of XM02 following SC dosing (TableXX). However, following XM02 IV administration, both AUC and C_{max} were reduced in females as compared to males. ANC

parameter values were similar between males and females regardless of XM02 dose or administration route. CD34+ AUC and C_{max} values were slightly decreased in females compared to males regardless of XM02 dose or administration route.

Study XM02-05-DE: Effect of Gender on XM02 SC Single dose PK or PD.

Parameter Geomean (CV%)	XM02 5 µg/kg SC		XM02 10 µg/kg SC	
	Male (N=18)	Female (N=15)	Male (N=15)	Female (N=15)
AUC _{0-t} (ng/mL*h)	166 (34)	148 (41)	455 (32)	488 (20)
C _{max} (ng/mL)	18.7 (37)	17.2 (47)	43.3 (39)	49.4 (24)
ANC AUC _{0-t} (h*10 ⁹ /L)	968.9 (33)	942.8 (26)	1385.9 (23)	1230.6 (34)
ANC _{max} (10 ⁹ /L)	22.9 (28)	22.3 (20)	27.2 (21)	26.7 (27)

Insufficient data were available to determine the effects of other intrinsic factors.

Specific renal impairment PK/PD studies were not conducted. In the three oncology clinical trials, renal impairment was defined as a baseline serum creatinine > 2 mg/dl; there was only 1 patient enrolled in XM02-04-INT (NHL trial) with a baseline serum creatinine meeting the protocol definition. However, creatinine clearance (CrCL) was retrospectively calculated using the Cockcroft-Gault formula for all patients enrolled in the oncology trials. Based on the analysis, additional patients with renal impairment were identified. Of the patients with available PK data, 23 were identified to have normal renal function (CrCL >89 mg/ml), 11 had mild renal impairment (CrCL 60-89 ml/min), and 2 had moderate renal impairment (CrCL 30-59 ml/min). Bone pain was the most prominent and specific adverse event known to be related to treatment. Therefore, it would be expected that any change in G-CSF blood concentrations would potentially change the incidence of bone pain. The incidence of bone pain following chemotherapy Cycle 1 is presented in Table XX. Although the number of patients in each group is small, degree of renal impairment was not associated with an increased incidence of bone pain. No PMCs or PMRs will be required of the applicant with regard to renal impairment.

Incidence of Bone Pain in Patients with Renal Impairment (All Studies)

		Normal RF	Mildly impaired RF	Moderately impaired RF
Study XM02-02	XM02	7.8% (6)	3.8% (2)	0
	Neupogen [®]	11% (9)	8% (4)	0
Study XM02-03	XM02	4% (3)	5.6% (4)	0
	Neupogen [®]	4.3% (2)	0	0
Study XM02-04	XM02	10.8% (4)	9.5% (2)	0
	Neupogen [®]	0	0	0

There were no hepatic impairment studies conducted; however 10 patients in the three oncology trials met the definitions of hepatic impairment included in the protocols (i.e., baseline ALT > 3 times the upper limit of normal [ULN], or baseline AST > 3 times ULN). None of the patients identified had PK data available for analysis. No PMCs or PMRs will be required of the applicant with regard to hepatic impairment.

There are no clinical data on the safety of using XM02 in pregnancy, or its effects on the development of the fetus. Preclinical studies on reproductive and developmental toxicity were not performed. There are reports in the scientific literature in which transplacental passage of filgrastim has been demonstrated in humans. The potential risk for humans, however, is unknown.

Filgrastim and human G-CSF products are poorly secreted in breast milk and G-CSF is not orally absorbed by neonates.

There were inadequate data submitted to assess the potential effects of XM02 on the QTc interval since ECGs were obtained at times when XM02 was cleared from systemic circulation. However, summary data of post-marketing safety reports since XM-02 was approved in Europe (September, 2008) indicate no prolongation of the QTc in (b) (4) daily doses administered (through March 31, 2010). One case of syncope was reported and an ECG obtained during the episode was reported as normal. In addition, there were no sudden deaths reported in the post marketing period. From the scientific literature, a study by *Guneysel et al.* demonstrated no statistically significant differences between baseline and any subsequent QTc interval measurements in a population of 102 neutropenic patients, treated with Neupogen® (Roche, Basel, Switzerland) 5 µg/kg/day SC for 2 days (Clin Drug Invest. 2009;29:551-55). The overall weight of these data suggest the potential risk of XM02 to prolong the QTc interval appears to be minimal. However, a study to evaluate the effects of XM-02 on the QTc will be required of the applicant in the postmarketing period.

The incidence of XM-02 binding and neutralizing antibodies reported from the clinical studies is not reliable because the assay methods employed were not validated (see additional discussion under section 3, above).

From a Clinical Pharmacology perspective, the application is acceptable provided that an adequately designed thorough QT study is conducted to evaluate the effects of Neutroval on the QTc interval.

6. Clinical Microbiology

Not applicable to this BLA.

7. Clinical/Statistical- Efficacy

The following excerpts and summary, revised for this review, are based on the reviews provided by Laura Lu, Ph.D., statistical reviewer, Division of Biometrics V and Thomas Herndon, M.D., clinical reviewer, Division of Biologic Oncology Products.

Based on the efficacy data provided in this submission, the primary statistical reviewer (Office of Biostatistics, Division of Biometrics V) and primary clinical reviewer (Office of Oncology Drug Products, Division of Biologic Oncology Products) recommend approval of this application. Secondary reviews were in agreement with the primary reviews.

The clinical development program for XM02 was designed to support a filing for Marketing Authorization as a biosimilar product in the European Union (EU). XM02 was approved by the EMEA as Tevagrastim in September, 2008 with EU-approved Neupogen as the referenced

product. The first interaction between FDA and the Applicant occurred during a pre-IND/pre-BLA meeting (under IND 103188) held on November 25, 2008. The Applicant informed FDA of their intention to submit a BLA for XM02 that would be based on the completed data from their EMEA filing. Since the development plan, design of the study intended to support efficacy, and the statistical analysis plan were not discussed with FDA prior to initiation and completion of development, FDA discussed the specific requirements necessary to support a regulatory filing for XM02 in the United States with the Applicant. The following issues were addressed:

Demonstration of Clinical Benefit: FDA advised that based on historical information, a clinically important incidence of febrile neutropenia is deemed present only when the duration of severe neutropenia is 5 or more days in the absence of prophylactic antibiotics. An application should provide evidence that the clinical setting (average DSN in the placebo arm for the same patient population/chemotherapy regimen) in which XM02 was evaluated is one that requires growth factor support to avoid a clinically important risk of febrile neutropenia. This evidence is necessary to support a proposed claim of a clinical benefit (reduction in incidence of febrile neutropenia) based on the surrogate of reduction in duration of severe neutropenia (DSN).

Replication of Treatment Effect in Multiple Trials: FDA advised that, in general, a minimum of two adequate and well-controlled trials are required to support a regulatory filing.

Active Control Comparisons: To support active control comparisons, data (defined by the patient population and background chemotherapy regimen) establishing the treatment effect size (i.e., difference in DSN between the placebo and Neupogen) is required in the clinical setting in which XM02 was studied. In addition, justification of the proposed non-inferiority margin, i.e., the fraction of the treatment effect for the active control that is to be established for XM02, should be sufficient to confer a clinical benefit. Finally, comparisons should be performed in both the intent-to-treat and the per-protocol populations; and a definition for the per-protocol population should be included in the statistical analysis plan.

No Abbreviated Approval Pathway for Biologics: FDA informed the Applicant that in light of the absence of an abbreviated approval pathway under section 351 of the PHS Act, the proposed study would not support claims based on comparability to US-approved Neupogen, nor would it support claims based on extrapolation to other indications for US-approved Neupogen.

Study XM02-02 was submitted as the single trial to support efficacy for the proposed indication, a reduction in the duration of severe neutropenia (DSN) and the incidence of febrile neutropenia in patients treated with myelosuppressive chemotherapy. The study was a multinational, controlled, randomized (2:2:1) trial which enrolled 350 patients with high-risk stage II, or stages III or IV breast cancer who received XM02 (n=140), EU-approved filgrastim (n=136), or placebo (n=72). The primary efficacy endpoint was duration of severe neutropenia (DSN) during cycle 1 of chemotherapy (doxorubicin 60 mg/m² IV bolus and

docetaxel 75 mg/m² IV). Study treatments were initiated at doses of 5 µg/kg/day subcutaneously the day after the end of chemotherapy (CTX) and discontinued when an absolute neutrophil count of $\geq 0 \times 10^9/L$ after nadir was reached.

The efficacy data for study XM02-02 were obtained from 348 patients (out of 350 randomized) included in the primary analysis dataset (two patients were excluded after randomization because they failed screening). The primary efficacy endpoint, DSN in cycle 1, was defined as NCI CTCAE Grade 4 neutropenia with an absolute neutrophil count (ANC) $< 0.5 \times 10^9/L$. The DSN statistical analysis plan included an analysis of covariance (ANCOVA) to include the factors "treatment", "country" and "adjuvant vs. metastatic therapy", with the baseline ANC as covariate. Missing ANC values were imputed 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 statistically significant in favor of XM02 (two-sided $p \leq 0.05$ with shorter DSN for XM02), non-inferiority between XM02 and EU-filgrastim was assessed. To demonstrate non-inferiority, the two-sided 95% confidence interval (CI) for the difference in DSN in Cycle 1 had to lie entirely within the range of (- 1 day, + 1 day). This 1 day difference was considered to be the maximum clinically acceptable difference.

Primary analysis of the efficacy data demonstrated that XM02 was superior to placebo for DSN. Observed was a highly statistically significant reduction in DSN (2.7 days reduction in DSN, $p < 0.0001$), and XM02 was non-inferior to EU-filgrastim with the 95% confidence interval (-0.26, 0.33) for the mean difference in DSN lying within the 1 day margin. Because of the highly statistically significant result for the primary analysis, a second trial to support efficacy will not be required.

Subgroup analyses results based on age, race, and type of chemotherapy were consistent with the results of the primary analysis. Subgroup analysis by gender was not performed because the large majority of patients in the study were women (99.4%).

The statistical reviewer expressed concerns focused on the Applicant's methods for data replacement and imputation. In order to address the concerns and test whether the data were robust, sensitivity analyses were performed. The results were consistent with the primary analysis and confirmed the Applicant's findings.

With regard to the Applicant's claim of equivalence to US-approved Neupogen, although the data demonstrated that the 95% confidence interval (-0.26, 0.33) for the mean difference between XM02 and EU-filgrastim in DSN lay within the 1 day non-inferiority margin deemed clinically acceptable, a demonstration of non-inferiority does not confer (under US law) a right to make a claim of equivalence. In addition, no comparability data for EU-filgrastim and US-filgrastim were provided in the application. During the review cycle, the Applicant was requested to provide additional data to support their comparative claim; however, they argued

(b) (4)

. FDA does not agree with this argument.

(b) (4)

(b) (4). Any effort to establish comparability between the two products would require the submission of the results from adequate comparability studies.

8. Safety

The following excerpts and summary, revised for this review, are based on the review provided by Thomas Herndon, M.D., clinical reviewer, Division of Biologic Oncology Products.

Safety data for this application were obtained from 877 subjects (200 healthy volunteers, 677 patients with cancer) who received at least one dose of XM02. The primary safety review focused on analyses of the data obtained from the 677 patients with cancer in three clinical trials (Studies XM02-02, XM02-03, and XM02-04) who received XM02 at the dose proposed for labeling, 5µg daily administered subcutaneously. Adverse events (AEs) reported in the three trials were analyzed, and pooled analyses of the data were also performed. In addition to analyses of the adverse events from these trials, the primary reviewer evaluated the safety database for adverse events known to be associated with other marketed G-CSF products (i.e., splenic rupture, allergic reactions, and acute respiratory distress syndrome). The safety profile of XM02 compared favorably with the active comparator, EU-filgrastim, in all three trials. Bone pain was the most common adverse event identified in the pooled analysis of all cycles of therapy. Searches of the database for known toxicities associated with other G-CSF products identified only one case of an allergic reaction (bronchospasm during cycle 1 following the 10th dose of XM02).

The primary clinical reviewer evaluated all available data (i.e., line listings, case report forms, clinical narratives) in completing the analyses related to patient deaths, serious adverse events (SAEs), discontinuations due to AEs, general AEs, and laboratory test results. Because of the randomization scheme employed by the trials, more patients received XM02 than received either placebo or the active comparator. This fact, the relatively small number of patients in the safety database, and the chemotherapy regimens utilized for each study are the reasons for any imbalances observed in reporting of the data. In general, however, data for adverse events were balanced among treatment groups.

There were a total of 27 deaths reported from all three trials, with the greatest number (22) reported in study XM02-03, which was conducted in patients with lung cancer. In the majority of cases, deaths resulted from either progressive disease or toxicity related to chemotherapy and its sequelae. Across all studies and including all cycles of chemotherapy, 20% of patients reported serious adverse events (SAEs). However, the majority of SAEs were attributed by the investigator, Applicant, and clinical reviewer to chemotherapy, with only 1% of SAEs attributed to XM02. The reasons for study dropout or discontinuation were balanced between the XM02 and EU-filgrastim treatment arms. There were more chemotherapy related withdrawals from the placebo arm. The most common adverse event of clinical significance was bone pain, reported for 24% of patients receiving XM02 and 31% of patients receiving EU-filgrastim. There were no statistically significant or clinically meaningful laboratory abnormalities associated with XM02 treatment for all three trials, except those expected based on the chemotherapy regimen and treatment with XM02 or EU-filgrastim.

Immunogenicity data were collected and evaluated. However, neither the antibody binding nor the neutralizing antibody assays were validated. As a result, the results obtained and submitted to support the application are considered unreliable. The Applicant will be instructed to validate both assays, re-test patient samples, and submit the data for FDA review.

Other licensed G-CSF products have had additional toxicities identified either pre or post marketing which were a focus of the clinical reviewer's analysis. Of specific interest were splenomegaly and splenic rupture, allergic reactions, acute respiratory distress syndrome (ARDS), and activation of sickle cell crisis. Across all studies from which the safety population was obtained, there were no cases of splenomegaly or splenic rupture, no cases of ARDS, no cases of sickle cell crisis, and one case of an allergic reaction (bronchospasm during cycle 1 following the 10th dose of XM02) reported.

The safety profile of XM02 compares favorably with EU-filgrastim and other G-CSF products. There are no outstanding safety issues to be resolved.

9. Advisory Committee Meeting

Not applicable to this BLA.

10. Pediatrics

A pediatric deferral request and a pediatric plan were submitted with this application and reviewed by FDA's Pediatric Review Committee (PeRC) (August 11, 2010) and the Division of Clinical Pharmacology. The pediatric plan proposed to (b) (4)

[REDACTED]

The PeRC recommended that the Applicant proceed with PK/PD and safety studies followed by an efficacy study. If the data obtained from the PK/PD study are consistent with the known data in adults, the committee would be inclined to forego the efficacy study since similar efficacy would be expected. Final committee recommendations are pending. The Clinical Pharmacology Review resulted in proposed comments to the Applicant as follows:

- "Your proposed 3 pediatric age-groups and planned number of subjects (N=50) appear acceptable. However, the maximum age in the adolescent group should be modified to 16 yr 11 mo., which will then be consistent with the pediatric population definitions cited in 21 CFR 201.57 (f)(9).
- Adequate pharmacokinetic data should be collected in the pediatric trial such that systemic exposures (AUC_{0-t}) achieved in pediatric patients may be compared to those achieved in adults. Based on a 30 - 40% variability (coefficient of variation, CV%) in AUC_{0-t} value observed for adults, at least 8 to 10 patients per pediatric age-group

should have extensive pharmacokinetic samples collected. The remaining set of patients should have sparse pharmacokinetic samples collected as proposed.

- The pharmacodynamic (absolute neutrophil count) profile should also be evaluated in patients so that exposure-response relationships may be evaluated.”

11. Other Relevant Regulatory Issues

Financial Disclosures: The Applicant provided a dataset which detailed every investigator’s declaration as well as signed financial disclosure forms administered by the Applicant’s CRO for all investigators. In addition, there was an official statement from the clinical sponsor confirming that investigators were paid reasonable and customary professional compensation for participation in the clinical trials. While no investigator or sub-investigator declared a conflict, data from 11 sub-investigators was missing. The Applicant reported that due diligence was exercised in attempting to obtain the missing information. The clinical reviewer was of the opinion that neither the financial arrangement between the sponsor and investigators nor the missing financial disclosure data represented conflicts of interest which influenced trial results.

DSI audits: The efficacy findings for XM02 were obtained from Study XM02-02 which compared XM02 to EU-filgrastim, and XM02 to placebo in patients with breast cancer receiving chemotherapy. It was this study, conducted entirely outside of the United States, which was targeted for inspection by DSI. Two clinical centers, sites 2513 in St. Petersburg, Russia and 2519, in Moscow, Russia, as well as the sponsor of Study XM02-02, BioGenerix AG, and a CRO, (b) (4), were inspected by FDA field investigators in accordance with FDA’s BioResearch Monitoring Compliance Program.

There were no major irregularities identified after inspection of the clinical sites. DSI was informed by the Applicant’s point of contact that the best location to conduct an inspection of the sponsor was at the (b) (4) with (b) (4) AG present. The inspection was conducted from (b) (4). During the inspection the FDA field investigator was unable to verify the validity of the clinical database. A review of records at the sponsor/CRO site in (b) (4) revealed at least two events during which the unblinded database was unlocked without adequate documentation and justification. As provided by the FDA field investigator, the initial database lock and unblinding of data took place on January 2, 2006. On January 17, 2006 the database was unlocked, then relocked on January 23, 2006. The database was again unlocked on or after January 23, 2006 and there was a final database lock on February 27, 2006.

Based on the findings from this inspection, there are unresolved questions with regard to the integrity of the database for the single efficacy trial conducted and submitted in support of this application. DSI submitted an information request to the Applicant on August 17, 2010 requesting information on their standard operating procedures with regard to the management, oversight, quality control, and security of the database since the initial data lock and currently. A response was received from the Applicant on September 2. Because of the complexity and magnitude of information received, the response will not be reviewed during this review cycle. In the CR Letter, the Applicant will be asked to indicate where in the September 2 submission their specific responses can be located, or to submit additional information. In addition, the Applicant must also submit a detailed analysis of the impact of their findings on the evaluation

of the efficacy and safety data for all database changes made after initial database lock and unblinding.

12. Labeling

Proprietary name: The applicant submitted the proposed proprietary name, Neuroval, which is acceptable.

Proper name: The proper name submitted by the applicant, (b) (4), is not acceptable

(b) (4)

(b) (4)

(b) (4) This decision is intended to address the following potential consequences:

- (b) (4)

(b) (4)

(b) (4)

Physician Labeling: FDA labeling review was substantially complete at the time of this review. Sections of the label containing unresolved issues because the data submitted to inform these sections of the label were deemed inadequate from a regulatory perspective are:

Section 8.1, Pregnancy, especially with regard to how reproductive risks should be communicated.

Section 13.1, Carcinogenesis, Mutagenesis, and Impairment of Fertility, especially with regard to how reproductive risks should be communicated.

Major Issues: Discussed at great length throughout the conduct of this review cycle are the requirements for a BLA filing under section 351 (a) of the PHS Act with regard to nonclinical assessment of the potential developmental and reproductive risks associated with a product. As noted previously, the applicant in this case has not performed an embryo-fetal toxicology study, and has not submitted data for review. However, the applicant has provided a literature assessment of the developmental and reproductive risks associated with other G-CSF products. These risks are known, well documented in the scientific literature, and labeled for the US-approved filgrastim products. Because the risks are severe, (i.e., increased risk for spontaneous abortions) a class labeling approach was identified by the nonclinical review team as the preferred approach to communicating important risk information. A legal opinion on such an approach was sought from ORP and OCC who concluded that a literature assessment of the potential reproductive toxicity of XM02 is not sufficient to fulfill the regulatory requirements for nonclinical developmental and reproductive toxicity studies. Further, a BLA submitted under the 351(a) pathway cannot rely on published literature to fulfill a requirement for approval, without written authorization from the license holder of the relied upon BLA. This issue has been further discussed by the Biosimilar Review Committee, The Biosimilar

Implementation Committee. In order to fulfill the regulatory requirements under section 351 (a) for the assessment of developmental and reproductive risks associated with a product, an application must contain the battery of fertility, embryo-fetal and pre/post natal nonclinical development toxicity studies consistent with ICH S5(R2) and ICH S6 guidance.

13. Recommendations/Risk Benefit Assessment

Recommended Regulatory Action: It is recommended that a Biologic License not be granted for this application and a Complete Response Letter be issued to the Applicant for XM02 (Neutroval) for reduction in the duration of severe neutropenia and the incidence of febrile neutropenia in patients treated with established myelosuppressive chemotherapy for cancer.

Risk Benefit Assessment: At this time, the risks to patients outweigh the benefits associated with treatment of XM02 (Neutroval). Although analyses of the submitted efficacy and clinical safety data support approval for XM02, there are deficiencies in the application that have a significant impact on a determination of the effectiveness and safety of this product. The integrity of the data submitted in support of the efficacy of the product is in doubt as a result of DSI inspections. (b) (4)

, and the integrity of the device closure system for the final product has not been evaluated appropriately. In addition, the required developmental and reproductive toxicology studies have not been performed to support appropriate risk communication in labeling. Immunogenicity data, although submitted and analyzed, are unreliable because the assays utilized to obtain the data were not validated. There continue to be manufacturing issues with regard to the drug substance which will not be resolved until after the action date for this application. Finally, no proper name has been approved. Each of these deficiencies relates in some way to safety, either safe administration of the product or risk communication, and at least one of the deficiencies could have an impact on the effectiveness of this agent. As a result of the foregoing deficiencies in this application, which preclude a definitive risk benefit assessment for XM02 (Neutroval), this reviewer recommends that the Applicant, Teva Pharmaceuticals, USA, be issued a Complete Response (CR) Letter.

Recommendation for Postmarketing Risk Evaluation and Management Strategies: Not applicable to this BLA.

Recommendation for other Postmarketing Requirements and Commitments: The following comments include potential postmarketing requirements and postmarketing commitments for Neutroval as well as requests for additional data that should be sent to the Applicant in the Complete Response letter:

1. You have not provided adequate information for assessing whether Neutroval can prolong the QT interval. In the clinical trials, ECGs were monitored at times when XM02 was completely cleared from systemic circulation. To address this issue, provide results of a single-dose, three-way crossover thorough QT clinical trial in a sufficient number of healthy volunteers receiving the highest subcutaneous dose of Neutroval

studied (10 mcg/kg). The clinical trial should perform continuous cardiac monitoring (telemetry or Holter monitors) and/or concurrent detailed serial electrocardiogram (ECG) monitoring, and electrophysiologic studies. In addition, serum Neutroval pharmacokinetic and pharmacodynamic measurements should be performed at multiple time points prior to and following Neutroval administration. Time points should include, but are not limited to: during pre-treatment, at the estimated T_{max} of Neutroval blood concentration, several other time points up to 24 hours post-dose, and at a post-therapy washout time point. Serial ECGs should be collected in triplicate and read by a qualified physician. The clinical trial protocol and data analysis plan should be submitted to us for review prior to starting trial enrollment.

2. Your assays to screen for anti-product and anti-native human GCSF antibody response to Neutroval were not adequate. Please propose a plan for further assay development and validation that includes the date when you will submit the assay validation package to the IND. You should have your validated assay reviewed by us prior to testing clinical samples. If you require clarification on the deficiencies of the current assay, we recommend that you request a meeting with us.
3. Your assay to confirm the presence of anti-product and anti-native human GCSF antibodies was inappropriate, as many antibodies to native protein do not recognize the denatured protein in the gel. Please propose a plan for developing and validating a confirmatory assay that verifies the antigen specificity of the antibody response. You should have your validated assay reviewed by us prior to testing clinical samples. If you require clarification on the deficiencies of the current assay, we recommend that you request a meeting with us.
4. Your assay to detect anti-product and anti-native human GCSF neutralizing antibodies was not adequate. Please propose a plan for further assay development and validation that includes the date when you will submit the assay validation package to the IND. You should have your validated assay reviewed by us prior to testing clinical samples. If you require clarification on the deficiencies of the current assay, we recommend that you request a meeting with us.
5. Please provide a plan for assessing for the presence, persistence, and effects of anti-Neutroval and anti-native human GCSF binding and neutralizing antibodies using a validated assay in at least 500 patients enrolled or to be enrolled in one or more clinical trials. You should provide a listing of the clinical trials in which this assessment will be conducted.
6. Provide results of shipping validation studies which include an assessment of plunger movement, container closure integrity and package integrity after shipping of the filgrastim DP from Kfar Saba, Israel to the U.S. distribution site and use worst case conditions (temperature, duration, shock impact, and loads). Submit the shipping qualification data as a CBE-30 supplement. [TEVA: Propose timeframes for submission of the revised protocol for the shipping validation study, and for submission of the study results in a CBE-30 supplement].

7. Provide the results of the re-evaluation of the bioburden limit after 30 commercial batches are manufactured and to propose a new (b) (4) bioburden action limit that more accurately reflects process capability. Propose timeframe for production of 30 commercial batches and for submission of the supplement containing the results and proposed new (b) (4) bioburden action limit.
8. You use SE-HPLC to measure aggregates in the DS and DP. This assay detects monomers, dimers and high molecular weight (HMW) species. You have validated the assay for the detection of monomers and dimers using AUC as your orthogonal method. We note that you did this study using release (unstressed) samples. Because of the low amount of aggregates at release, there is little sensitivity for determining whether the assay provides accurate results regarding aggregate content. Because AUC may monitor species of aggregates that are not detected by SEC and that different aggregates can accumulate over time, it is important to understand whether SEC provides accurate information on aggregate content over the shelf-life of the product. Provide data indicating that SEC provides an accurate measure of aggregate content through the product's shelf life and conditions of use, or consider use of an alternative assessment of aggregate content. As one possible approach, we suggest that you stress the product under multiple conditions (such as temperature, agitation and light) and determine if SEC provides an accurate assessment of aggregate contents as compared to AUC.
9. You are proposing to set specifications for sub-visible particles after (b) (4) of the DP have been produced. Instead, we suggest you provide a risk assessment of the potential impact these particulates may have on the quality, safety and efficacy of your product and propose a strategy that provides an appropriate level of control. As part of the risk assessment, we suggest that you conduct a robust characterization of the subvisible particle content at release, on stability and in use. This characterization should include the use of multiple orthogonal techniques to quantitate the amount and types of particulates and the use of multiple stress conditions to fully understand the propensity to form large protein aggregates. You should provide timelines in your response to the complete response letter for submission of a protocol and data supporting your risk assessment and proposed control strategy.
10. You currently use peptide mapping as an identity test. However, when appropriately analyzed, the peptide map data also provide a measure of the purity of the DS and DP. Please revise the peptide mapping assay to include quantitative acceptance criteria for peak areas, relative peak heights, and new peaks and provide a timeline in your response to the complete response letter when this information will be submitted to the application. We also recommend, when validating the assay for purity that the acceptance criteria should be based on more than one lot of DS and DP.
11. You have provided extractable/leachable data for the (b) (4) used for the container closure system of the DP. You did not provide extractable/leachable data on the (b) (4) in the presence of the DP or diluent. Because the presence of leachates in the DP may impact product quality in multiple ways, you should assess the

risk to product quality posed by such leachates. Please include leachable testing at the end-of-shelf-life for the DP in the final container closure system in presence of the DP and diluent alone and provide a timeline in your response to the complete response letter for submission of these data and your evaluation of the risk to product quality.

12. The plasmid copy number varies between the Master Cell Bank (b) (4), Working Cell Bank (b) (4) and batches of end-of-production cells (b) (4). Please provide a timeline in your response to the complete response letter for the submission of optimization data for the current assay used to determine plasmid copy number or develop a new assay.
13. You have revised the release and retest specification for in Polysorbate 80 to be not more than (NMT) (b) (4) and you have submitted information on how an investigation will be conducted for any lots formulated with out of specification Polysorbate 80. However you have not provided long-term product quality data for XM02 formulated with Polysorbate 80 at the upper limit of (b) (4). Also, your investigation procedure is inadequate to assess XM02 product quality in that you do not require affected lots to be placed on stability. Please provide a timeline in your response to the complete response letter for submission of data showing that Polysorbate 80 with (b) (4) values at or close to the upper limit of the specification does not impact the quality of your G-CSF product over time. In addition please revise your investigation procedure to include a provision for assessing long-term stability of the product when formulated with expired Polysorbate 80. Please note, if lots have been released with out of specification Polysorbate 80, you will need to submit a Biologic Product Deviation Report to the Agency.

Comments for the Regulatory Action Letter: The following comments are proposed for the Complete Response Letter:

14. The literature assessment of the potential reproductive toxicity of Neutroval provided in support of BLA 125294 does not fulfill the regulatory requirements for nonclinical developmental and reproductive toxicity studies with Neutroval. Your BLA submitted under section 351(a) of the PHS Act may not rely on published literature describing studies of other biological products, including studies regarding a licensed biological product, to fulfill this requirement for approval.

To fulfill the nonclinical regulatory requirements for BLA 125294 under section 351(a), provide the results of a nonclinical embryo-fetal toxicity study conducted with Neutroval in rabbits as a single, pharmacologically responsive species [refer to ICH S9 Nonclinical Evaluation for Anticancer Pharmaceuticals (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm085389.pdf>)]. We recommend that you submit a draft protocol for this study as an amendment to the BLA for review and comment by the nonclinical reviewers prior to initiation of this study.

15. You have not provided substantial evidence from adequate and well controlled clinical trials establishing the safety and effectiveness of Neutroval for reduction in the duration of severe neutropenia and the incidence of febrile neutropenia in patients treated with established myelosuppressive chemotherapy for cancer. Based on an FDA Office of Regulatory Affairs inspection of the study sponsor, BioGeneriX AG (at (b) (4) there is concern that the integrity of the database for Study XM02-02, the single trial submitted to support the efficacy of your product, may have been compromised. Specifically, after the initial database lock on January 2, 2006, and subsequent data unblinding, the database was unlocked and the data were altered on at least two separate dates, January 17th and January 23rd, 2006. Describe the quality control and/or quality assurance activities at each stage of data handling, from initial entry into the database through the final database lock, that were undertaken to ensure the integrity of safety and efficacy data. In addition, provide documentation, including justification and the audit trail, for all changes made to the database after unblinding. Finally, provide a detailed analysis of the impact of all changes made to the database after initial lock and unblinding on the evaluation of safety and efficacy data.
16. (b) (4)
17. Microbial control for the XM-02 drug substance (DS) is inadequate. Although you have proposed several changes to the DS manufacturing process to improve microbial control, studies for these changes are ongoing. Submit the following data as soon as they are available:
- In-process and final XM-02 bioburden and endotoxin data for the (b) (4) following the proposed changes
 - Microbial control data for storage (b) (4)

- c. Any other changes and data that could affect microbial process control (for example, changes in hold times)
18. You have not provided adequate information concerning the analysis of your device closure system. Based on our assessment, you appear to be relying solely on the fill weight as the definitive property to decide if the correct amount of therapy is being delivered through the syringe. There are physical aspects of syringes and needles such as dead space/volume, bond strength between the syringe/needle, and spacing of volumetric graduation markings that can impact the performance of the device. We are also aware that there have been several complaints from the medical community regarding the (b) (4) and the ability for the user to manipulate these pre-filled syringes. Additionally, based on our review of DMF (b) (4) (Drug Master File for (b) (4)) it appears that your syringes may not conform to current FDA consensus standards regarding syringes and needles.

Provide performance testing to demonstrate that your pre-filled glass syringe is safe and effective to deliver your drug product (DP) and that this syringe meets the specifications of the following guidance document and FDA Consensus Standards (most recent editions):

- (b) (4)
- (b) (4)
- (b) (4)

In addition, there are aspects of other syringe standards that may still apply to your device. Specifically, the device constituent of this combination product consists of a (b) (4). In this capacity, all specifications of the current consensus standards such as (b) (4)

(b) (4). However, you must still consider the application of specific elements of these standards as they impact your device. For example, (b) (4)

(b) (4)

Modify your testing procedures and pass/fail criteria to reflect the relevant portions of the standards that affect the performance of your device (such as bond strength).

19. We have determined that your proposed proper name (b) (4) is not acceptable for the product submitted for this BLA under section 351(a) of the PHS Act. (b) (4)

[REDACTED] (b) (4)
[REDACTED]

- [REDACTED] (b) (4)

[REDACTED]
[REDACTED]

[REDACTED]
[REDACTED]
[REDACTED]

[REDACTED]

[REDACTED] (b) (4)
[REDACTED]
[REDACTED]

- [REDACTED] (b) (4)
[REDACTED]

Once we evaluate your proposal, you may contact the United States Adopted Names Council (USANC) as may be necessary.

CLINICAL REVIEW

Application Type BLA
Application Number(s) 125294/0
Priority or Standard Standard

Submit Date(s) 30-Nov 2009
Received Date(s) 30-Nov 2009
PDUFA Goal Date 30-Sep-2010
Division / Office DBOP/OODP

Reviewer Name(s) Thomas M. Herndon *Thomas M. Herndon*
Review Completion Date 30-Jul-2010 *2010 Aug 06*

Established Name (Not available)
(Proposed) Trade Name Neutroval
Therapeutic Class Granulocyte-colony stimulating growth factor
Applicant Teva Pharmaceuticals USA

Formulation(s) 300 mcg/0.5 ml and 480 mcg/0.8 ml in single-use, prefilled syringes
Dosing Regimen 5 mcg/kg/day
Indication(s) reduction in the duration of severe neutropenia and the incidence of febrile neutropenia
Intended Population(s) patients with cancer treated with myelosuppressive chemotherapy

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

Approval of this biologic license application (BLA) for XM02 (Neutroval™) is not recommended for reduction in the duration of severe neutropenia and the incidence of febrile neutropenia in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a clinically significant incidence of febrile neutropenia. XM02 demonstrated efficacy in decreasing the incidence of severe neutropenia compared to placebo, and has a safety profile that closely resembles a similar product, Neupogen® (EU-Neupogen) that is marketed in the European Union. The efficacy of XM02 is based on the results of a single, 3 arm, randomized (2:2:1) double-blind, active- and placebo-controlled trial of 348 patients with breast cancer receiving myelosuppressive chemotherapy (doxorubicin 60 mg/m² and docetaxel 75 mg/m² administered every 21 days for up to 4 cycles). The major efficacy outcome measure was the duration of severe neutropenia in cycle 1, defined as the number of days with an ANC < 0.5 x 10⁹/L. XM02, an active G-CSF comparator (EU-Neupogen), and a placebo were administered at a dose of 5 mcg/kg subcutaneously daily starting 24 hours after the completion of chemotherapy until an ANC of 10 x 10⁹/L occurred following a nadir or after 14 days of dosing, whichever occurred first.

The mean duration of severe neutropenia in cycle 1 was highly statistically significant, 3.8 and 1.1 days ($p < 0.0001$, χ^2 test) when the XM02 and placebo arms, respectively, were compared with a difference of -2.7 days (95% confidence interval -3.2 days, -2.2 days). The incidence of febrile neutropenia was lower in the XM02 arm compared to the placebo arm (12.1% versus 36.1%). Patients in the EU-Neupogen arm had a mean duration of severe neutropenia of 1.1 days. The difference in mean duration of severe neutropenia between the XM02 and EU-Neupogen arms was 0.03 days (95% confidence interval -0.26 days, +0.33 days).

The safety database in cancer patients includes 677 patients who received at least one dose of XM02 following myelosuppressive chemotherapy in three clinical trials. Study XM02-02 was a placebo-controlled and active-controlled, randomized clinical trial in patients with breast cancer (N = 348) and Study XM02-03 and Study XM02-04 were active-controlled, randomized clinical trials conducted in patients with lung cancer (N = 237) and patients with lymphoma (N = 92). Both XM02 and EU-Neupogen were administered at a dose of 5 mcg/kg per day. In Study XM02-02, the most frequent treatment-emergent adverse reaction that occurred at a higher incidence in patients treated with Neutroval compared with patients treated with placebo was bone pain (3.4% vs. 1.4% in cycle 1). In Study XM02-02 and Study XM02-03, Adverse Events occurred at similar frequencies and intensities in the XM02 and EU-Neupogen arms.

There are several issues that are of major concern to the review team which have led to this application becoming the subject of a Complete Response letter. These are:

1. [REDACTED] (b) (4)
[REDACTED]
[REDACTED]
2. Inadequate validation for microbial control for the drug substance manufacturing process. The sponsor has attempted to correct this deficiency, but additional validation studies are required and the projected date of completion for these is 20 Sep 2010, which is the PDUFA goal date.
3. [REDACTED] (b) (4), the proper named proposed by the sponsor, was found to be unacceptable by FDA.
4. Reproductive-Toxicology studies are required for applications, such as this, submitted under Section 351(a) of the Public Health Service Act. The literature assessment of the potential reproductive toxicity of XM02 provided by the sponsor in support of BLA 125294 does not fulfill the regulatory requirements for nonclinical developmental and reproductive toxicity studies. A BLA submitted under the 351(a) pathway cannot rely on published literature, including publications regarding a licensed biologic product, without written authorization from the license holder of that BLA, to fulfill a requirement for approval.
5. The assays used for immunogenicity testing were not validated, therefore, all immunogenicity data submitted with this application cannot be relied upon. Immunogenicity samples will have to be re-assayed once the assays are validated.

1.2 Risk Benefit Assessment

The risks identified outweigh the benefits noted in this clinical review. There are issues in the disciplines of CMC and Non-clinical, as well as several regulatory issues, that support the recommendation to not approve. There are also 2 similar drugs that are already approved for the indications Teva seeks for XM02. As noted previously, the CMC issues are [REDACTED] (b) (4)

[REDACTED]. Microbial control for the drug substance manufacturing process will require additional validation studies. The projected date for completion of these studies is 30 September 2010.

Regarding non-clinical studies, this BLA was submitted under 351(a) of the US Public Health Service Act. Reproductive-toxicology studies are required under 351(a). Other FDA approved G-CSF receptor agonists as well as similar products approved in the European Union and Japan are known to be abortifacient and appropriate risk communication would dictate including this information in the label for XM02. Additional reproductive-toxicology studies could be required. Since the submission of this application, recent legislation has created a new approval pathway for biologics that are

similar to approved biologic. This pathway, 351(k) of the US Public Health Service Act may not require reproductive-toxicology studies.

Although not having a major impact on the risk/benefit ratio, (b) (4), the proper name proposed by Teva was found to be unacceptable by the FDA. A schema for a new proper name will be provided to the Sponsor who will be asked to propose a new proper name.

In summary, although there is a highly statistically significant reduction in the duration of severe neutropenia in patients receiving myelosuppressive anti-cancer drugs associated with a clinically significant incidence of febrile neutropenia and a safety profile similar to EU-Neupogen, the recommendation to not approve is based on (b) (4)

(b) (4), additional microbial control studies for the drug substance manufacturing process requiring additional validation studies, and uncertainty about the need for reproductive-toxicology studies.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

None

1.4 Recommendations for Postmarket Requirements and Commitments

Clinical Pharmacology is recommending that Teva conduct a TQT study to evaluate the potential of XM02 to prolong the QTc interval.

2 Introduction and Regulatory Background

This Biologic License Application, submitted on 30 November 2009, seeks approval for the following indication: XM02 for the reduction in the duration of severe neutropenia and the incidence of febrile neutropenia in patients treated with established myelosuppressive chemotherapy for cancer. The PDUFA goal date is 30-Sep-2010.

The prior regulatory history for this application begins with a pre-IND/pre-BLA meeting held on 25 November 2008 with the sponsor, Teva, who had completed numerous studies before approaching FDA. Among the pre-clinical studies were 26 week rat and monkey toxicology studies. Teva had also completed 7 clinical studies including 2 PK/PD studies, 2 safety studies with patients randomized to XM02 or EU-Neupogen and a 3 arm (placebo controlled and active comparator with EU-Neupogen) non-inferiority study with duration of severe neutropenia as the end point in patients with breast cancer.

In this submission, Teva proposes the use of XM02 to reduce the duration of neutropenia in patients receiving myelosuppressive chemotherapy for the treatment of solid tumors.

Neutropenic Fever in the Patient Receiving Chemotherapy

Intensive cytotoxic chemotherapy for the treatment of cancer often causes profound neutropenia, which may result in hospitalization for treatment of fever or cause potentially fatal infections. The definition of neutropenia varies from institution to institution but is usually defined as an absolute neutrophil count (ANC) < 500 cells/mcL or < 1,000 cells/mcL with a predicted nadir of < 500 cells/mcL (Robbins, 2009; Hughes, 2002). There is an increased risk of an occult infection in patients with an ANC < 1,000 cells/ μ L, and the risk of infection increases as the ANC decreases. Fever in a neutropenic patient is usually defined as a single temperature of > 38.3°C (101°F), or a sustained temperature > 38°C (100.4°F) for more than one hour. Occasionally a neutropenic patient may not present with fever despite the presence of infection. This occurs more often in elderly patients or patients receiving corticosteroids or other anti-pyretics.

Contributory factors to the pathogenesis of febrile neutropenia include the direct effects of chemotherapy on mucosal barriers and immune deficits related to the underlying malignancy (Mermel, 2002). Chemotherapy-induced mucositis followed by seeding of the blood stream with endogenous flora from the entire GI tract is believed to explain a majority of febrile neutropenic episodes. Obstruction of the lymphatics, biliary tract, bronchial, gastrointestinal or urinary systems by tumors, or as a result of surgical procedures, or infections related to indwelling catheters are also common causes of infections. Immune defects related to underlying hematologic disorders, in addition to the immunosuppressive effects of chemotherapy also place patients at higher risk for infections.

Colony Stimulating Factors

Colony Stimulating Factors (CSFs) have been evaluated for prophylactic use following the administration of chemotherapy when neutropenia is anticipated ("primary prophylaxis"), during retreatment after a previous cycle of chemotherapy that caused febrile neutropenia ("secondary prophylaxis"), and to shorten the duration of severe chemotherapy-induced neutropenia without fever ("afebrile neutropenia") (Larson, 2009). The use of CSFs has also been evaluated as an adjunct to other therapies in patients with febrile neutropenia. The likelihood of developing febrile neutropenia is the primary factor that determines whether or not prophylactic CSFs are indicated. The incidence of febrile neutropenia following treatment is also influenced by the intensity of chemotherapy, the degree of injury to the gastrointestinal mucosa, the presence of underlying damage to the patient's hematopoietic stem cells, the concurrent use of radiation, and the overall clinical status of the patient.

Current Clinical Practice

For primary prophylaxis (Larson, 2009), ASCO guidelines (Smith, 2006) recommend that if the incidence of febrile neutropenia is expected to be less than 10 percent following chemotherapy, CSFs should not be routinely administered for primary prophylaxis. When the expected incidence of febrile neutropenia is over 20 percent, prophylactic CSFs are suggested to reduce the need for hospitalization for antibiotic therapy. CSFs may also be used to maintain dose-dense or dose-intense chemotherapy strategies that have survival benefits or in settings where reductions in chemotherapy dose-intensity or dose-density are known to be associated with a poorer prognosis. If the estimated risk of febrile neutropenia is between 10 and 20 percent, the decision to use hematopoietic growth factor support should be individualized. Patients who may be at risk for increased complications from prolonged neutropenia for whom primary prophylaxis might be justified are patients who are age 65 and older, have a poor performance status, have had prior episodes of febrile neutropenia, large radiation portals, or receiving combined chemoradiotherapy, cytopenias due to marrow involvement, poor nutritional status, open wounds or active infection, advanced cancer or other serious comorbidities.

For secondary prophylaxis (Larson, 2009), patients who had an episode of febrile neutropenia after an earlier cycle of palliative chemotherapy, a dose reduction or delay should be the primary therapeutic option and CSFs should not be administered routinely. However, when the risk of febrile neutropenia would prevent the administration of full doses of potentially curative chemotherapy, we suggest the use of CSFs for secondary prophylaxis rather than dose reduction (Smith, 2006). In patients with afebrile neutropenia CSFs should not be used (Larson, 2009).

2.1 Product Information

XM02 is an E. coli derived protein consisting of 175 amino acids. Unlike the corresponding human G-CSF, XM02 is not glycosylated and additionally contains methionine in its NH₂ terminal end. XM02 is a clear, colorless, aqueous liquid supplied in pre-filled syringes, each containing 0.8 ml of sterile, clear, colorless, preservative-free solution for injection consisting of 480 µg (48 MIU) XM02 as well as excipients (b) (4) sorbitol, polysorbate 80 and water for injection). Administration is by subcutaneous injection.

2.2 Tables of Currently Available Treatments for Proposed Indications

The treatments for the reduction in the duration of severe neutropenia and the incidence of febrile neutropenia in patients treated with established myelosuppressive chemotherapy for cancer in the United States are filgrastim marketed as Neupogen and peg-filgrastim marketed as Neulasta® (Table 1).

Table 1 Currently Available Treatments for Proposed Indication

Drug	Class	Approval Date
------	-------	---------------

Drug	Class	Approval Date
filgrastim (Neupogen)	leukocyte growth factor	20-Feb-1991
pegfilgrastim (Neulasta)	leukocyte growth factor	31-Jan-2002

2.3 Availability of Proposed Active Ingredient in the United States

The proposed active ingredient in XM02 has the identical structure as filgrastim (Neupogen) which is currently available in the United States. The major safety concerns for Neupogen are discussed in Section 2.4. In studies of Neupogen administration following chemotherapy, the most reported side effects were consistent with those usually seen as a result of cytotoxic chemotherapy. In the randomized, double-blind, placebo-controlled trial of Neupogen therapy following combination chemotherapy in patients with small cell lung cancer, the 19 most common adverse events are associated with chemotherapy. Splenic rupture has been seen in patients receiving Neupogen for the mobilization and collection of peripheral blood progenitor cells. There have been postmarketing reports for Neupogen of the occurrence of acute respiratory distress syndrome (ARDS) and the precipitation of sickle cell crises in patients with sickle cell disease.

2.4 Important Safety Issues With Consideration to Related Drugs

Allergic Reactions

Allergic-type reactions occurring on initial or subsequent treatment have been reported in < 1 in 4000 patients treated with filgrastim (Neupogen). These have generally been characterized by systemic symptoms involving at least 2 body systems, most often skin (rash, urticaria, facial edema), respiratory (wheezing, dyspnea), and cardiovascular (hypotension, tachycardia). Some reactions occurred on initial exposure. Reactions tended to occur within the first 30 minutes after administration and appeared to occur more frequently in patients receiving Neupogen by intravenous infusion. Rapid resolution of symptoms occurred in most cases after administration of antihistamines, steroids, bronchodilators, and/or epinephrine. Symptoms recurred in more than half the patients who were rechallenged.

Splenic Rupture

Splenic Rupture, including fatal cases, has been reported following the administration of Neupogen.

Acute Respiratory Distress Syndrome (ARDS)

ARDS has been reported in patients receiving Neupogen, and is postulated to be secondary to an influx of neutrophils to sites of inflammation in the lungs.

Alveolar Hemorrhage and Hemoptysis

Alveolar hemorrhage manifesting as pulmonary infiltrates and hemoptysis requiring hospitalization has been reported in healthy donors undergoing peripheral blood progenitor cell (PBPC) mobilization with Neupogen. Hemoptysis resolved with discontinuation of Neupogen. The use of Neupogen for PBPC mobilization in healthy donors is not an approved indication.

Sickle Cell Disorders

Severe sickle cell crises, in some cases resulting in death, have been associated with the use of Neupogen in patients with sickle cell disorders. Only physicians qualified by specialized training or experience in the treatment of patients with sickle cell disorders should prescribe Neupogen for such patients, and only after careful consideration of the potential risks and benefits.

Patients With Severe Chronic Neutropenia

The safety and efficacy of Neupogen in the treatment of neutropenia due to other hematopoietic disorders (eg, myelodysplastic syndrome) has not been established. Care should be taken to confirm the diagnosis of SCN before initiating Neupogen therapy.

MDS and acute myelogenous leukemia (AML) have been reported to occur in the natural history of congenital neutropenia without cytokine therapy. Cytogenetic abnormalities, transformation to MDS, and AML have also been observed in patients treated with Neupogen for SCN. Based on available data including a postmarketing surveillance study, the risk of developing MDS and AML appears to be confined to the subset of patients with congenital neutropenia. Abnormal cytogenetics and MDS have been associated with the eventual development of myeloid leukemia. The effect of Neupogen on the development of abnormal cytogenetics and the effect of continued administration in patients with abnormal cytogenetics or MDS are unknown.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

All of the studies submitted in support of this BLA were conducted outside of the United States. The following list summarizes meetings with Teva that were held prior to the submission.

25 Nov 2009

Teva inquired if their clinical development program for filgrastim, which was performed in accord with the ICH S7, S8, and EMEA guidances was sufficient to support the submission of a BLA?

FDA had the following response:

Teva has completed two studies designed to look at safety (XM02-03, XM02-04) and a single study designed to look at efficacy (XM02-02). The only efficacy endpoint that incorporated appropriate alpha adjustment was the duration of severe neutropenia endpoint (DSN) in Study XM02-02. All other efficacy endpoints in the three studies were exploratory analyses. The study design and statistical analysis plan were not discussed

with FDA prior to initiation. We have the following comments that would need to be addressed in order to file the proposed license application:

- a. Based on historical information, a clinically important incidence of febrile neutropenia is present only when the duration of severe neutropenia is 5 or more days in the absence of prophylactic antibiotics. The application should provide evidence that the clinical setting (average DSN in the placebo arm for the same patient population/chemotherapy regimen) in which XM02 was evaluated is one that requires growth factor support to avoid a clinically important risk of febrile neutropenia. Such evidence is necessary to support the proposed claim of a clinical benefit (reduction in incidence of febrile neutropenia) based on the surrogate of reduction in DSN.
- b. Replication of the treatment effect in multiple trials. Ordinarily, a minimum of two adequate and well-controlled trials are required.
- c. For comparisons to an active control (Neupogen) to be considered, the following information should be provided in the BLA:
 - 1) Data establishing the treatment effect size (i.e., difference in DSN between the placebo and Neupogen) in this clinical setting defined by the patient population and background chemotherapy regimen. Ordinarily, such evidence should be replicated across multiple studies.
 - 2) Justification of the proposed non-inferiority margin; the fraction of the treatment effect for the active control that is to be established for XM02 should be sufficient to confer a clinical benefit.
 - 3) The comparisons should be performed in both the intent-to-treat and the per-protocol populations. A definition for the per-protocol population should be included in the statistical analysis plan. If substantial differences are observed between the two populations, this may be indicative of poor study conduct.
- d. In light of the absence of an abbreviated approval pathway under section 351 of the PHS Act, this study will not support claims based on comparability to Neupogen nor will it support claims based on extrapolation to other indications for which Neupogen is approved.

2.6 Other Relevant Background Information

Non-clinical and clinical development of XM02 formulation was conducted by BioGenerixX AG, a member of (b) (4). Under a license agreement between BioGenerixX AG and Sicor Biotech UAB in Lithuania, XM02 was brought to market in the European Union as a biosimilar product (reference to Neupogen) and approved in September 2008. Sicor Biotech UAB is an indirect wholly-owned subsidiary of TEVA Pharmaceuticals USA, Inc. (TUSA). (b) (4) formulations of parenteral XM-02 are registered under the following tradenames: Biograstim®,

Filgrastim-Mepha, Filgrastim ratiopharm, Ratiograstim®, and TEVAGRASTIM® and are marketed in Europe by BioGeneriX AG, RatioPharm, or TEVA.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The BLA submission was not submitted in CDISC format as Teva had previously agreed to do. The data submitted were of adequate quality, but some datasets lacked information needed for particular analyses. Specifically, the define files for the data sets did not contain definitions for each entry. Teva eventually sent revised data sets with revised define files.

The reviewer randomly evaluated 10% of the Case Report Forms for each study and compared them to content in the submitted adverse event analysis file for each study. While the reviewer did not identify any issues that questioned the integrity of the study, the numbering of the study patients in the data sets and in the Case Report Forms used different numbering systems making it tedious to go from one to the other.

3.2 Compliance with Good Clinical Practices

All studies contained a statement that the trials were conducted in accordance with the Declaration of Helsinki and Good Clinical Practice.

The number of protocol violations was balanced across all 3 arms (Table 2). The most common reason for a protocol violation was due to no study drug given on greater than 2 consecutive days in cycle 1.

Table 2 Protocol Violations for Study XM02-02

	XM02 N=140		EU-Neupogen N=136		Placebo N=72	
VIOLATION	N	%	N	%	N	%
No study drug on >2 consecutive days in cycle 1	4	3	4	3	2	3
No study drug on >30% of days in cycle 1	4	3	4	3	1	1
CTX dose in cycle 1 <= 90% of required dose	3	2	1	1	1	1
Insufficient ANC data in cycle 1	1	1	1	1	0	0
Previous chemotherapy	1	1	2	1	0	0

	XM02 N=140		EU-Neupogen N=136		Placebo N=72	
Wrong medication on all days in cycle 1	1	1	1	1	0	0
Baseline ANC < 1.5 x 10 ⁹ /L in cycle 1	0	0	0	0	1	1
G-CSF medication received	0	0	0	0	11	15

3.3 Financial Disclosures

The sponsor provided a dataset detailing every investigator's declaration and each signed financial disclosure form administered by (b) (4) for each investigator as well as an official statement from the clinical sponsor confirming that investigators were paid reasonable and customary professional compensation for participation in the clinical trials. While no investigator or sub-investigator declared a conflict, there was no data available from 11 sub-investigators. The sponsor exercised due diligence in attempting to obtain this information. The arrangement did not raise questions about the integrity of the data.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

(b) (4)

Immunogenicity assays were not fully validated, therefore the determination of positive samples for binding and neutralizing antibodies is questionable. The assays will need to be validated and the samples re-assayed.

Inspections at DS Manufacturing Site (Vilnius, Lithuania) occurred 31 May 2010. The DP Manufacturing facility inspection was waived.

For a full analysis, see the Office of Biological Products/Division of Therapeutic Proteins review.

4.2 Clinical Microbiology

The drug substance filgrastim is manufactured by SICOR Biotech UAB in Vilnius, Lithuania (FEI 3008110727). A pre-license inspection was conducted May 31-June 4, 2010. Several recommendations were made to the firm but there were no 483 observations. Initial classification is NAI.

The application contains inadequate validation for microbial control for the drug substance manufacturing process. The sponsor has attempted to correct this deficiency by changes in their manufacturing processes, but additional validation studies are required. The projected date of completion for these studies is 20 September 2010, which is the PDUFA goal date for this application.

4.3 Preclinical Pharmacology/Toxicology (excerpted from Non-clinical review)

The nonclinical safety of XM02 was assessed in two GLP 26-week repeat dose toxicity studies with 4-week recovery periods in rats (0, 5, 50, and 500 mcg/kg/day) and monkeys (0, 5, 25, and 125 mcg/kg/day), as well as a standard battery of GLP safety pharmacology studies. From the repeat dose toxicity studies, the rat was determined to be the most sensitive species due to a significant number of mortalities (12/60; 20%) in the high dose group attributable to severe pain caused by enlarged, swollen joints in hind paws and limbs. As a result of these mortalities, 50 µg/kg/day was determined as the maximum tolerated dose (MTD) of XM02 in the rat. In contrast, there were no mortalities or adverse clinical signs in the monkey repeat dose toxicity study at doses of XM02 up to 125 mcg/kg/day. The major toxicities associated with XM02 treatment in both species, were bone marrow hypercellularity, enlarged spleens, increased alkaline phosphatase (ALP), and extramedullary hematopoiesis (rat)/granulocyte infiltrations (monkey), were dose-dependent, related to the exaggerated pharmacology of G-CSF, and reversible in recovery animals. Similarly, the bone (joint) findings of painful, swollen hind limbs that led to the premature euthanization of several high dose animals in the rat GLP repeat dose toxicity study, were dose-dependent, reversible, and also likely related to the exaggerated pharmacology of G-CSF as there were histological findings of hyperostosis and granulocytic infiltrates in articular surfaces and surrounding soft tissue of the bone. There were no detectable effects on the respiratory or central nervous system in rats or the cardiovascular system in dogs after a single dose of 3500 mcg/kg XM02 in the GLP safety pharmacology studies.

There were no specific genotoxicity or carcinogenicity studies performed with XM02 as genotoxicity studies are not appropriate for large molecular weight proteins and a carcinogenicity assessment is not warranted for the intended patient population.

There were no developmental and reproductive toxicology studies conducted with XM02. The Sponsor's proposed justification for the absence of these studies was based on the clinical indication, which limits use of XM02 to cancer patients receiving

concomitant therapy with anti-cancer agents with known reproductive and developmental risks. Upon review of this justification, it was determined that it would be unethical to not communicate the potential reproductive and developmental risks associated with XM02 to prescribers and patients as there are currently two US-licensed recombinant G-CSF products that do contain this information in the label. As a result, Teva was requested to “provide an assessment of the potential reproductive toxicity of XM02 as an amendment to the Biologics Licensing Application.” In response to this request, Teva submitted a literature-based assessment of the reproductive toxicities associated with other G-CSF receptor agonists to support a ‘class-labeling’ approach. Upon review of the submitted literature, it was determined that the developmental and reproductive toxicities associated with recombinant G-CSF products, primarily an abortifacient effect, were well-characterized and consistent within the class.

4.4 Clinical Pharmacology

The following are preliminary comments excerpted from the Division of Clinical Pharmacology 5 draft review. Final conclusions will be contained in the Division of Clinical Pharmacology 5 review.

4.4.1 Mechanism of Action

XM02 is a glycoprotein growth factor, produced by recombinant DNA technology that regulates the proliferation and differentiation of myeloid progenitor cells and results in an increase in the number of mature functional neutrophils in the peripheral blood. XM02 exerts its effects through a specific, high-affinity receptor on the surface of myeloid cells. XM02 binding to this receptor results in an increase in the number of neutrophils in the periphery.

4.4.2 Pharmacodynamics

In healthy subjects who received a single, subcutaneous dose of 5 or 10 mcg/kg of XM02, a transient decrease in the absolute neutrophil count (ANC) occurred during the first hour, followed by an increase in ANC. Following a subcutaneous 5 mcg/kg dose (N = 61), the mean maximum ANC was $22 \times 10^9/L$; the median time to peak ANC was 12 hours. After a subcutaneous 10 mcg/kg dose (N = 58), the mean maximum ANC was $26 \times 10^9/L$; the median time to peak ANC was between 14 to 18 hours. The ANC returned to baseline by 4 days post-dose.

In cancer patients receiving various chemotherapies (N = 361), a subcutaneous 5 mcg/kg dose of XM02 was administered daily starting 24 hours after the completion of chemotherapy until an ANC of $10 \times 10^9/L$ after a nadir was reached or after 14 days of XM02 dosing, whichever occurred first. During cycle 1, the time to maximum mean ANC was between 3 to 5 days, and then ANC decreased to a nadir by 7 to 11 days following

chemotherapy. Mean ANC values returned to baseline by 21 days following completion of chemotherapy. The ANC profile was similar in subsequent chemotherapy cycles.

The potential effects of XM02 on the QTc interval were not adequately evaluated in clinical trials included in the BLA since ECGs were monitored at times when XM02 was cleared from systemic circulation. In a study by Guneyssel (Guneyssel, 2009) there were no statistically significant differences between baseline and any QTc interval measurements in a population of 102 neutropenic patients, treated for 2 days with Neupogen (Roche, Basel, Switzerland) at a dose of 5 mcg/kg/day SC were observed (Clin Drug Invest. 2009;29:551-55). Teva provided a summary of its XM02 European September 2008 approval post-marketing safety reports to support the lack of QTc prolongation signal. The post-marketing safety data collected up to March 31, 2010 includes (b) (4) daily XM02 doses and only 1 case of syncope was reported and an ECG taken during the syncopal episode was reported to be normal. No sudden death was reported in the post marketing period. Based on all these data together, the potential risk of XM02 to prolong the QTc interval appears to be minimal and no further evaluation is warranted at this time.

4.4.3 Pharmacokinetics

In healthy subjects, the absolute bioavailability of a 5 mcg/kg subcutaneous dose of XM02 was 33%. After single dose subcutaneous administration of 5 mcg/kg of XM02 (N = 33), the geometric mean (CV%) of serum C_{max} was 18 ng/mL (41%) and of AUC 0-48 h was 158 ng•h/mL (37%). The median T_{max} was 6 hours and the median half-life (t_{1/2}) was 8.9 hours. Increasing the dose of XM02 from 5 to 10 mcg/kg resulted in an approximately 3-fold increase in both C_{max} and AUC 0-48h.

Pharmacokinetic data were also obtained from patients with breast cancer, lung cancer and NHL (N = 12 per group) who received subcutaneous XM02 5 mcg/kg/day. Following the first XM02 dose in cycle 1, the geometric mean (CV%) of serum C_{max} and AUC_{0-24h} were 36 ng/mL (41%) and 305 ng•h/mL (35%) in breast cancer, 25 ng/mL (60%) and 273 ng•h/mL in lung cancer (61%), and 20 ng/mL (24%) and 184 ng•h/mL (23%) in NHL, respectively. For the 3 groups combined, the median T_{max} was between 4 to 6 hours and the median t_{1/2} was between 3.2 to 3.8 hours. The terminal half-life was calculated from serum levels measured up to 24 hours as compared to up to 48 hours in the healthy subjects. Accumulation after repeated dosing was not observed. No dose adjustment based on cancer type is warranted.

No gender-related differences were observed in the pharmacokinetics of XM02 following subcutaneous administration. The pharmacokinetic profile in patients with renal or hepatic impairment has not been assessed.

5 Sources of Clinical Data

Five trials were submitted in support of this BLA (Table 3) and reviewed. Two studies compared pharmacodynamic and pharmacokinetic properties of XM02 to EU-Neupogen in healthy volunteers (XM02-01 and XM02-05). Both were single blind, randomized, single-dose, two-period crossover (XM02 and EU-Neupogen, with 2- or 3-week washout periods between applications), two arm studies 5 mcg/kg and 10 mcg/kg in healthy volunteers (all males in study XM02-01; males and females in XM02-05). Three studies were randomized, double blinded clinical trials (XM02-02, XM02-03, XM02-04) on 677 patients. In these three studies, full blinding was not done, because of the different fill volumes of the XM02 and EU-Neupogen syringes and the body-weight dosing, so the drug administrator and the pharmacist were unblinded. Study XM02-02 was the only trial with efficacy as the primary endpoint. Study XM02-03 and Study XM02-04 were powered for safety endpoints. All five studies compared XM02 to EU-Neupogen. Study XM02-02 also included a placebo control comparison.

5.1 Tables of Studies/Clinical Trials

Table 3 Clinical Trials Submitted

Study	Phase	Design	Indication	Treatment (mcg/kg)	Number of Subjects
XM02-01	1	SB, R, SD, 2X, 2A	HV (M)	5, 10	56
XM02-02	3	DB, R, SD, placebo	Breast cancer	5	348
XM02-03	3	DB, R, SD	Lung cancer	5	240
XM02-04	3	DB, R, SD	NHL	5	92
XM02-05	1	SB, R, SD, 2X, 2A	HV	5, 10	140

SB = single blind, R = randomized, SD = single dose, 2X = two period crossover, 2A = two arms, HV = healthy volunteers, M = male, DB = double blind, NHL = non-Hodgkin lymphoma

5.2 Review Strategy

The BLA submission contained three trials addressing the efficacy and safety of XM02 in patients with cancer. These trials were the major focus of this review. Only one of the trials (Study XM02-02) was powered to adequately address efficacy and was the sole source of efficacy data. Study XM02-02, Study XM02-03, and Study XM02-04 comprised the safety set of 677 patients. The PK/PD studies, although containing some safety data were excluded from pooled safety analyses as these studies were performed with healthy volunteers. The review of the BLA was divided among several review divisions.

CMC reviewed the product, the drug substance, immunogenicity assays and other data related to the manufacturing of the product. Non-clinical reviewed all non-clinical data,

the Division of Clinical Pharmacology 5 reviewed the PK studies in normal volunteers, and other Clinical Pharmacology Issues. A Division of Biometrics V reviewer reviewed the statistics in the efficacy study. The safety and efficacy studies and integration of the other review disciplines was done by the clinical reviewer.

5.3 Discussion of Individual Studies/Clinical Trials

The studies reviewed are Study XM02-02, "Efficacy and Safety of XM02 compared to filgrastim in patients with breast cancer receiving chemotherapy", Study XM02-03, "Safety and efficacy of XM02 in patients with small cell or non small cell lung cancer receiving platinum-based chemotherapy", and Study XM02-04, "Safety and efficacy of XM02 in patients with Non-Hodgkin Lymphoma receiving chemotherapy".

Study XM02-02 was a multinational, multicenter, randomized, controlled trial assessing the efficacy of XM02. Randomized (2:2:1) were 348 patients (XM02 = 140, EU-Neupogen = 136, and placebo = 72) with breast cancer (high-risk Stage II, Stage III or Stage IV) who received doxorubicin 60 mg/m² IV bolus and docetaxel (75 mg/m² IV). Subjects in the placebo group switched to XM02 after completion of cycle 1. The primary efficacy endpoint was the duration of severe neutropenia (DSN) in cycle 1. Equivalence of XM02 and EU-Neupogen was assessed based on the per protocol set using the ANCOVA model to calculate a 2-sided 95% CI. Patients who received placebo in cycle 1 received XM02 for subsequent cycles.

Study XM02-03 was a multinational, multicenter, randomized and controlled study assessing the safety of XM02. Randomized (2:1) were 240 patients (XM02 = 160 and EU-Neupogen = 80) with lung cancer (SCLC or advanced NSCLC with no more than 1 prior chemotherapy cycle) who received myelosuppressive platinum-based chemotherapy. Patients who received EU-Neupogen in cycle 1 received XM02 for subsequent cycles.

Study XM02-04 was a multinational, multicenter, randomized and controlled study assessing the safety of XM02. Randomized (2:1) were 92 patients (XM02 = 63 and EU-Neupogen = 29) with chemotherapy naive aggressive NHL (allowed subtypes: diffuse large B-cell lymphoma, mediastinal large B-cell lymphoma, follicular lymphoma grade 3, anaplastic large cell lymphoma) requiring chemotherapy who received cyclophosphamide 750 mg/m² IV, doxorubicin 50 mg/m² IV, vincristine 1.4 mg/m² IV on Day 1 of each cycle and prednisolone 100 mg/day orally from Day 1 to Day 5) Some subjects received rituximab. Patients who received EU-Neupogen in cycle 1 received XM02 for subsequent cycles.

XM02-02 Efficacy and Safety of XM 02 compared to Filgrastim in patients with breast cancer receiving chemotherapy.

Objectives

Primary Objective

Demonstration of equivalence of XM 02 and EU-Neupogen in patients with breast cancer during the first cycle of chemotherapy with respect to the primary endpoint duration of severe neutropenia (DSN) in cycle 1, defined as grade 4 neutropenia with an ANC $< 0.5 \times 10^9/L$. Confirmation of assay sensitivity with respect to DSN by comparing XM 02 versus placebo.

Secondary Objectives

Demonstration of efficacy and safety of XM 02 in comparison to EU-Neupogen in patients with breast cancer receiving chemotherapy.

Evaluation of pharmacokinetic properties of XM 02 in comparison to EU-Neupogen.

Trial Design

This was a randomized double blinded trial comparing XM02 to EU-Neupogen and placebo in patients receiving myelosuppressive chemotherapy for the treatment of breast cancer. Patients were randomized to treatment with either XM02, EU-Neupogen, or placebo (2:2:1). Patients in the placebo group were switched to treatment with XM02 after completion of cycle 1 (Figure 1). The patients underwent a maximum of 4 chemotherapy cycles (3 weeks per cycle), each cycle beginning with a day of chemotherapy. On Day 2 of each cycle, the patients received daily subcutaneous (sc) injections with XM02, EU-Neupogen, or placebo (in the first cycle only) for a minimum of 5 days and a maximum of 14 days, or until an absolute neutrophil count (ANC) $\geq 10 \times 10^9/L$ after nadir was documented.

In cycle 1, blood samples to determine ANC were taken within 24 hours before chemotherapy and then daily until Day 15, or longer until ANC reached $\geq 2.0 \times 10^9/L$. In cycles 2, 3, and 4, ANC was assessed within 24 hours before chemotherapy and then daily starting on Day 5 until Day 15, or longer until ANC reached $\geq 2.0 \times 10^9/L$. In each cycle, body temperature (axillary) was measured daily until Day 15, or longer until ANC reached $\geq 2.0 \times 10^9/L$. Safety assessments (laboratory parameters, antibody sampling, physical examination, vital signs) were performed at screening, within 24 hours before chemotherapy in each cycle (Day 1), and at the end of study visit. Patients were monitored for adverse events (AEs) and concomitant medication throughout the study.

Three weeks after the last chemotherapy infusion (Day 85 ± 1), end of study assessments were performed. On Day 180 ± 5 , there was an additional assessment for determination of antibodies against XM 02 or EU-Neupogen.

Endpoints

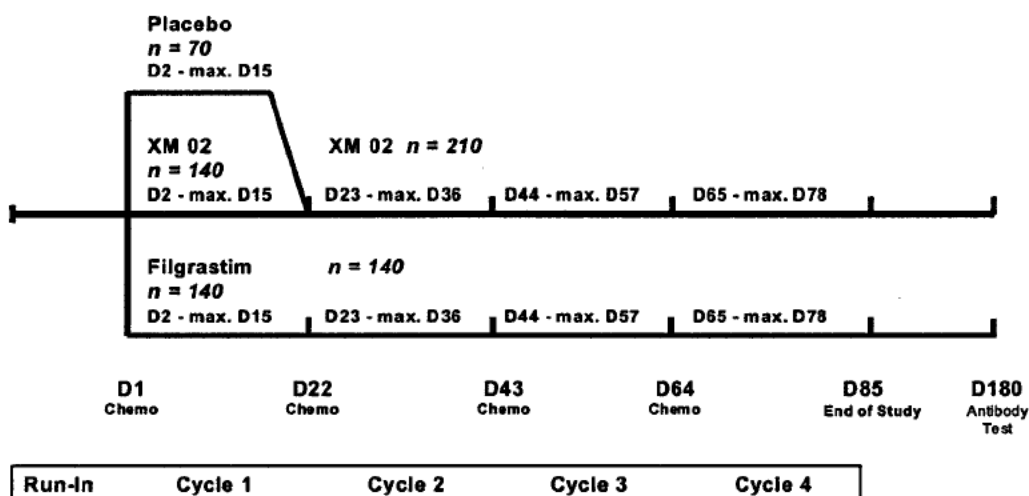
Primary Endpoint

The primary endpoint was the Duration of Severe Neutropenia (DSN) in cycle 1, defined as grade 4 neutropenia with an ANC $< 0.5 \times 10^9/L$.

Secondary Endpoints

- Incidence of febrile neutropenia per cycle and across all cycles (febrile neutropenia defined as body temperature of $> 38.5^{\circ}\text{C}$ for more than one hour, axillary measurement with a calibrated standard device, and $\text{ANC} < 0.5 \times 10^9/\text{L}$)
- DSN in cycles 2 to 4
- Depth of ANC nadir in cycles 1 to 4
- Times to ANC recovery in cycles 1 to 4
- Mortality
- Incidence of AEs
- Changes of safety laboratory parameters
- Immunogenicity (development of antibodies against XM 02 and EU-Neupogen)

Figure 1 Study Design of Study XM02-02 (excerpted from the protocol)



Inclusion Criteria (excerpt from the protocol)

Female and male patients of any ethnic origin with a diagnosis of breast cancer meeting all criteria listed below, were included in the study.

- Signed and dated written informed consent
- Age ≥ 18 years
- Breast cancer high risk stage II, or stage III or IV (classification according to American Joint Committee on Cancer)
- Patients planned/eligible to receive treatment with docetaxel/doxorubicin as routine chemotherapy for their breast cancer disease
- Chemotherapy naïve
- Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2
- $\text{ANC} \geq 1.5 \times 10^9/\text{L}$
- Platelet count $\geq 100 \times 10^9/\text{L}$

- Adequate cardiac function (including left ventricular ejection fraction $\geq 50\%$ as assessed by echocardiography within 4 weeks prior to randomization)
- Adequate hepatic function i.e., alanine and aspartate aminotransferases (ALT/AST) $< 2.5 \times \text{ULN}$, alkaline phosphatase $< 5 \times \text{ULN}$, bilirubin $< \text{ULN}$

Exclusion Criteria (excerpt from the protocol)

Patients presenting with any of the following will not be included in the study:

- Participation in a clinical trial within 30 days before randomization
- Previous exposure to filgrastim, pegfilgrastim or lenograstim
- Known hypersensitivity to Docetaxel
- Underlying neuropathy of grade 2 or higher
- Treatment with systemically active antibiotics within 72 hours before chemotherapy
- Treatment with lithium
- Chronic use of oral corticosteroids
- Prior radiation therapy within 4 weeks before randomization
- Prior bone marrow or stem cell transplantation
- Prior malignancy within the previous 5 years other than basal cell or squamous cell carcinomas or in situ carcinoma of the cervix.
- Any illness or condition that in the opinion of the investigator may affect the safety of the patient or the evaluation of any study endpoint
- Pregnant or nursing women are excluded. Women of child-bearing potential must agree to use a chemical or barrier contraceptive during the treatment period

Study Discontinuation Criteria

Patients must be withdrawn under the following circumstances:

- The patient withdraws consent (withdrawal of consent may take place at any time; no justification for such a decision is required)
- Blind is broken
- Toxicity of chemotherapy
- The disease progresses under chemotherapy.

Patients may be withdrawn for the following reasons:

- At the discretion of the investigator
- Violation of eligibility criteria or deviation from the treatment plan specified in the protocol.

Treatment Plan

All patients received myelosuppressive chemotherapy (Doxorubicin, 60 mg/m^2 , i.v. bolus injection, Docetaxel, 75 mg/m^2 i.v. infusion) on Day 1 of each cycle.

Prophylactic corticosteroid treatment accompanied the docetaxel therapy (e.g., 8 mg dexamethasone twice daily for 3 days starting one day before chemotherapy).

Chemotherapy was repeated every 3 weeks for a maximum of 4 cycles. A delay of the next cycle for up to 14 days was acceptable. For longer delays the patient was

withdrawn from the study, and assessments (Table 4) of the end of study visit were performed.

Table 4 Schedule of Assessments (excerpt from the protocol)

	Screening	Baseline	Cycles 1 to 4	End of Study ¹	Antibody Follow-up
	Day -14 to -1	within 24 h before start of CTX in cycle 1	Days 1 to 84	Day 85 (±1)	Day 180 (±5)
Written informed consent	X		See Table 3 for cycle 1, Table 4 for cycles 2, 3, and 4		
Demographics / Medical history	X				
ECOG status ²	X				
Urine pregnancy test (in females of child-bearing potential)	X				
Physical examination, body weight	X	X		X	
Vital signs	X	X		X	
Safety laboratory	X	X		X	
Antibody determination	X	X		X	X
Adverse events		X		X	
Concomitant medication	X	X		X	X ³
ANC	X	X		X	
Body temperature	X	X		X	
Eligibility assessment	X	X			
Randomisation		X			

- 1 In case of premature termination, end of study assessments are to be performed at 3 weeks after last CTX infusion. In addition, details on the patient's status will be collected during a phone call on Day 85 (±1)
- 2 ECOG status at Screening and before start of cycle 3 only
- 3 Concomitant medication (with regard to G-CSF only) will be documented

Assessments in cycle 1 (excerpt from the protocol)

Assessments in chemotherapy cycle 1																
Day	1 ¹	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16-21
ANC		X	X	X	X	X	X	X	X	X	X	X	X	X	X ²	
Body temperature		X	X	X	X	X	X	X	X	X	X	X	X	X	X ²	
AEs / CM							X ³								X ³	
Chemotherapy ⁵	X															
Study drug s.c.		X	X	X	X	X	X ⁴	X ⁴	X ⁴	X ⁴	X ⁴	X ⁴	X ⁴	X ⁴	X ⁴	
Pharmacokinetics ⁶		X														

- 1 Cycle 1 Day 1 assessments are baseline assessments and displayed in Table 2. Note that the baseline assessments can be performed in the morning of Day 1. Day 1 assessments are to be completed within 24 h before start of CTX

Assessments in cycles 2, 3, and 4 (excerpt from the protocol)

Assessments in chemotherapy cycles 2, 3, and 4																
Day	1 ¹	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16-21
ANC	X				X	X	X	X	X	X	X	X	X	X	X ²	
Body temperature	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X ²	
Physical exam body weight, inj. site complaints	X															
Vital signs	X															
Safety lab	X															
Antibodies	X															
AEs / CM	X						X ³								X ³	
Chemotherapy ⁵	X															
Study drug s.c.		X	X	X	X	X	X ⁴	X ⁴	X ⁴	X ⁴	X ⁴	X ⁴	X ⁴	X ⁴	X ⁴	
Pharmacokinetics ⁶		X														

- 1 Day 1 assessments are to be completed within 24 h before start of CTX
- 2 Or longer, until the patient's ANC reaches $\geq 2.0 \times 10^9/L$
- 3 Visits on Days 7 and 15 should be clinical visits, however, it is acceptable if AEs and concomitant medication are elicited by telephone contact on these days
- 4 Study drug must be stopped when ANC $\geq 10 \times 10^9/L$ after nadir is reached
- 5 Doxorubicin 60 mg/m², i.v. bolus injection + Docetaxel 75 mg/m², at least 1 hour i.v. infusion
- 6 Pharmacokinetics in a subset of patients in cycle 1 and cycle 4 (for details see Section 8.1)

Safety Endpoints

Adverse events with onset prior to first administration of study treatment (XM02 or EU-Neupogen or placebo) and which either stopped prior to first administration of

study treatment or which were ongoing but did not deteriorate with respect to severity and/or relationship to study treatment, were only listed by patient including the relevant individual information. In this listing, adverse events with onset after start of chemotherapy were flagged.

All other adverse events were considered as treatment emergent adverse events (TEAEs) and were used in frequency tables for statistical summaries. Percentages for each cycle were based on the number of patients who entered into the respective cycle and compared between treatment groups by means of Fisher's exact test. Additional tables were presented with respect to maximum severity and to strongest relationship to study drug. Multiple occurrences of the same TEAE were counted only once following a worst-case approach with respect to severity and relationship to study treatment. Similar tables were provided for TEAEs for which a relationship to study treatment could not be excluded (possibly treatment related TEAEs). All serious TEAEs were listed.

XM02-03

XM02-03 Safety and Efficacy of XM02 in patients with small cell or non small cell lung cancer receiving platinum-based chemotherapy

Objectives

Primary Objective

Demonstration of safety of XM02 when administered for up to a maximum of six cycles in patients with lung cancer.

Secondary Objectives

Demonstration of efficacy of XM02 (in the first cycle compared to EU-Neupogen in patients with lung cancer.

Evaluation of pharmacokinetic properties of XM 02 in comparison to EU-Neupogen.

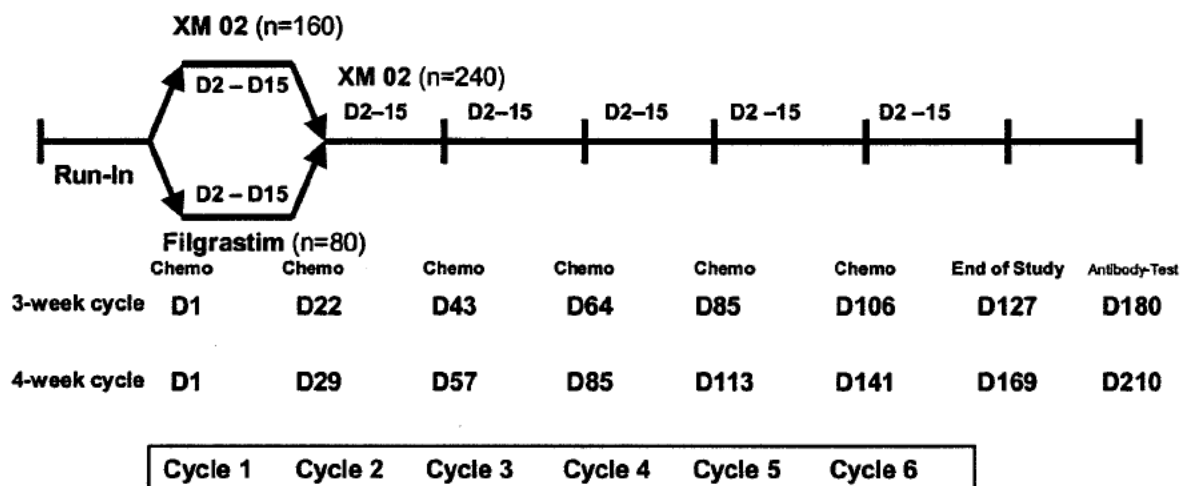
Study Design

This was a randomized, double blinded, trial comparing XM02 to EU-Neupogen in patients receiving myelosuppressive chemotherapy for the treatment of lung cancer. Patients were randomized to treatment with either XM02, or EU-Neupogen (2:1) (Figure 2). The patients underwent a maximum of 6 chemotherapy cycles (3 or 4 weeks per cycle), each cycle beginning with a day of chemotherapy. One day after chemotherapy on Day 2 of each cycle, the patients received daily s.c. injections with XM02, or EU-Neupogen, (in the first cycle only) for at least 5 days and a maximum of 14 days, or until an absolute neutrophil count (ANC) $\geq 10 \times 10^9/L$ after nadir was documented.

In cycle 1, blood samples for the determination of the ANC were taken within 24 hours before chemotherapy and then daily until Day 15, or longer until ANC reaches $\geq 2.0 \times 10^9/L$. In cycles 2, 3, 4, 5, and 6, ANC was assessed within 24 hours before chemotherapy and then daily starting on Day 5 until Day 15, or longer until ANC reaches $\geq 2.0 \times 10^9/L$. In each cycle, body temperature (axillary) was measured daily

until Day 15, or longer until ANC reached $\geq 2.0 \times 10^9/L$. Safety assessments (laboratory parameters, antibody sampling, physical examination, vital signs) were performed at screening, within 24 hours before chemotherapy in each cycle (Day 1), and at the end of study visit. Patients were monitored for adverse events and concomitant medication throughout the study.

Figure 2 Study Design of Study XM02-03 (excerpted from the protocol)



Endpoints

Primary Evaluation Criteria

- Incidence of adverse events
- Changes of safety laboratory parameters
- Immunogenicity (development of antibodies against study drug)

Secondary Evaluation Criteria

- Incidence of febrile neutropenia by cycle and across all cycles
- Duration of severe neutropenia (DSN), defined as grade 4 neutropenia with an ANC $< 0.5 \times 10^9/L$ in cycles 1 and 4
- Depth of ANC nadir in cycles 1 and 4
- Times to ANC recovery in cycles 1 and 4
- Mortality
- Other: Pharmacokinetics in a subset of patients

Inclusion Criteria (excerpt from the protocol)

Female and male patients of any ethnic origin with a diagnosis of lung cancer meeting all criteria listed below were included in the study.

- Signed and dated written informed consent
- Age ≥ 18 years

- Patients with small cell lung cancer, histologically or cytologically documented or Patients with advanced disease non small cell lung cancer.
- Patients planned/eligible to receive a platinum-based, myelosuppressive chemotherapy requiring G-CSF support
- Chemotherapy naïve or have received no more than one prior regimen
- Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2
- ANC $\geq 1.5 \times 10^9/L$
- Platelet count $\geq 100 \times 10^9/L$
- Adequate hepatic, cardiac, and renal function for the chosen chemotherapy

Exclusion Criteria (excerpt from the protocol)

Patients presenting with any of the following were not included in the study:

- Participation in a clinical trial within 30 days before randomization
- Previous exposure to filgrastim, pegfilgrastim or lenograstim
- Patient planned for non-myelosuppressive chemotherapy
- Patient meeting any contraindication for the chosen chemotherapy
- Treatment with systemically active antibiotics within 72 hours before chemotherapy
- Treatment with lithium
- Candidate for combined chemo-/radiotherapy
- Chronic use of oral corticosteroids
- Prior radiation therapy within 4 weeks before randomization
- Prior bone marrow or stem cell transplantation
- Prior malignancy within the previous 5 years other than basal cell or squamous cell carcinomas or in situ carcinoma of the cervix.
- Any illness or condition that in the opinion of the investigator may affect the safety of the patient or the evaluation of any study endpoint
- Pregnant or nursing women are excluded. Women of child-bearing potential must agree to use a chemical or barrier contraceptive during the treatment period

Study Discontinuation Criteria

Patients were withdrawn under the following circumstances:

- The patient withdraws consent (withdrawal of consent may take place at any time; no justification for such a decision is required)
- Blind is broken
- The disease progresses under chemotherapy.

Patients may be withdrawn for the following reasons:

- At the discretion of the investigator
- Toxicity of chemotherapy
- Violation of eligibility criteria or deviation from the treatment plan specified in the protocol.

Treatment Plan

All patients received a platinum-based, myelosuppressive chemotherapy requiring G-CSF support on Day 1 of each cycle. Chemotherapy was repeated every 3 or 4 weeks depending on the chemotherapy protocol for a maximum of 6 cycles. A delay of the next cycle for up to 14 days was acceptable. Longer delays lead to the withdrawal of the patient from the study, and assessments of the end of study visit were to be performed.

Table 5 Schedule of Assessments (from the protocol)

	Screening	Baseline	Cycles 1 to 6	End of Study ¹	Antibody Follow-up
If CTX regimen requires 3-week cycles	Day -14 to -1	within 24 h before start of CTX in cycle 1	Days 1 to 126	Day 127 (±1)	Day 180 (±5)
If CTX regimen requires 4-week cycles			Days 1 to 168	Day 169 (±1)	Day 210 (±5)
Written informed consent	X		See Table 3 for cycle 1, Table 4 for cycle 4 and Table 5 for cycles 2, 3, 5 and 6		
Demographics / Medical history	X				
Physical examination, body weight	X	X		X	
Previous anti-cancer treatments	X				
Vital signs	X	X		X	
ECOG status ²	X				
Safety laboratory	X	X		X	
Urine pregnancy test (in females of child-bearing potential)	X				
Antibody determination	X	X		X	X
Adverse events		X		X	
Concomitant medication	X	X		X	X ³
ANC	X	X		X	
Body temperature	X	X		X	
Eligibility assessment	X	X			
Randomisation		X			

1 In case of premature termination, end of study assessments are to be performed at 3 weeks (4 weeks in 4-week cycles) after last CTX infusion (first infusion day in last cycle). In addition, details on the patient's status will be collected during a phone call on Days 127 (±1) and 169 (±1), respectively.

2 ECOG at Screening and before start of cycle 3 only

3 Concomitant medication (with regard to G-CSF only) will be documented

Assessments in cycle 1 (from the protocol)

Assessments in chemotherapy cycle 1																
Day	1 ¹	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16-21 (28)
ANC		X	X	X	X	X	X	X	X	X	X	X	X	X	X ²	
Body temperature		X	X	X	X	X	X	X	X	X	X	X	X	X	X ²	
AEs / CM							X ³								X ³	(X) ³
Chemotherapy ⁵	X															
Study drug s.c.		X	X	X	X	X	X ⁴	X ⁴	X ⁴	X ⁴	X ⁴	X ⁴	X ⁴	X ⁴	X ⁴	
Pharmacokinetics ⁶		X														

- 1 Cycle 1 Day 1 assessments are baseline assessments and displayed in Table 2. Note that the baseline assessments can be performed in the morning of Day 1. Day 1 assessments to be completed within 24 h before start of CTX.

Assessments in cycle 4 (from the protocol)

Assessments in chemotherapy cycle 4																
Day	1 ¹	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16-21 (28)
ANC	X				X	X	X	X	X	X	X	X	X	X	X ²	
Body temperature	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X ²	
Physical exam, body weight, inject. site compl.	X															
Vital signs	X															
Safety lab	X															
Antibodies	X															
AEs / CM	X						X ³								X ³	(X) ³
Chemotherapy ⁵	X															
Study drug s.c.		X	X	X	X	X	X ⁴	X ⁴	X ⁴	X ⁴	X ⁴	X ⁴	X ⁴	X ⁴	X ⁴	
Pharmacokinetics ⁶		X														

- 1 Day 1 assessments to be completed within 24 h before start of CTX
- 2 Or longer, until the patient's ANC reaches $\geq 2.0 \times 10^9/L$
- 3 Visits on Days 7 and 15 (and on Day 21 in 4-week cycles) should be clinical visits, however, it is acceptable if AEs and concomitant medication will be elicited by telephone contact on these days
- 4 Study drug must be stopped when $ANC \geq 10 \times 10^9/L$ after nadir is reached
- 5 The tables show assessments with a CTX protocol requiring one infusion day. If the CTX protocol requires more than one infusion day, study drug will start one day after the last infusion day (e.g., on Day 4 with a CTX protocol requiring 3 infusion days). The duration of days with ANC and body temperature measurements will be prolonged accordingly
- 6 Pharmacokinetics in a subset of patients in cycle 1 and cycle 4 (for details see Section 8.1)

Assessments in cycles 2, 3, 5, and 6 (from the protocol)

Assessments in chemotherapy cycles 2, 3, 5, and 6																
Day	1 ¹	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16-21 (28)
ANC ²	X				X		X			X					X	
Body temperature	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
physical exam, body weight, inject. site compl.	X															
Vital signs	X															
Safety lab	X															
Antibodies	X															
AEs / CM	X						X ³								X ³	(X) ³
Chemotherapy ⁵	X															
Study drug s.c.		X	X	X	X	X	X ⁴	X ⁴	X ⁴	X ⁴	X ⁴	X ⁴	X ⁴	X ⁴	X ⁴	

- Day 1 assessments to be completed within 24 h before start of CTX
- ANC assessment additionally on Days when body temperature is >38.5°C
- Visits on Days 7 and 15 (and on Day 21 in 4-week cycles) should be clinical visits, however, it is acceptable if AEs and concomitant medication will be elicited by telephone contact on these days
- Study drug must be stopped when ANC $\geq 10 \times 10^9/L$ after nadir is reached
- The table shows assessments with a CTX protocol requiring one infusion day. If the CTX protocol requires more than one infusion day, study drug will start one day after the last infusion day (e.g., on Day 4 with a CTX protocol requiring 3 infusion days). The duration of days with ANC and body temperature measurements will be prolonged accordingly

Safety Endpoints

Adverse events with onset prior to first administration of study treatment (XM02 or EU-Neupogen) and which either stopped prior to first administration of study treatment or which were ongoing but did not deteriorate with respect to severity and/or relationship to study treatment, were only listed by patient including the relevant individual information. In this listing, adverse events with onset after start of chemotherapy will be flagged.

All other adverse events were considered as treatment emergent adverse events (TEAEs) and were used in frequency tables for statistical summaries. Percentages for each cycle will be based on the number of patients who entered into the respective cycle and will be compared between treatment groups for cycle 1 and for the overall summary by means of Fisher's exact test. Additional tables will be presented with respect to maximum severity and to strongest relationship to study drug. Multiple occurrences of the same TEAE will be counted only once following a worst-case approach with respect to severity and relationship to study treatment. Similar tables will be provided for TEAEs for which a relationship to study treatment

cannot be excluded (possibly treatment related TEAEs). All serious TEAEs will be listed.

XM02-04

XM02-04 Safety and Efficacy of XM 02 in patients with Non-Hodgkin-Lymphoma receiving chemotherapy

Objectives

Primary Objective

Demonstration of safety of XM02 when administered for up to a maximum of six cycles in patients with Non-Hodgkin-Lymphoma receiving CHOP chemotherapy

Secondary Objectives

Demonstration of efficacy of XM02 (in the first cycle compared to EU-Neupogen) in patients with Non-Hodgkin-Lymphoma.

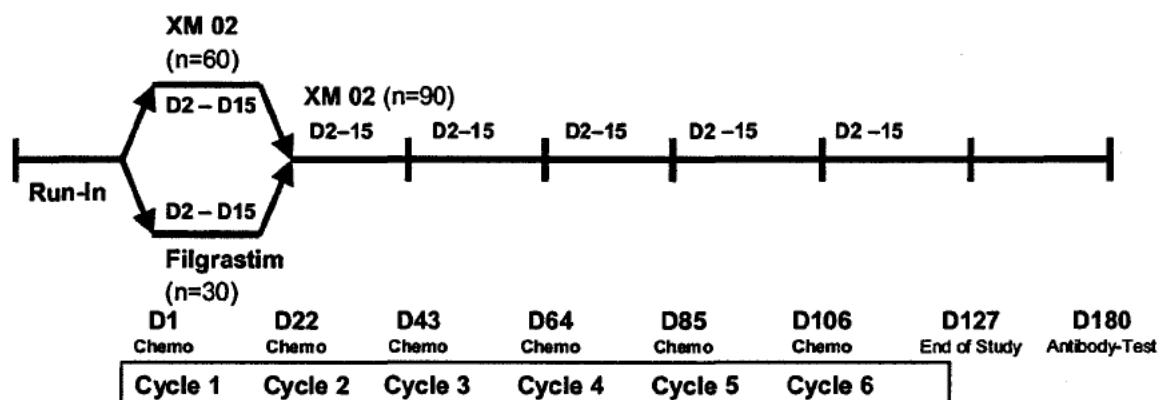
Evaluation of pharmacokinetic properties of XM02 in comparison to EU-Neupogen.

Study Design

This was a randomized double blinded study comparing XM02 to EU-Neupogen in patients receiving myelosuppressive chemotherapy for the treatment of Non-Hodgkins Lymphoma (Figure 3). Patients were randomized to treatment with either XM02, or EU-Neupogen, (2:1). The patients underwent a maximum of 6 chemotherapy cycles (3 weeks per cycle), each cycle beginning with a day of chemotherapy . One day after on Day 2 of each cycle, the patients received daily s.c. injections with XM 02, or EU-Neupogen, (in the first cycle only) for at least 5 days and a maximum of 14 days, or until an absolute neutrophil count (ANC) $\geq 10 \times 10^9/L$ after nadir was documented.

In cycle 1, blood samples for the determination of the ANC were taken within 24 hours before chemotherapy and then daily until Day 15, or longer until ANC reaches $\geq 2.0 \times 10^9/L$. In cycles 2, 3, 4, 5, and 6, ANC was assessed within 24 hours before chemotherapy and then daily starting on Day 5 until Day 15, or longer until ANC reaches $\geq 2.0 \times 10^9/L$. In each cycle, body temperature (axillary) was measured daily until Day 15, or longer until ANC reached $\geq 2.0 \times 10^9/L$. Safety assessments (laboratory parameters, antibody sampling, physical examination, vital signs) were performed at screening, within 24 hours before chemotherapy in each cycle (Day 1), and at the end of study visit. Patients were monitored for adverse events and concomitant medication throughout the study.

Figure 3 Study Design of Study XM02-04 (excerpted from the protocol)



Endpoints

Primary Evaluation Criteria

- Incidence of adverse events
- Changes of safety laboratory parameters
- Immunogenicity (development of antibodies against study drug)

Secondary Evaluation Criteria

- Incidence of febrile neutropenia by cycle and across all cycles
- Duration of severe neutropenia (DSN), defined as grade 4 neutropenia with an ANC $< 0.5 \times 10^9/L$ in cycles 1 and 4
- Depth of ANC nadir in cycles 1 and 4
- Times to ANC recovery in cycles 1 and 4
- Mortality
- Other: Pharmacokinetics in a subset of patients

Inclusion Criteria (from the submission)

Patients of any ethnic origin with aggressive Non-Hodgkin-Lymphoma meeting all criteria listed below, were included in the study.

- Signed and dated written informed consent
- Age ≥ 18 years
- Aggressive Non-Hodgkin Lymphoma, defined as diffuse large B-cell lymphomas, mediastinal large B-cell lymphoma, follicular lymphomas grade 3, or anaplastic large cell lymphoma
- Patients planned/eligible to receive CHOP regimen as routine chemotherapy for their Non-Hodgkin Lymphoma requiring G-CSF support
- Chemotherapy naïve
- International Prognostic Index score ≤ 3
- ANC $\geq 1.5 \times 10^9/L$
- Platelet count $\geq 100 \times 10^9/L$

- Adequate hepatic (ALT/AST < 3 x upper limit of normal, bilirubin < 2 x upper limit of normal), cardiac, and renal (creatinine < 2 x upper limit of normal) function for the chosen chemotherapy

Exclusion Criteria (from the submission)

Patients presenting with any of the following were not included in the study:

- Participation in a clinical trial within 30 days before randomization
- Lymphoblastic lymphoma, Burkitt's lymphoma, transformed lymphoma, CNS-lymphoma
- Previous exposure to filgrastim, pegfilgrastim or lenograstim
- Underlying neuropathy of grade 2 or higher
- Treatment with systemically active antibiotics within 72 hours before chemotherapy
- Treatment with lithium
- Candidate for combined chemo-/radiotherapy
- Chronic use of oral corticosteroids
- Prior radiation therapy within 4 weeks before randomization
- Prior bone marrow or stem cell transplantation
- HIV infections, positive for hepatitis B surface antigen and/or hepatitis C virus
- Prior malignancy within the previous 5 years other than basal cell or squamous cell carcinomas or in situ carcinoma of the cervix.
- Any illness or condition that in the opinion of the investigator may affect the safety of the patient or the evaluation of any study endpoint
- Pregnant or nursing women are excluded. Women of child-bearing potential must agree to use a chemical or barrier contraceptive during the treatment period

Study Discontinuation Criteria

Patients must be withdrawn under the following circumstances:

- The patient withdraws consent (withdrawal of consent may take place at any time; no justification for such a decision was required)
- Blind was broken
- The disease progressed under chemotherapy.

Patients may be withdrawn for the following reasons:

- At the discretion of the investigator
- Toxicity of chemotherapy
- Violation of eligibility criteria or deviation from the treatment plan specified in the protocol.

Treatment Plan

All patients received CHOP or CHOP-R, myelosuppressive chemotherapy requiring G-CSF support on Day 1 of each cycle. Chemotherapy was repeated every 3 weeks for a maximum of 6 cycles. A delay of the next cycle for up to 14 days was

acceptable. Longer delays lead to the withdrawal of the patient from the study, and assessments of the end of study visit were to be performed.

Table 6 Schedule of Assessments (from the protocol)

	Screening	Baseline	End of Study ¹	Antibody Follow-up
	Day -14 to -1	within 24 h before start of CTX in cycle 1	Day 127 (±1)	Day 180 (±5)
Written informed consent	X			
Demographics / Medical history	X			
HIV and Hepatitis B/C testing	X			
IPI score ²	X			
Physical examination, body weight	X	X	X	
Vital signs	X	X	X	
Safety laboratory	X	X	X	
Antibody determination	X	X	X	X
Adverse events		X	X	
Concomitant medication		X	X	X ³
ANC	X	X	X	
Body temperature	X	X	X	
Eligibility assessment	X	X		
Randomisation		X		

1 In case of premature termination, end of study assessments are to be performed at 3 weeks after last CTX infusion

2 IPI score at Screening and before start of cycle 3 only

3 Concomitant medication (with regard to G-CSF only) will be documented

Assessments in cycle 1 (from the protocol)

Assessments in chemotherapy cycle 1																
Day	1 ¹	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16-21
ANC	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X ²	
Body temperature	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X ²	
Physical exam	X															
Vital signs	X															
Safety lab	X															
Antibodies	X															
AEs / CM	X						X ³								X ³	
Chemotherapy ⁵	X	X	X	X	X											
Study drug s.c.		X	X	X	X	X	X ⁴	X ⁴	X ⁴	X ⁴	X ⁴	X ⁴	X ⁴	X ⁴	X ⁴	
Pharmacokinetics ⁶		X														

Assessments in cycle 4 (from the protocol)

Assessments in chemotherapy cycle 4																
Day	1 ¹	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16-21
ANC	X				X	X	X	X	X	X	X	X	X	X	X ²	
Body temperature	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X ²	
Physical exam	X															
Vital signs	X															
Safety lab	X															
Antibodies	X															
AEs / CM	X						X ³								X ³	
Chemotherapy ⁵	X	X	X	X	X											
Study drug s.c.		X	X	X	X	X	X ⁴	X ⁴	X ⁴	X ⁴	X ⁴	X ⁴	X ⁴	X ⁴	X ⁴	
Pharmacokinetics ⁶		X														

- Day 1 assessments to be completed within 24 h before start of CTX
- Or longer, until the patient's ANC reaches $\geq 2.0 \times 10^9/L$
- Visits on Days 7 and 15 should be clinical visits, however, it is acceptable if AEs and concomitant medication will be elicited by telephone contact at these days
- Study drug must be stopped when $ANC \geq 10 \times 10^9/L$ after nadir is reached
- CHOP: CTX infusion on Day 1, oral prednisolone daily from Day 1 to Day 5
- Pharmacokinetics in a subset of patients in cycle 1 and cycle 4 (for details see Section 8.1)

Assessments in cycles 2, 3, 5, and 6 (from the protocol)

Assessments in chemotherapy cycles 2, 3, 5, and 6																
Day	1 ¹	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16-21
ANC ²	X				X		X			X					X	
Body temperature	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Physical exam	X															
Vital signs	X															
Safety lab	X															
Antibodies	X															
AEs / CM	X						X ³								X ³	
Chemotherapy ⁵	X	X	X	X	X											
Study drug s.c.		X	X	X	X	X	X ⁴	X ⁴	X ⁴	X ⁴	X ⁴	X ⁴	X ⁴	X ⁴	X ⁴	

- 1 Day 1 assessments to be completed within 24 h before start of CTX
- 2 ANC assessment additionally on Days when body temperature is $\geq 38.5^{\circ}\text{C}$
- 3 Visits on Days 7 and 15 should be clinical visits, however, it is acceptable if AEs and concomitant medication will be elicited by telephone contact at these days
- 4 Study drug must be stopped when $\text{ANC} \geq 10 \times 10^9/\text{L}$ after nadir is reached
- 5 CHOP: CTX infusion on Day 1, oral prednisolone daily from Day 1 to Day 5

Safety Endpoints

Adverse events with onset prior to first administration of study treatment (XM02 or EU-Neupogen) and which either stopped prior to first administration of study treatment or which were ongoing but did not deteriorate with respect to severity and/or relationship to study treatment, were only listed by patient including the relevant individual information. In this listing, adverse events with onset after start of chemotherapy were flagged.

All other adverse events were considered as treatment emergent adverse events (TEAEs) and were used in frequency tables for statistical summaries. Percentages for each cycle will be based on the number of patients who entered into the respective cycle and will be compared between treatment groups for cycle 1 and for the overall summary by means of Fisher's exact test. Additional tables will be presented with respect to maximum severity and to strongest relationship to study drug. Multiple occurrences of the same TEAE will be counted only once following a worst-case approach with respect to severity and relationship to study treatment. Similar tables will be provided for TEAEs for which a relationship to study treatment cannot be excluded (possibly treatment related TEAEs). All serious TEAEs will be listed.

6 Review of Efficacy

Efficacy Summary

The trial data submitted to support efficacy, Study XM02-02 demonstrated that XM02 was superior to placebo in the reduction in the duration of severe neutropenia (DSN) with a statistically significant reduction in DSN (2.7 days reduction in DSN, $p < 0.0001$), and XM02 was equivalent to EU-Neupogen with a 95% confidence interval (-0.26, 0.33) in DSN difference lying within the 1 day margin. However, a claim that XM02 is equivalent to EU-Neupogen is not established due to the lack of comparative results between US-licensed Neupogen and EU-Neupogen.

Study XM02-02 was a multicenter, randomized, placebo and active controlled clinical trial in patients with breast cancer. The primary objectives were to demonstrate the equivalence of XM02 and EU-Neupogen in DSN (95% CI within (-1,1) day range and superiority of XM02 to placebo. The study utilized a non-inferiority design comparing XM02, EU-Neupogen and placebo with DSN as the primary endpoint. A total of 350 patients with no prior exposure to chemotherapy for high-risk stage II, stage III or IV breast cancer and requiring chemotherapy were randomized. There were 348 patients included in the full analysis set as two patients were erroneously randomized with screen failures. Randomization was 2:2:1 to XM02, EU-Neupogen or placebo stratified by country and adjuvant vs. metastatic therapy. There was a maximum of 4 cycles of treatment. On the day after chemotherapy, XM02, EU-Neupogen, or placebo were given for at least 5 days and up to a maximum of 14 days. The dose was 5 mcg/kg/day. The ANC's were evaluated within 24 hours before chemotherapy and then daily from Day 2 until Day 15, or longer until ANC reached $2.0 \times 10^9/L$. Placebo patients switched to XM02 after completion of cycle 1.

The primary efficacy endpoint was DSN in cycle 1, defined as the number of days of grade 4 neutropenia with an ANC $< 0.5 \times 10^9/L$. The secondary efficacy endpoints were the incidence of observed febrile neutropenia, 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. The secondary endpoints were exploratory.

6.1 Indication

The sponsor proposed the following indication for this submission: Neutroval for the reduction in the duration of severe neutropenia and the incidence of febrile neutropenia in patients treated with established myelosuppressive chemotherapy for cancer.

6.1.1 Methods

The efficacy review contains results from Study XM02-02. XM02 vs. placebo analyses were performed using ANCOVA with factors treatment, country, type of chemo, and baseline ANC value as covariates. There was a 1-sided alpha 0.025. The full analysis population was all patients randomized excluding two screening failures who received random numbers erroneously. XM02 vs. EU-Neupogen analyses were performed using ANCOVA for 95% CI and in the PP population. A sample size of 140:140:70 has 90% power to show equivalence between XM02 and EU-Neupogen (95% CI within (-1, 1) day) and 90% power to show superiority of XM02 to placebo with 1-sided alpha 0.025. Missing values were imputed by interpolation of non-missing ANC's before and after the missing value. For patients with placebo receiving therapeutic G-CSF treatment, the DSN values in cycle 1 were replaced with the median DSN value of patients with placebo who received no G-CSF treatment.

The statistical reviewer noted the sponsor's method in data replacement and data imputation. In the sponsor'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 the placebo arm, and exaggerate the statistical significance of the difference in DSN. Missing ANCs were imputed by linear interpolation of the ANC values immediately before and after the missing value. The validity of this method is questionable because it assumes? 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 sponsor's results, the statistical reviewer performed the following sensitivity analyses:

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 primarily by linear interpolation. (For full details see the Appendix of the Statistics Review)
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 $< 0.5 \times 10^9/\text{L}$ (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 $< 0.5 \times 10^9/\text{L}$ in XM02 arm, but as $\geq 0.5 \times 10^9/\text{L}$ in placebo arm. This is the worst case analysis.

The results of the sensitivity analyses performed by FDA are consistent with that of the sponsor's analysis.

6.1.2 Demographics

Study XM02-02 was conducted in 52 study centers in 10 countries (Belarus, Slovenia, South Africa, Brazil, Chile, Russia, Hungary, Lithuania, Romania, and Poland). A total of 350 patients with high-risk stage II, stages III or IV breast cancer requiring chemotherapy were randomized. Among these, 348 patients were included in the full analysis set by excluding two patients erroneously randomized after screening failures. The patient demographics of the full analysis set are presented in Table 7 below. The patients in the efficacy trial were primarily older white women. There was one male randomized to both the XM-02 and EU-Neupogen arms and no males to the placebo arm. The mean age of the trial population was approximately 51 years. Approximately half of all patients were diagnosed as having stage III disease. Overall, demographics were balanced across treatment arms.

Table 7 Patient Demographics for Study XM02-02 Cycle 1

	XM02 (N=140) N (%)	EU-Neupogen (N=136) N (%)	Placebo (N=72) N (%)
Age			
mean	51	51	50
min	25	28	28
max	75	74	74
Gender			
Female	139 (99)	135 (99)	72 (100)
Male	1 (1)	1 (1)	0 (0)
Race			
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			
Stage II	23 (16)	36 (26)	15 (21)
Stage III	79 (56)	69 (51)	38 (53)
Stage IV	38 (27)	31 (23)	19 (26)

6.1.3 Subject Disposition

Table 8 summarizes the disposition of study subjects including the protocol violations and reasons for withdrawal from treatment and follow-up. The majority of patients completed the study. The "Withdrawn due to other reasons" category is primarily due to

withdrawal of consent. These withdrawals did not adversely impact the efficacy analyses.

Table 8 Disposition of Patients

	XM02 N=140		EU-Neupogen N=136		Placebo N=72	
DISPOSTION	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 CTX	1	1	1	1	1	1
DEATH	1	1	0	0	2	3
OTHER	3	2	5	4	0	0

6.1.4 Analysis of Primary Endpoint(s)

After adjusted by "treatment", "country" and "adjuvant vs. metastatic therapy", and baseline ANC value, the mean difference between XM02 and placebo was -2.7 days with $p < 0.0001$. The mean difference between XM02 and EU-Neupogen was -0.03 day with a 95% confidence interval (-0.32, 0.26) and $p < 0.0001$ (Table 9). The results in the per protocol population are consistent with that in the full analysis population (Table 10).

Table 9 DSN Results in Full Analysis Population (from statistics review)

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

Table 10 DSN Results in Per Protocol Population (from statistics review)

	XM02	EU-Neupogen	Placebo
N	133	129	58

	XM02	EU-Neupogen	Placebo
Mean (day)	1.1	1.1	3.9
Difference from XM02 in LSMEAN (95% CI)		-0.03 (-0.33, 0.26)	2.7 (2.1, 3.4)
P-value (χ^2)		0.83	<0.0001

The primary regulatory endpoint of study XM02-02 was duration of severe neutropenia.

6.1.5 Analysis of Secondary Endpoints(s)

Analyses for secondary endpoints were exploratory. The results for febrile neutropenia in Cycle 1 are presented in Table 11.

Table 11 Results for Febrile Neutropenia in Cycle 1 (from statistics reviewer)

Type of Febrile Neutropenia	XM02 N=140		EU-Neupogen 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	1 6	(11.4%) [7.2%,17.8%]	1 7	(12.5%) [8.0%,19.1%]	2 2	(30.6%) [21.1%,42.0%]
Observed or protocol defined FN	1 7	(12.1%) [7.7%,18.6%]	1 7	(12.5%) [8.0%,19.1%]	2 6	(36.1%) [26.0%,47.6%]

FN = febrile neutropenia

6.1.6 Other Endpoints

Immunogenicity studies are discussed in Section 7.4.6 Immunogenicity.

6.1.7 Subpopulations

Subgroup results on DSN were analyzed by age and race by the statistics reviewer. Subgroup analysis by gender was not conducted since the population was almost entirely women (99%). The subgroup results are generally consistent with that of the primary analyses, except that XM02 appears to have a longer DSN than EU-Neupogen in the Hispanic group. Detailed results are available in the Statistics Review.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

PK data were obtained from patients with breast cancer, lung cancer and NHL (N = 12 per group) who received XM02 5 mcg/kg/day. Following the first XM02 dose in cycle 1,

the geometric mean (CV%) of serum C_{max} and AUC_{0-24h} were 36 ng/mL (41%) and 305 ng*h/mL (35%) in breast cancer, 25 ng/mL (60%) and 273 ng*h/mL in lung cancer (61%), and 20 ng/mL (24%) and 184 ng*h/mL (23%) in NHL, respectively. For the 3 groups combined, the median T_{max} was between 4 to 6 hours and the median t_{1/2} was between 3.2 to 3.8 hours. The terminal half-life was calculated from serum levels measured up to 24 hours as compared to up to 48 hours in the healthy subjects. Accumulation after repeated dosing was not observed. No dose adjustment based on cancer type is warranted.

According to the analyses performed by the Clinical Pharmacology reviewer, no gender-related differences were observed in the PK of Neutroval following sc administration. Analyses of the PK profile in patients with renal or hepatic impairment were attempted based on the available data; however, the data were inadequate to inform any conclusions.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

None apparent at this time.

6.1.10 Additional Efficacy Issues/Analyses

Study XM02-02 was the only efficacy study submitted in this BLA in support of the proposed indication of reduction in the duration of DSN. Study XM02-02 is a multinational, multicenter, randomized, controlled study in 350 patients with high-risk stage II, or with stage III or IV breast cancer needing chemotherapy. Although this was a single trial, the efficacy result was highly statistically significant with a p value of > 0.0001. An equivalence claim of XM02 can not be established because no data on the treatment effect size of EU-Neupogen compared to US-licensed Neupogen was submitted with this application.

7 Review of Safety

Safety Summary

The application submitted data from 877 subjects who were exposed to XM02. Of these 877 subjects, 200 were healthy volunteers who participated in 2 Phase 1 studies. These studies were single dose, single blind, randomized, 2 period crossover studies that compared PK and PD characteristics of XM02 to those of EU-Neupogen. Subjects received 5 or 10 mcg/kg by sc or iv administration. There were few adverse events associated with the study drugs and adverse events occurred at similar frequencies in subjects receiving XM02 and EU-Neupogen.

The review of safety was focused on the analyses of 677 patients with cancer who received the XM02 dosing regimen proposed for labeling, 5 mcg subcutaneously once daily. Analyses of the safety databases were performed to analyze the individual XM02 trials, and pooled safety data for the three key XM02 trials in patients with cancer. Drug

exposure and overall safety were evaluated to include summaries of deaths and common, serious, or significant adverse events. In addition, adverse events of special interest based on the known toxicity profile of marketed G-CSF receptor agonist products were summarized.

In general, XM02 appears to be safe with a side effect profile similar to EU-Neupogen, the active comparator in the clinical trials. Following is a list of safety issues pertinent to this application. These issues are discussed in full in section 7.3.5 Submission Specific Primary Safety Concerns.

- Bone pain – the most common adverse event associated with XM02 was bone pain.
- AE associated with other G-CSF products - there were no cases of ARDS, or splenic rupture, conditions associated with marketed G-CSF products.

Tumor Promotion: For supportive care agents

XM02 is a growth factor that stimulates neutrophils. However the possibility that XM02 can act as a growth factor for any tumor type cannot be excluded. In a randomized study evaluating the effects of Neupogen vs. placebo in patients undergoing remission induction for AML, there was no significant difference in remission rate, disease-free survival or overall survival (Heil G, 1997).

No incidences of XM02 or EU-Neupogen induced tumor promotion were reported as a result of the studies submitted in this package, however these studies were not designed to address this issue.

7.1 Methods

The safety profile for XM02 was evaluated in 5 clinical studies. As XM02 was developed as a biosimilar in Europe, the safety of XM02 was compared to that of EU-licensed Neupogen. Safety was assessed in each of the studies individually and as an integrated assessment of all the clinical studies. This was appropriate as all clinical studies in patients with cancer had designs which were similar and the dosing was the same. The actual analysis submitted by the Sponsor was performed by the (b) (4) data management department. (b) (4) set up an XM02 Clinical Safety Database after recoding for AEs to be consistent with MedDRA terminology. AEs were coded using lower level terms and recoded for all studies using MedDRA version 7.1. AEs that began prior to the first administration of XM02, EU-Neupogen, or placebo and which stopped prior to first administration of the drug or which were ongoing but did not deteriorate with respect to severity and/or relationship to study treatment were excluded from all listings and summary of data. Statistical analyses were performed on the Safety Set (All randomized patients who received at least one dose of XM02, EU-Neupogen or Placebo), Healthy Subjects Set (All subjects of the safety set who were randomized in one of the 2 studies involving healthy subjects), and the Cancer Patients Set (All subjects of the Safety Set who were randomized in one of the 3 cancer studies). Statistical analyses were performed for the healthy subjects set and the cancer patients set, but not for the pooled safety set of patients with cancer and healthy volunteers. Although the Summary of Clinical Safety states that the actual treatment was used in

the analysis, the analysis files are setup by group randomized. The sponsor subsequently provided a list of patients who received a treatment other than the one to which they were randomized.

Safety laboratory evaluations were performed at regular intervals and summaries of the data were compiled.

In general, the approach taken by the applicant and the analyses of the data utilized to identify the safety profile for XM02 were adequate.

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

For a complete summary of the trials examined by the applicant during the safety evaluation of the trials submitted with this application, see Section 5.1 Tables of Clinical Studies. For the purposes of this review, the safety analyses will be limited primarily to the 3 studies in patients with cancer (Study XM02-02, Study XM02-03, Study XM02-04). There were 677 patients from the studies with patients with cancer, 348 from Study XM02-02, 237 from Study XM02-03, and 92 from Study XM02-04. All studies evaluated XM02 at the doses and schedule for which the applicant is seeking approval.

7.1.2 Categorization of Adverse Events

For the key trials, adverse events were coded utilizing MedDRA version 7.1 and were presented to show all five levels of the MedDRA hierarchy. Most AEs were graded using a system corresponding to grades of mild, moderate, or severe which were coded as a numbered scale of 1 through 3. For safety laboratory assessments, adverse events were graded according to NCI CTC AE (version 3.0). A side-by-side comparison of verbatim term to MedDRA Lower Level Term was performed by reviewing approximately 6400 line listings of AEs to verify the accuracy of the coding process. Coding was appropriate in the majority of cases. The cases where the judgment of this reviewer differed from that of the coder were not clinically meaningful.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

Data from all three studies were re-coded by the (b) (4) data management department using MedDRA version 7.1. The numerator and denominators for each trial were combined. No formal weighing methods were performed. Pooling the data provided a database of 677 patients for the comparative safety analyses and other explorations of the safety profile for XM02. This approach was taken as these trials were the key trials submitted in support of safety and efficacy and as previously noted were similar in trial design and used the same dose. As noted above, AEs with onset prior to first administration of study drug (XM02, EU-Neupogen, placebo) and which stopped prior to first administration of study drug (or which were ongoing but did not

deteriorate with respect to severity and/or relationship to study treatment), were excluded from all listings and summaries in this safety summary. Treatment Emergent Adverse Events (TEAEs) were considered as being ‘possibly drug related’ and as possibly chemotherapy related’ (cancer patients set only), if the corresponding relationship was assessed as “unclassified”, “possible” or “probable” or if the assessment of relationship was missing.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

For the three key trials submitted in support of this application, the dosing regimen was identical to the dose suggested for labeling (5 mcg/kg sc daily). A total of 677 patients received at least one dose of XM02 during the conduct of the three key trials. This is an adequate number of overall patients. Patient demographics are summarized in Table 7 and Table 12. The demographics for the studies in patients with cancer were balanced across all arms. Study XM02-02 was conducted in patients with breast cancer in Europe, therefore there is a larger proportion of middle age, Caucasian women in that study compared to the XM02-03 and XM02-04 studies. The median age of the safety population was 56 years (20 to 80 years) and 65% were female,

The dose and duration of exposure was adequate to assess safety for the intended use. The use of EU-Neupogen as the active comparator was adequate to answer critical questions such as, was the safety profile of XM02 similar to other GCSF receptor agonists. Potential class effects such as bone pain, splenomegaly, ARDS, and allergic reactions were evaluated. The exclusion criteria did not limit the relevance of the safety assessment.

Table 12 Demographics for Cycle 1 of Study XM02-03 and Study XM02-04

	XM02-03		XM02-04	
	XM02 (N=158) N (%)	EU-Neupogen (N=79) N (%)	XM02 (N=63) N (%)	EU-Neupogen (N=29) N (%)
Age (years)				
mean	59	55	50	57
min	34	35	18	33
max	78	78	83	83
Gender				
female	31 (20)	18 (23)	32 (51)	12 (41)
male	127 (80)	61 (77)	31 (49)	17 (59)

Race				
Hispanic	8 (5)	3 (4)	5 (8)	3 (10)
White	149 (94)	76 (96)	55 (87)	26 (90)
Other	1 (1)	0 (0)	3 (5)	0 (0)
Lung Cancer Type				
Small Cell				
Non Small Cell	26 (16)	13 (16)	-	-
Lymphoma Type	132 (84)	66 (84)	-	-
DLBC	-	-	50 (79)	18 (62)
FL Gr 3	-	-	6 (10)	4 (14)
Anaplastic LC	-	-	4 (6)	5 (17)
Other	-	-	3 (5)	(2 (7)

Table 13 Age and Gender for Combined Safety Set

	XM02 only N=356) N (%)	EU- Neupogen only N=134) N (%)	EU- Neupogen/ XM02 N=115 N (%)	Placebo/ XM02 (N=72) N (%)	Any XM02 (N=541) N (%)	Overall (N=677) N (%)
Age (years)						
mean	54	52	57	50	54	54
min	18	28	33	28	18	18
median	55	51	57	48	55	54
max	83	75	83	74	83	83
Age Categories						
< 65 years	285 (80)	115 (86)	83 (72)	63 (88)	430 (80)	546 (81)
≥ 65 years	71 (20)	19 (14)	32 (28)	9 (13)	11 (21)	131 (19)
Gender						
Female	199 (56)	129 (96)	39 (34)	72 (100)	308 (57)	439 (65)
Male	157 (44)	5 (4)	76 (66)	0 (0)	233 (43)	238 (35)
Race						
Caucasian	319 (90)	116 (87)	109 (95)	62 (86)	488 (90)	606 (90)
Other	37 (10)	18 (13)	6 (5)	10 (14)	53 (10)	71 (11)

7.2.2 Explorations for Dose Response

Assessments for dose response were not included in trials in patients with cancer. All patients in those trials received the dose intended for labeling.

7.2.3 Special Animal and/or In Vitro Testing

There were no special animal or in vitro testing relevant to safety.

7.2.4 Routine Clinical Testing

Routine clinical testing and monitoring were analyzed and the results of the analysis are in the laboratory and adverse event sections of this review. Overall, the monitoring of patients in the trial was adequate.

7.2.5 Metabolic, Clearance, and Interaction Workup

Patients with renal impairment were not enrolled in XM02 clinical trials (Inclusion criteria: Creatinine < 1.5 x ULN). The sponsor's proposed labeling: (b) (4)

There were no formal drug-drug interaction studies conducted and no in vitro or in vivo PK drug interaction data/information were included in the BLA submission. ECG monitoring occurred at screening & follow up (14 days post-dose) within the two single-dose phase 1 trials. For this reason and because ECGs were not collected during treatment, the ECG data in the BLA is inadequate.

These issues are being discussed at the time that this review is being finalized. There is the potential for three Post Marketing Requirements; one for a renal impairment study, one for DDI evaluation, and one for a TQT study.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

Potential adverse events known for other G-CSF receptor agonists were evaluated by the Sponsor during the course of development. These potential adverse events are splenic rupture, acute respiratory distress syndrome, serious allergic reactions, and the use in patients with sickle cell disorders. The analysis for these potential adverse events is described in detail in Section 7.3.5 Submission Specific Primary Safety Concerns. Briefly, an independent review of all relevant CRF and narratives showed no occurrences of splenic rupture, acute respiratory distress syndrome, or true serious allergic reactions. The use of other G-CSF receptor agonists has been associated with sickle cell crises in patients with sickle cell disease in the setting of using filgrastim for the mobilization of stem cells. The use of G-CSF receptor agonists in patients with sickle cell disease who also have cancer and are receiving myelosuppressive anti-cancer drugs has not been studied. The enrollment criteria for the studies done in patients with cancer as part of this BLA submission did not screen for sickle cell disease, therefore the effect of XM02 in patients with sickle cell disease could not be assessed.

7.3 Major Safety Results

7.3.1 Deaths

The review of the causes of death in the three studies performed in patients with cancer consisted of a review of the line listings of all patients who died followed by review of the corresponding CRFs and narratives. The causes of death are summarized in Table 14. In the majority of cases, the reviewer agreed with the sponsor's attributed causes of death. In Study XM02-03, the reviewer attributed 1 case to progression of disease which the sponsor attributed to a more specific cause of haemoptysis. As the sponsor's determination was more conservative, the cause of death for that patient (80-807-07) was left as attributed by the sponsor in all tables and summaries. If death occurred in any patient who received XM02 at any time during the study, that patient was grouped in the XM02 category. Patients were placed in the EU-Neupogen or placebo category only if that patient died after receiving only EU-Neupogen and/or placebo and no XM02. Due to the design of the studies, this would only occur during cycle 1. No deaths were attributed to the study drug.

Table 14 Summary of Deaths by Trial and Arm

	Study XM02-02			Study XM02-03		Study XM02-04	
	XM02 N=140 N (%)	EU- Neupogen* N=136 N (%)	Placebo* N=72 N (%)	XM02 N=158 N (%)	EU- Neupogen* N=49 N (%)	XM02 N=63 N (%)	EU- Neupogen* N=29 N (%)
All Deaths	2 (1)	0 (0)	2 (3)	5 (3) * 20 (13)	2 (4)	1 (2)	0 (0)
Deaths from Progressive Disease	2 (1)	0 (0)	0 (0)	1 (1)* 8 (5)	2 (4)	1 (2)	0 (0)
Deaths From Other Causes	0 (0)	0 (0)	2 (3)	4 (3)* 13 (8)	0 (0)	0 (0)	0 (0)

*Cycle 1 only

Other Causes of Death in Patients Receiving Placebo: Sepsis (1), Cardiorespiratory Arrest (1)

Other Causes of Death in Patients Receiving XM02: Cardiac Failure (3), Cardiopulmonary Arrest (3), Cardiopulmonary Failure (1), Haemoptysis (3), PE (1), Respiratory Failure (2), Sepsis (1)

In Study XM02-02, the study in patients with breast cancer, there were a total of 4 deaths during the study or within 30 days of the last investigational product dose, 2 on the XM02 arm, 0 on the EU-Neupogen arm, and 2 on the placebo arm. Subjects 50-519-09 and 70-702-02 on the XM02 arm died of progressive disease. Subjects 20-221-08 and 80-802-19 on the placebo arm died of progressive disease.

In Study, XM02-03, the study in lung cancer patients, there were a total of 22 deaths during the study, 12 in the XM02 arm and 10 in the EU-Neupogen/XM02 arm. Of the subjects in the EU-Neupogen/XM02 arm, 2 subjects (90-902-04 and 90-908-06) died during cycle 1 (no exposure to XM02) and 40-403-01, 50-510-06, 60-605-03, 80-801-03, 80-805-02, 80-805-06, and 90-901-08) died after cycle 1 (exposed to XM02). Subject 80-805-14 on the XM02 arm and subjects 80-805-02, 90-901-08, and 90-902-04 on the EU-Neupogen/XM02 arm died of disease progression. Subjects 60-604-04, 80-802-09, 80-804-04, 40-403-91, 50-510-06, 60-605-01, 60-606-03, 80-801-03, 80-805-06, and 90-908-06 died of cardiac failure, cardiopulmonary failure or cardiac arrest. Subjects 80-807-08 and 80-807-13 died of respiratory failure. Subject 60-605-01 died of sepsis. Subject 70-711-01 died of pulmonary embolism. Subjects 80-803-01 and 80-807-07 died of hemoptysis. Subject 80-805-06 died of cervical cord compression. Subject 90-902-04 died of metastatic disease to the central nervous system. There were 12 deaths within 30 days of the end of study (10 due to disease progression and 2 due to unknown causes).

In Study XM02-04, Subject 50-527-03 (EU-Neupogen/XM02 group receiving XM02) died due to progression of disease.

7.3.2 Nonfatal Serious Adverse Events

The protocol definition of a Serious Adverse Event (SAE) was all AEs or intercurrent illnesses or clinically abnormal laboratory values occurring during the study that resulted in death, is life-threatening, requires in-patient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability or incapacity, results in a congenital anomaly or birth defect, a medically significant event or events requiring intervention to prevent the previous outcomes. This definition is in accordance with ICH E6 Good Clinical Practice Guidelines.

For all reports of SAE, line listings were reviewed as well as the corresponding CRF and narratives. SAE are summarized in Table 15.

Table 15 Severe Adverse Events

	Any XM02 N=541 N (%)	EU-Neupogen only N=134 N (%)	Placebo N=72 N (%)	Overall N=677 N (%)
Cycle 1				
Any SAE	59 (11)	13 (10)	16 (22)	74 (11)
Study Drug Related	2 (0.4)	0 (0)	0 (0)	2 (0.3)
Chemo Related	49 (9)	9 (7)	15 (21)	59 (9)
All cycles				
Any SAE	118 (22)	15 (11)	-	135 (20)

	Any XM02 N=541 N (%)	EU-Neupogen only N=134 N (%)	Placebo N=72 N (%)	Overall N=677 N (%)
Study drug related	5 (1)	0 (0)	-	5 (1)
Chemo related	90 (17)	11 (8)	-	102 (15)

In cycle 1 of all studies, 74 (11%) of patients experienced a serious adverse event. In the XM02 treated group there were 11%, 22% in the placebo group, and 10% in the EU-Neupogen treated group. Less than 1% of the SAEs in the XM02 group were considered study drug related by the investigator and sponsor. For all cycles of all cancer studies, 5 patients experienced SAEs that were thought to be study drug related by the investigator and the sponsor. Review of these cases showed that in study XM02-02, one patient (80-803-03) had an allergic reaction (bronchospasm) in cycle 1 following the 10th dose of study drug, and one patient (90-903-04) had an episode of syncope after receiving XM02. In study XM02-03, three patients had four SAEs that were at least thought to be possibly related to the study drug by the investigator. One patient (50-516-01) had a myocardial infarction that was thought to have a possible relationship to the study drug and chemotherapy by the investigator, but not the sponsor. Review of this case showed that the patient had extensive disease in the mediastinum, and was receiving cisplatin which are likely to be causative than the study drug. Patient 80-805-16 experienced thrombocytopenia that the reviewer believes was more likely related to chemotherapy than to the study drug and patient (80-807-16) had thrombocytopenia and hyperuricemia that the reviewer attributes to chemotherapy instead of to the study drug. However, these SAEs are considered study drug related for the purposes of this review.

7.3.3 Dropouts and/or Discontinuations

AEs leading to premature discontinuation of the study drug were evaluated by reviewing information provided by the sponsor in the study report, adverse event and follow-up for early withdrawal data sets, and accompanying case report forms. The results are summarized in Table 16. Summary tables for the individual studies are contained in the Appendix (Table 23, Table 24, and Table 25). For cycle 1, 11 patients withdrew from the XM02 arm of the study due to a TEAE, and for all cycles, 27 patients withdrew from the XM02 arm. The majority of these TEAE were related to chemotherapy with 2 related to study drug. Although documentation in the submission package was difficult to locate, the two patients that discontinued XM02 due to TEAE were patients 80-803-03 for allergic reaction and 90-903-04 for syncope. Patients 50-531-09, and 80-802-20 on the XM02 arm withdrew consent. The reasons for drop-out and discontinuation were balanced between the XM02 and EU-Neupogen arms, but there were more chemotherapy related withdrawals in the placebo arm.

Table 16 Dropouts and Discontinuations

	Any XM02	EU-Neupogen	Placebo	Overall
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	N=541 N (%)	only N=134 N (%)	N=72 N (%)	N=677 N (%)
Cycle 1				
Any TEAE	11 (2)	4 (3)	0 (0)	15 (2)
Study Drug Related	0 (0)	1 (1)	0 (0)	1 (0.1)
Chemo Related	8 (2)	2 (2)	0 (0)	10 (15)
All cycles				
Any TEAE	27 (8)	5 (4)	-	40 (6)
Study drug related	2 (1)	2 (2)	-	6 (1)
Chemo related	17 (5)	3 (2)	-	25 (4)

7.3.4 Significant Adverse Events

This section of the review describes significant adverse events. For the purposes of this review, a significant adverse event is any Adverse Event that was given a severity grade of 3 (severe) on the 3 tier (1 (mild), 2 (moderate), 3 (severe)) grading criteria for most adverse events identified in this study. Laboratory findings were graded using the CTC AE version 3.0 and are discussed in Section 7.4.2 Laboratory Finding Safety.

These significant adverse events were primarily chemotherapy related and occurred at similar frequencies in all 3 arms. The major significant adverse events associated with the study drug were those associated with bone pain which is discussed in Section 7.3.5 Submission Specific Primary Safety Concerns. Tables showing the Grade 3 adverse events for XM02 by MedDRA hierarchy are in the Appendix (Table 26, Table 27, Table 28, Table 29). For details on the data analysis for these tables, see Section 7.4.1 Common Adverse Events.

7.3.5 Submission Specific Primary Safety Concerns

There are adverse events that have been identified with other G-CSF receptor agonists, primarily Neupogen. These are bone pain, splenic rupture, allergic reactions, and acute respiratory distress syndrome (ARDS). Splenic rupture, and ARDS were identified during the post-approval period for Neupogen.

The definition of bone pain was broadened by the sponsor to include the following MedDRA version 7 Preferred Terms: arthralgia, back pain, bone pain, musculoskeletal pain, neck pain, pain in extremity, pain in jaw, pelvic pain, and sacral pain. These terms are appropriate to capture occurrences of bone pain. In cycle 1, the incidence of bone pain using these criteria was 14.2% for the XM02 arm, 19% for the EU-Neupogen arm, and 9.7% for the placebo arm (Table 17). For all studies in patients with cancer, the incidence of bone pain was 23.5% for Any XM02, 30.6% for EU-Neupogen, and 9.7% for placebo. No patients discontinued the study drug due to bone pain (Table 18).

Table 17 Bone Pain in Patients with Cancer Study XM02-02 Cycle 1

	XM02 N=141 N (%)	EU-Neupogen N=147 N (%)	Placebo N=72 N (%)
Cycle 1			
At least 1 PT for bone pain	20 (14.2)	28 (19.0)	7 (9.7)
Study Drug Related	11 (7.8)	19 (12.9)	1 (1.4)
Grade 3	1 (0.7)	1 (0.7)	0 (0)

Table 18 Bone Pain in Patients with Cancer (All Studies)

	Any XM02 N=541 N (%)	EU-Neupogen Only N=134 N (%)	Placebo N=72 N (%)
Cycle 1			
At least 1 PT for bone pain	65 (12)	28 (20.9)	7 (9.7)
Study Drug Related	27 (5.2)	19 (14)	1 (1.4)
Grade 3	1 (0.2)	0 (0)	0 (0)
All Cycles			
At least 1 PT for bone pain	130 (23.5)	42 (30.6)	-
Study Drug Related	54 (10.4)	0 (0)	-
Grade 3	1 (0.2)	0 (0)	-

Splenomegaly is known to occur following administration of G-CSF receptor agonists. In one study, the incidence of splenomegaly was 24% with the median increase of 34 % (range 2% to 148%) (Dale, 1993), and splenic rupture has been reported (Becker, 1997). The sponsor reported no cases of splenic rupture for this application. A review of 37 patients who received XM02 with an AE of abdominal pain resulted in identification of no cases of splenic rupture. None of the AEs was grade 3.

Allergic reactions were considered potentially present by the sponsor when the following Preferred Terms were identified: angioneurotic oedema, dermatitis allergic, drug hypersensitivity, hypersensitivity, rash, rash pruritic, and urticaria. In all cycles, the incidence of allergic reactions deemed to be study drug related was 3.7% for both any XM02 and only EU-Neupogen. A review of the patients with the relevant AE Preferred Terms who were receiving XM02 identified one patient (80-803-03) had an allergic reaction (bronchospasm) in cycle 1 following the 10th dose of study drug. The patients symptoms were relieved with corticosteroids and the patient received subsequent doses of the study drug.

The sponsor considered ARDS present when the Preferred Terms identified were: acute respiratory failure and respiratory failure. In cycle 1, the sponsor identified one patient in study XM02-03 with symptoms matching this definition. This was not

attributed to study drug. Across all cycles, there were 3 (0.4%) patients with respiratory failure or acute respiratory failure, all in study XM02-03, and all in the XM02 only arm. None of these cases were study-drug related by the sponsor. Using the same preferred term search, this reviewer was not able to identify patients with ARDS as defined by these terms.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

All adverse events were analyzed using data sets, clinical study reports, and additional documentation from individual studies and data pooled from studies performed with patients with cancer by the sponsor. In addition, adverse event data sets using the per protocol population from individual studies in patients with cancer were combined together by this reviewer. Patients were placed into treatment arms based on the following criteria: Any XM02 - if the patient received any amount of XM02 at any time during the study, EU-Neupogen Only – if the patient received only EU-Neupogen and Placebo- if the patient received only placebo. If the patient was in the sponsor's Placebo/XM02 group, they were placed in the Placebo group for cycle 1 and the Any XM02 group for Cycle 2 and beyond. If the patient was in the Filgrastim/XM02 group, they were placed in the EU-Neupogen Only group for cycle 1, and the Any XM02 group for cycles 2 and beyond. The sponsor analyzed safety data to include the placebo, but did not compare the patients who received placebo to the other patients in the other arms in cycles other than cycle 1. This method resulted in differences in the number of patients per group. There was a total difference of 8 patients between the data sets created by the sponsor and this reviewer (677 and 669, respectively). Independent analyses of both the sponsor's data sets and the one created by this reviewer lead to results that were similar both statistically and clinically. The analysis using the reviewer's data sets are depicted in the tables that follow and the analysis based on the sponsor's data set are included in the Appendix (Section 7.4.1 Common Adverse Events Table 30).

The reviewer's safety set pooled from patients in all of the studies in cancer patients was analyzed for AEs that occurred at $\geq 5\%$ difference between the XM02 arm and the EU-Neupogen arm or the placebo arm for each level of the MedDRA hierarchy. AEs that were graded at all severities are shown in the following tables. For a discussion of AEs at the highest severity grade, see Section 7.3.4 Significant Adverse Events. At the PT level, there were no mild, moderate, or severe AEs that were $\geq 5\%$ difference between the 3 arms (Table 19). At the HLT level, there was an increase in Gastrointestinal Disorders at all grades comparing XM02 to EU-Neupogen. There were no severe AEs that were $\geq 5\%$ difference among the 3 arms (Table 20). At the HLGT level, there was an increase in Gastrointestinal Signs and Symptoms, Respiratory Disorders, Infections – Pathogen Class Unspecified and Platelet Disorders at all grades

comparing XM02 to EU-Neupogen. There were no severe AEs that were $\geq 5\%$ difference among the 3 arms (Table 21). At the SOC level, there was an increase in Blood and Lymphatic System Disorders and Infections and Infestations comparing XM02 to EU-Neupogen at all grades (Table 22). Review of these differences found them to be primarily due to chemotherapy and not clinically meaningful.

Table 19 Common Adverse Events at the PT level (all studies)

PT Name	Any XM02 N=488		EU-Neupogen Only N=221		Placebo N=60	
	N	%	N	%	N	%
NAUSEA	250	51	98	44	19	32
VOMITING	147	30	43	19	4	7
ASTHENIA	136	28	64	29	17	28
ALOPECIA	121	25	87	39	21	35
ANAEMIA	116	24	16	7	2	3
NEUTROPENIA	97	20	51	23	19	32
DIARRHOEA	78	16	54	24	12	20
HEADACHE	65	13	23	10	2	3
COUGH	64	13	9	4	2	3
ANOREXIA	63	13	28	13	1	2
WEIGHT DECREASED	54	11	8	4	1	2
BONE PAIN	53	11	31	14	3	5
PYREXIA	52	11	23	10	5	8
THROMBOCYTOPENIA	48	10	11	5	1	2
CONSTIPATION	40	8	16	7	2	3
FATIGUE	40	8	18	8	3	5
CHEST PAIN	39	8	9	4	1	2
ABDOMINAL PAIN	37	8	24	11	2	3
ABDOMINAL PAIN UPPER	37	8	15	7	2	3
INSOMNIA	37	8	12	5	2	3

Table 20 Common Adverse Events at the HLT level (all studies)

HLT Name	Any XM02 N=488		EU-Neupogen Only N=221		Placebo N=60	
	N	%	N	%	N	%
NAUSEA AND VOMITING SYMPTOMS	267	55	105	48	21	35
ASTHENIC CONDITIONS	172	35	79	36	21	35
ALOPECIAS	131	27	95	43	24	40
ANAEMIAS NEC	116	24	16	7	2	3
NEUTROPENIAS	115	24	67	30	27	45

HLT Name	Any XM02 N=488		EU-Neupogen Only N=221		Placebo N=60	
COUGHING AND ASSOCIATED SYMPTOMS	82	17	10	5	2	3
DIARRHOEA (EXCL INFECTIVE)	78	16	54	24	12	20
PHYSICAL EXAMINATION PROCEDURES	77	16	11	5	2	3
APPETITE DISORDERS	71	15	30	14	3	5
GASTROINTESTINAL AND ABDOMINAL PAINS (EXCL ORAL AND THROAT)	66	14	32	14	3	5
HEADACHES NEC	65	13	23	10	2	3
MUSCULOSKELETAL AND CONNECTIVE TISSUE SIGNS AND SYMPTOMS NEC	63	13	34	15	2	3
BONE RELATED SIGNS AND SYMPTOMS	54	11	31	14	3	5
FEBRILE DISORDERS	52	11	23	10	5	8
THROMBOCYTOPENIAS	48	10	11	5	1	2
PAIN AND DISCOMFORT NEC	48	10	9	4	1	2
GASTROINTESTINAL ATONIC AND HYPOMOTILITY DISORDERS NEC	40	8	17	8	2	3
BREATHING ABNORMALITIES	40	8	7	3	3	5
DISTURBANCES IN INITIATING AND MAINTAINING SLEEP	37	8	12	5	2	3
LOWER RESPIRATORY TRACT AND LUNG INFECTIONS	34	7	7	3	0	0

Table 21 Common Adverse Events at the HGLT level (all studies)

HGLT Name	Any XM02 N=488		EU-Neupogen Only N=221		Placebo N=60	
	N	%	N		N	%
GASTROINTESTINAL SIGNS	287	59	118	53	26	43

HGLT Name	Any XM02 N=488		EU-Neupogen Only N=221		Placebo N=60	
AND SYMPTOMS						
GENERAL SYSTEM DISORDERS NEC	218	45	88	40	23	38
SKIN APPENDAGE CONDITIONS	138	28	95	43	24	40
WHITE BLOOD CELL DISORDERS	126	26	70	32	28	47
ANAEMIAS NONHAEMOLYTIC AND MARROW DEPRESSION	118	24	17	8	3	5
RESPIRATORY DISORDERS NEC	114	23	23	10	5	8
GASTROINTESTINAL MOTILITY AND DEFAECATION CONDITIONS	104	21	61	28	15	25
INFECTIONS - PATHOGEN CLASS UNSPECIFIED	79	16	22	10	8	13
PHYSICAL EXAMINATION TOPICS	77	16	11	5	2	3
APPETITE AND GENERAL NUTRITIONAL DISORDERS	71	15	30	14	3	5
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS NEC	65	13	34	15	2	3
HEADACHES	65	13	23	10	2	3
BODY TEMPERATURE CONDITIONS	55	11	26	12	6	10
ELECTROLYTE AND FLUID BALANCE CONDITIONS	55	11	16	7	1	2
BONE DISORDERS (EXCL CONGENITAL AND FRACTURES)	54	11	31	14	3	5
PLATELET DISORDERS	53	11	12	5	1	2
NEUROLOGICAL DISORDERS NEC	49	10	21	10	2	3
SLEEP DISORDERS AND DISTURBANCES	39	8	13	6	2	3
MUSCLE DISORDERS	37	8	22	10	1	2
ORAL SOFT TISSUE CONDITIONS	36	7	30	14	11	18

Table 22 Common Adverse Events at the SOC level (all studies)

SOC Name	Any XM02 N=488		EU-Neupogen Only N=221		Placebo N=60	
	N	%	N		N	%
GASTROINTESTINAL DISORDERS	316	65	137	62	36	60
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	246	50	101	46	26	43
BLOOD AND LYMPHATIC SYSTEM DISORDERS	227	47	87	39	30	50
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	164	34	102	46	26	43
METABOLISM AND NUTRITION DISORDERS	140	29	51	23	5	8
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	140	29	74	33	4	7
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	130	27	26	12	5	8
INVESTIGATIONS	119	24	23	10	3	5
NERVOUS SYSTEM DISORDERS	119	24	44	20	4	7
INFECTIONS AND INFESTATIONS	106	22	28	13	10	17
VASCULAR DISORDERS	59	12	24	11	2	3
CARDIAC DISORDERS	50	10	9	4	4	7
PSYCHIATRIC DISORDERS	50	10	20	9	5	8
EYE DISORDERS	24	5	7	3	0	0
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	19	4	3	1	1	2
EAR AND LABYRINTH DISORDERS	18	4	7	3	0	0
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	17	3	3	1	1	2
REPRODUCTIVE SYSTEM AND BREAST DISORDERS	16	3	8	4	3	5

SOC Name	Any XM02 N=488		EU-Neupogen Only N=221		Placebo N=60	
RENAL AND URINARY DISORDERS	13	3	8	4	0	0
HEPATOBIILIARY DISORDERS	8	2	2	1	0	0
SURGICAL AND MEDICAL PROCEDURES	8	2	0	0	1	2
IMMUNE SYSTEM DISORDERS	3	1	0	0	0	0

A SAS tool for implementing SMQs and performing MedDRA based analyses of AE Data, the MedDRA-based Adverse Event Diagnostics (MAED) tool was employed to search the individual studies' data bases for SMQs. Data was analyzed using the MedDRA Version 10.1 dictionary as there were no SMQs available for MedDRA Version 7.1. Broad and narrow scope SMQs were ranked in ascending order by p-value derived from a Mantel-Haenszel test for ranking purposes only. Review of all SMQs with a p-value < 0.05 showed the most common ones to be associated with cytopenias related to chemotherapy or the incidence of these SMQs by percentage were higher in either the EU-Neupogen or placebo arms. There were no SMQs relevant to XM02 that were clinically meaningful. Tables of the SMQ results are in the Appendix (Table 32, Table 33, Table 34, Table 35, Table 36).

7.4.2 Laboratory Findings

Laboratory data from all 3 clinical studies in patients with cancer were analyzed for this review using the pooled lab data set provided in the application package. The following parameters were analyzed: hemoglobin, platelets, white blood count, and differential count (absolute neutrophil count, absolute lymphocyte count, absolute monocyte count, absolute eosinophil count, and absolute basophil count), and the clinical chemistry parameters of ALT, AST, bilirubin, AP, gamma-glutamyltransferase, LDH, glucose (non-fasting), uric acid, creatinine, sodium, potassium and phosphate and were assessed at the screening visit and end of study. Distribution analysis or analysis of central tendencies to identify outlier results and matched pairs analysis were performed. The matched pairs analyses evaluated minimum, maximum, and mean baseline and after treatment laboratory results utilizing the paired t-test. This test compares results for the chosen variable at different time points, usually before and after an event, in this case, treatment with XM02. The analysis of central tendency for the clinical laboratory results revealed few outliers. These were compared to analyses performed by the sponsor at screening, on Day 1 of each cycle, and at the end of study visit. In addition hematology and chemistry laboratory data from Study XM02-02 was analyzed using the same

methods. There were no relevant differences between the treatment groups with regard to changes over time compared to baseline.

7.4.3 Vital Signs

Vital signs including systolic and diastolic blood pressures, pulse rate, body temperature, body weight, and BMI were assessed at each visit in all phase 3 clinical trials. Body temperature was assessed additionally on Days 1 to 14 of each chemotherapy cycle. On days when the investigational product was administered, there were no requirements for pre and/or post administration vital sign assessments. Within the 3 cancer studies, there were no clinically significant changes in heart rate or blood pressure from baseline. Body temperature was without unexpected clinically significant changes. There was a slight decrease in mean body weight observed in the breast cancer study (-0.5 kg) and the lung cancer study (-1.7 kg), which was not seen in the NHL study.

7.4.4 Electrocardiograms (ECGs)

No data sets containing ECG data were provided for review.

7.4.5 Special Safety Studies/Clinical Trials

There were no special safety studies submitted with this application.

7.4.6 Immunogenicity

The assays used to test for immunogenicity were not properly validated; therefore the results obtained and submitted with this application are not considered reliable. The Sponsor will be asked to validate the assays and re-test samples from these trials. For full details, see the Chemistry Manufacturing and Controls review.

The results submitted and performed with the unvalidated assays showed that no patients had binding antibodies or neutralizing antibodies during the study treatment with XM02 during Study XM02-02 (N = 195). In Study XM02-03 (N = 237), one patient (40-407-05) was positive for both binding and neutralizing antibodies at several visits, but was neutralizing antibody negative at subsequent visits. Patient 50-513-01 was ELISA negative at all visits but was positive in the Luminex and Western blot assays at several visits. Patient 80-801-02 was Luminex negative at all visits but ELISA positive before Cycles 4, 5, and 6 and was neutralizing antibody positive at only one visit (before cycle 4). Patient 80-807-16 was positive for ELISA and neutralizing antibody at the EOS visit and the neutralizing antibody concentration was 10%. There were no patients positive for antibodies using the Biacore assay. In Study XM02-04 (N = 92) one patient was positive for binding and neutralizing antibodies at the follow-up visit and two patients had questionable antibody findings (before cycle 4 and at EOS). Another

patient was negative by ELISA at all visits but positive in the Luminex assay at several time points, and neutralizing antibody positive at the follow-up visit.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

There were no dose dependency studies submitted for Adverse Events.

7.5.2 Time Dependency for Adverse Events

There were no time dependency studies submitted for Adverse Events.

7.5.3 Drug-Demographic Interactions

Not applicable.

7.5.4 Drug-Disease Interactions

Not applicable

7.5.5 Drug-Drug Interactions

Not applicable

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

There were no human carcinogenicity studies submitted for review.

7.6.2 Human Reproduction and Pregnancy Data

Not applicable

7.6.3 Pediatrics and Assessment of Effects on Growth

Not applicable

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

Not applicable

7.7 Additional Submissions / Safety Issues

None

8 Postmarket Experience

None

9 Appendices

Section 7.3.3 Dropouts and Discontinuations

Table 23 Drop-outs and Discontinuations from Study XM02-02

	XM02-02 N=140 N (%)	EU-Neupogen N=136 N (%)	Placebo N=72 N (%)
Completed entire study	135 (96)	130 (96)	68 (94)
Terminated early	5 (4)	6 (4)	4 (6)
AE – study drug	-	-	1 (1)
AE - chemo	1 (0.7)	1 (0.7)	-
AE - other		2 (1.5)	-
Consent withdrawn	2 (1)	3 (2)	-
Death - PD	1 (0.7)	-	2 (2.8)
Death – not PD		-	-
Death - unknown	1 (0.7)	-	-
Other	1 (0.7)	-	-

Table 24 Drop-outs and Discontinuations from Study XM02-03

	XM02-02 N=160 N (%)	EU-Neupogen N=80 N (%)
Completed entire study	83 (52)	42 (53)
Terminated early	77 (48)	38 (48)
PD	26 (16)	15 (19)
AE – study drug	-	1 (1)
AE - chemo	12 (8)	1 (1)
AE - other	5 (3)	1 (1)
Consent withdrawn	12 (8)	9 (11)
Death - PD	6 (4)	4 (5)
Death – not PD	-	1 (1)

	XM02-02 N=160 N (%)	EU-Neupogen N=80 N (%)
Death - unknown	1 (0.7)	-
Other	11 (7)	4 (5)

Table 25 Drop-outs and Discontinuations from Study XM02-04

	XM02-02 N=63 N (%)	EU-Neupogen N=29 N (%)
Completed entire study	55 (87)	21 (72)
Terminated early	8 (13)	8 (28)
PD	3 (5)	3 (10)
AE – study drug	-	-
AE - chemo	2 (3)	2 (7)
AE - other	-	1 (3)
Consent withdrawn	1 (2)	1 (3)
Death - PD	-	-
Death – not PD	-	-
Death - unknown	-	-
Non-compliant	1 (2)	1 (3)
Other	1 (2)	
Lost to follow-up	-	1 (3)

Section 7.3.4 Significant Adverse Events

Table 26 Significant Adverse Events by PT

PT Name	Any XM02 N=488		EU-Neupogen Only N=221		Placebo N=60	
	N	%	N	%	N	%
NEUTROPENIA	31	6	19	9	12	20
ANAEMIA	27	6	0	0	0	0
ALOPECIA	25	5	12	5	6	10
THROMBOCYTOPENIA	25	5	2	1	0	0
FEBRILE NEUTROPENIA	10	2	9	4	6	10
ASTHENIA	7	1	0	0	1	2
NAUSEA	6	1	2	1	0	0
DYSPNOEA	5	1	1	0	0	0
VOMITING	4	1	2	1	0	0
LEUKOPENIA	4	1	2	1	2	3
PNEUMONIA	4	1	0	0	0	0

PT Name	Any XM02 N=488		EU-Neupogen Only N=221		Placebo N=60	
PLATELET COUNT DECREASED	4	1	1	0	0	0
DISEASE PROGRESSION	4	1	0	0	0	0
DIARRHOEA	3	1	0	0	0	0
BONE PAIN	3	1	1	0	0	0
HYPONATRAEMIA	3	1	0	0	0	0
HAEMOPTYSIS	3	1	0	0	0	0
HYPERGLYCAEMIA	3	1	1	0	0	0
HYPOTENSION	3	1	0	0	0	0
DEHYDRATION	3	1	0	0	0	0

Table 27 Significant Adverse Events by HLT

HLT Name	Any XM02 N=488		EU-Neupogen Only N=221		Placebo N=60	
	N	%	N	%	N	%
NEUTROPENIAS	38	8	26	12	19	32
ANAEMIAS NEC	27	6	0	0	0	0
ALOPECIAS	25	5	12	5	6	10
THROMBOCYTOPENIAS	25	5	2	1	0	0
ASTHENIC CONDITIONS	8	2	0	0	1	2
NAUSEA AND VOMITING SYMPTOMS	7	1	3	1	0	0
BREATHING ABNORMALITIES	6	1	2	1	0	0
COUGHING AND ASSOCIATED SYMPTOMS	5	1	0	0	0	0
HEART FAILURES NEC	5	1	0	0	0	0
LOWER RESPIRATORY TRACT AND LUNG INFECTIONS	4	1	0	0	0	0
LEUKOPENIAS NEC	4	1	2	1	2	3
GENERAL SIGNS AND SYMPTOMS NEC	4	1	0	0	0	0
PLATELET ANALYSES	4	1	1	0	0	0
DIARRHOEA (EXCL INFECTIVE)	3	1	0	0	0	0

HLT Name	Any XM02 N=488		EU-Neupogen Only N=221		Placebo N=60	
BONE RELATED SIGNS AND SYMPTOMS	3	1	1	0	0	0
SODIUM IMBALANCE	3	1	0	0	0	0
SUPRAVENTRICULAR ARRHYTHMIAS	3	1	0	0	0	0
HYPERGLYCAEMIC CONDITIONS NEC	3	1	1	0	0	0
VASCULAR HYPOTENSIVE DISORDERS	3	1	0	0	0	0
TOTAL FLUID VOLUME DECREASED	3	1	0	0	0	0

Table 28 Significant Adverse Events by HGLT

HLGT Name	Any XM02 N=488		EU-Neupogen Only N=221		Placebo N=60	
	N	%	N		N	%
WHITE BLOOD CELL DISORDERS	40	8	28	13	20	33
ANAEMIAS NONHAEMOLYTIC AND MARROW DEPRESSION	27	6	0	0	0	0
PLATELET DISORDERS	27	6	2	1	0	0
SKIN APPENDAGE CONDITIONS	25	5	12	5	6	10
GENERAL SYSTEM DISORDERS NEC	15	3	0	0	2	3
RESPIRATORY DISORDERS NEC	12	2	2	1	0	0
GASTROINTESTINAL SIGNS AND SYMPTOMS	8	2	5	2	0	0
ELECTROLYTE AND FLUID BALANCE CONDITIONS	8	2	1	0	0	0
CARDIAC ARRHYTHMIAS	7	1	0	0	2	3
INFECTIONS - PATHOGEN CLASS UNSPECIFIED	6	1	0	0	1	2

HLGT Name	Any XM02 N=488		EU-Neupogen Only N=221		Placebo N=60	
HEART FAILURES	5	1	0	0	0	0
HAEMATOLOGY INVESTIGATIONS (INCL BLOOD GROUPS)	4	1	1	0	0	0
GASTROINTESTINAL MOTILITY AND DEFAECATION CONDITIONS	3	1	0	0	0	0
BONE DISORDERS (EXCL CONGENITAL AND FRACTURES)	3	1	1	0	0	0
GLUCOSE METABOLISM DISORDERS (INCL DIABETES MELLITUS)	3	1	2	1	0	0
DECREASED AND NONSPECIFIC BLOOD PRESSURE DISORDERS AND SHOCK	3	1	0	0	0	0
PHYSICAL EXAMINATION TOPICS	2	0	1	0	0	0
APPETITE AND GENERAL NUTRITIONAL DISORDERS	2	0	1	0	0	0
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS NEC	2	0	2	1	0	0
NEUROLOGICAL DISORDERS NEC	2	0	0	0	0	0

Table 29 Significant Adverse Events by SOC

SOC Name	Any XM02 N=488		EU-Neupogen Only N=221		Placebo N=60	
	N	%	N	%	N	%
BLOOD AND LYMPHATIC SYSTEM DISORDERS	75	15	29	13	20	33
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	26	5	14	6	6	10

SOC Name	Any XM02 N=488		EU-Neupogen Only N=221		Placebo N=60	
GASTROINTESTINAL DISORDERS	15	3	6	3	1	2
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	15	3	0	0	2	3
CARDIAC DISORDERS	14	3	1	0	2	3
METABOLISM AND NUTRITION DISORDERS	13	3	4	2	0	0
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	13	3	2	1	0	0
INVESTIGATIONS	12	2	4	2	1	2
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	7	1	3	1	0	0
INFECTIONS AND INFESTATIONS	7	1	0	0	1	2
NERVOUS SYSTEM DISORDERS	4	1	0	0	0	0
VASCULAR DISORDERS	3	1	0	0	0	0
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	2	0	1	0	0	0
RENAL AND URINARY DISORDERS	2	0	0	0	0	0
EAR AND LABYRINTH DISORDERS	1	0	0	0	0	0
IMMUNE SYSTEM DISORDERS	1	0	0	0	0	0
PSYCHIATRIC DISORDERS	0	0	0	0	0	0
EYE DISORDERS	0	0	0	0	0	0
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	0	0	1	0	0	0
REPRODUCTIVE SYSTEM AND BREAST DISORDERS	0	0	0	0	0	0
HEPATOBIILIARY	0	0	0	0	0	0

SOC Name	Any XM02 N=488		EU-Neupogen Only N=221		Placebo N=60	
DISORDERS						
SURGICAL AND MEDICAL PROCEDURES	0	0	0	0	0	0

Section 7.4.1 Common Adverse Events

Table 30 Common Adverse Events by PT- Sponsor's Data Set (Cycle 1 of all studies) adapted from Summary of Clinical Safety Table 2.7.4.24

PT Name	Any XM02 N=541		EU-Neupogen Only N=134		Placebo N=72	
	N	%	N	%	N	%
NAUSEA	146	27	40	30	24	33
ALOPECIA	114	21	53	40	26	36
NEUTROPENIA	81	15	29	22	24	33
VOMITING	70	13	14	10	5	7
ASTHENIA	60	11	25	19	18	25
DIARRHOEA	54	10	31	23	14	19
PYREXIA	38	7	7	5	7	10
HEADACHE	32	6	8	6	6	8
BONE PAIN COUGH	27	5	13	10	2	3
ANAEMIA	27	5	5	4	3	4
ANOREXIA	27	5	8	6	2	3
FEBRILE NEUTROPENIA	27	5	4	3	17	24
THROMBOCYTOPENIA	27	5	3	2	3	4
ABDOMINAL PAIN	22	4	15	11	4	6
BACK PAIN	22	4	2	2	1	1
INSOMNIA	22	4	1	1	4	6
LEUKOPENIA	22	4	4	3	7	10
STOMATITIS	22	4	8	6	11	15
ALOPECIA TOTAL	16	3	7	5	4	6
MYALGIA	11	2	8	6	2	3

Table 31 Common Adverse Events by PT - Study XM02-02

PT Name	XM02 N=147		EU-Neupogen N=141		Placebo N=60	
	N	%	N	%	N	%
ALOPECIA	50	36	60	41	21	35

PT Name	XM02 N=147		EU-Neupogen N=141		Placebo N=60	
	N	%	N	%	N	%
VOMITING	17	12	17	12	2	3
HEADACHE	10	7	13	9	1	2
BONE PAIN	8	6	14	10	1	2
ANOREXIA	7	5	9	6	1	2
ABDOMINAL PAIN	6	4	18	12	2	3
MYALGIA	5	4	9	6	1	2
ABDOMINAL PAIN UPPER	4	3	6	4	1	1.7
MUSCULOSKELETAL PAIN	3	2	7	5	1	2

Table 32 Broad Scope Standardized MedDRA Queries for Study XM02-02 Cycle 1

p-Value*	SMQ (Broad Scope)	XM02 (N=141) N (%)	EU-Neupogen (N=137) N (%)	Placebo (N=72) N (%)
	At least one SMQ	122 (87)	123 (90)	69 (96)
0.0000	Agranulocytosis	7 (5)	10 (7)	23 (32)
0.0021	Leukopenia	49 (35)	50 (37)	42 (58)
0.0025	Haematopoietic cytopenias	59 (41.8%)	59 (43.1%)	47 (65.3%)
0.0126	Malignancy related therapeutic and diagnostic procedures	2 (1)	0 (0)	4 (6)
0.0208	Cytopenia and haematopoietic disorders affecting more than one type of blood cell	0 (0)	0 (0)	2 (3)
	Parkinson-like events	0 (0)	0 (0)	2 (3)
0.0219	Shock-associated circulatory or cardiac conditions (excl torsade de pointes)	0 (0)	1 (0.7)	3 (4)
0.0358	Accidents and injuries	1 (0.7)	4 (3)	5 (7)
0.0443	Systemic lupus erythematosus	5 (4)	2 (2)	6 (8)

*p-Values are derived from a Mantel-Haenszel test for ranking purposes only.

Table 33 Narrow Scope Standardized MedDRA Queries for Study XM02-02 Cycle 1

p-Value*	SMQ (Narrow Scope)	XM02 (N=141) N (%)	EU-Neupogen (N=137) N (%)	Placebo (N=72) N (%)
	At least one SMQ	114 (81)	112 (82)	63 (88)
0.0000	Agranulocytosis	4 (3)	8 (6)	21 (29)
0.0021	Leukopenia	49 (35)	50 (37)	42 (58)
0.0024	Haematopoietic cytopenias	52 (37)	51 (37)	43 (60)
0.0126	Malignancy related therapeutic and diagnostic procedures	2 (1)	0 (0)	4 (6)
0.0208	Shock-associated circulatory or cardiac conditions (excl torsade de pointes)	0 (0)	0 (0)	2 (3)

*p-Values are derived from a Mantel-Haenszel test for ranking purposes only.

Table 34 Broad Scope Standardized MedDRA Queries for Study XM02-03 Cycle 1

p-Value*	SMQ (Broad Scope)	XM02 (N=160) N (%)	EU-Neupogen (N=80) N (%)
	At least one SMQ	122 (87)	123 (90)
0.0155	Leukopenia	34 (21)	7 (0)
0.0239	Agranulocytosis	14 (9)	1 (1)
0.0450	Dementia	0 (0)	2 (3)
	Gastrointestinal haemorrhage	0 (0)	2 (3)
	Myocardial infarction	0 (0)	2 (3)

*p-Values are derived from a Mantel-Haenszel test for ranking purposes only.

Table 35 Narrow Scope Standardized MedDRA Queries for Study XM02-03 Cycle 1

p-Value*	SMQ (Narrow Scope)	XM02 (N=160) N (%)	EU-Neupogen (N=80) N (%)
	At least one SMQ	130 (81)	60 (75)
0.0155	Leukopenia	34 (21)	7 (9)
0.0442	Agranulocytosis	12 (8)	1 (1)
0.0450	Myocardial infarction	0 (0)	2 (3)

*p-Values are derived from a Mantel-Haenszel test for ranking purposes only.

Table 36 Broad Scope Standardized MedDRA Queries for Study XM02-04 Cycle 1

p-Value*	SMQ (Broad Scope)	XM02 (N=64) N (%)	EU-Neupogen (N=29) N (%)
	At least one SMQ	41 (64)	25 (86)
0.0174	Erythropenia	2 (3)	5 (17)

*p-Values are derived from a Mantel-Haenszel test for ranking purposes only.

There were no Narrow Scope SMQs with a p-value < 0.05 in Study XM02-04

9.1 Literature Review/References

Becker PS, Wagle TM, Matous S, et al. Spontaneous splenic rupture following administration of granulocyte colony-stimulating factor (G-CSF): occurrence in an allogeneic donor of peripheral blood stem cells. *Biol Blood Marrow Transplant* 1997; 3:45-9.

Dale DC, Bonilla MA, Davis MW, et al. A randomized controlled phase III trial of recombinant human granulocyte colony-stimulating factor (filgrastim) for treatment of severe chronic neutropenia. *Blood* 1993; 81: 2496-2502.

Guneyssel O, Onur OE, Denizbasi A. Effects of recombinant human granulocyte colony-stimulating factor (filgrastim) on ECG parameters in neutropenic patients: a single-centre, prospective study. *Clin Drug Investig*. 2009; 29: 551-5. doi: 10.2165/00044011-200929080-00005.

Heil G, Hoelzer D, Sanz MA, et al. A randomized, double-blind, placebo-controlled, phase III study of filgrastim in remission induction and consolidation therapy for adults with de novo acute myeloid leukemia. The International Acute Myeloid Leukemia Study Group. *Blood*. 1997;90:4710-8.

Hughes WT, Armstrong D, Bodey GP, et al. Guidelines for the use of antimicrobial agents in neutropenic patients with cancer. *Clin Infect Dis* 2002; 34:730-51.

Larson RA, Prophylaxis of infection during chemotherapy-induced neutropenia. (uptodate.com 2009).

Mermel, LA, Farr, BM, Sherertz, RJ, et al. IDSA guidelines for the management of intravascular catheter-related infections-I. *Clin Infect Dis* 2001; 32:124-72.

Robbins GK, Fever in the neutropenic adult patient with cancer (uptodate.com 2009).

Smith TJ, Khatcheressian J, Lyman GH, et al. 2006 update of recommendations for the use of white blood cell growth factors: an evidence-based clinical practice guideline. SO J Clin Oncol 2006;24:3187-205.

9.2 Labeling Recommendations

There are no final labeling recommendations.

9.3 Advisory Committee Meeting

There was not an Advisory Committee Meeting for this application.

Appears this way on original

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

NDA/BLA Number: 125294

Applicant: Teva
Pharmaceuticals USA

Stamp Date: 2009 NOV 30

Drug Name: Neutroval

NDA/BLA Type: Standard

On initial overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.				eCTD
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	X			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	X			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (e.g., are the bookmarks adequate)?	X			
5.	Are all documents submitted in English or are English translations provided when necessary?	X			some references were reviewed for English
6.	Is the clinical section legible so that substantive review can begin?	X			
LABELING					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?	X			unsure of package container requirements
SUMMARIES					
8.	Has the applicant submitted all the required discipline summaries (i.e., Module 2 summaries)?	X			
9.	Has the applicant submitted the integrated summary of safety (ISS)?	X			not called ISS
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?	X			
11.	Has the applicant submitted a benefit-risk analysis for the product?				not specifically identified
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2). If Application is a 505(b)(2) and if appropriate, what is the reference drug?				505(b)(1)
DOSE					
13.	If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product (i.e., appropriately designed dose-ranging studies)? Study Number: Study Title: Sample Size: Arms: Location in submission:	X			
EFFICACY					
14.	Do there appear to be the requisite number of adequate and well-controlled studies in the application? Pivotal Study #1 Indication:	X			

File name: 5_Clinical Filing Checklist for NDA_BLA or Supplement 010908

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	Pivotal Study #2 Indication:				
15.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	X			questionable fairness of randomization after Cycle 1
16.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.			X	no agreements made prior to study initiation
17.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?				not specifically identified in the submission
SAFETY					
18.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	X			
19.	Has the applicant submitted adequate information to assess the arrhythmogenic potential of the product (e.g., QT interval studies, if needed)?				not performed
20.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	X			
21.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure ¹) been exposed at the dose (or dose range) believed to be efficacious?				not applicable
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?	X			
23.	Has the applicant submitted the coding dictionary ² used for mapping investigator verbatim terms to preferred terms?	X			
24.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	X			
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?	X			

¹ For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

² The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
OTHER STUDIES					
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?		X		no in CDISC
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (e.g., label comprehension, self selection and/or actual use)?				
PEDIATRIC USE					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	X			
ABUSE LIABILITY					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			X	
FOREIGN STUDIES					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?				not specifically identified in the submission
DATASETS					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	X			col info for many variables not present
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?		X		
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?				at present appears to be adequate
34.	Are all datasets to support the critical safety analyses available and complete?				at present appears to be adequate
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?	X			
CASE REPORT FORMS					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	X			
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?			X	
FINANCIAL DISCLOSURE					
38.	Has the applicant submitted the required Financial Disclosure information?		X		
GOOD CLINICAL PRACTICE					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	X			

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? __yes__

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

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

1. Column info for many variables not present.
2. Adverse event data set for study XM02-01-LT dose not have HGLT and HLT variables as requested in the pre-BLA meeting.
3. Why are there two addendums to the final study dated 25-APR-06? What do these represent.? Why is there not a single final study report?

Thomas M. Herndon
Reviewing Medical Officer

Thomas M. Herndon

2009 January 12

Date

Jeff Summers
Clinical Team Leader

JS Summers 1/12/10

2009 January 12

Date