CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125294Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Clinical Pharmacology
Division of Clinical Pharmacology V

Memorandum

Date: August 28, 2012

To: Memo to File

From: NAM Atiqur Rahman

Subject: BLA 125294, tbo-filgrastim (XM02) Subcutaneous Injection via prefilled syringe or delivery device

Background:

Teva Pharmaceuticals submitted on November 30, 2009, BLA 125294 for XM02 for reducing the duration of severe neutropenia (DSN) in patients with non-myeloid malignancies receiving myelo-suppressive anti-cancer drugs. The submission included general pharmacokinetic (PK) and pharmacodynamic (PD) information on XM02 and comparative PK and PD information against a filgrastim product approved in certain European countries. The Clinical Pharmacology discipline had no input or interaction with the sponsor prior to their conduct of PK and PD studies, and the reviewer evaluated the data submitted in this 351(a) BLA, including the comparative studies. Although the original review contained certain statements characterizing the relationship between the XM02 and the comparator product, it should be noted that the overall focus of the Clinical Pharmacology discipline review is the adequacy of the submission with regard to the characterization of the PK and PD profile of XM02. Data comparing XM02 to a non-US-approved filgrastim product was not necessary or relied upon for the evaluation of the PK and PD of XM02. The PK and PD findings relevant to XM02 will be reflected in the labeling for this product. This memorandum provides highlights of the clinical pharmacology review of XM02 and describes our view regarding the adequacy of the submission dated November 30, 2009 and the resubmission dated February 29, 2012 for regulatory action.

Clinical Pharmacology Review:

The clinical pharmacology data demonstrated that in healthy volunteers the absolute bioavailability of 5 and 10 µg/kg tbo-filgrastim were 33% and 45%,

respectively. After a single subcutaneous (SC) administration of a 5 µg/kg tbo-filgrastim dose, the serum maximum concentration (C_{Max}) and exposure (AUC_{0-48h}) were 18 ng/mL and 158 ng*h/mL, respectively. The median T_{max} was 6 hours and the median half-life ($t_{½}$) was 8.9 hours. Increasing the dose of tbo-filgrastim from 5 to 10 µg/kg resulted in an approximately 3-fold increase in both C_{max} and AUC_{0-48h}.

Pharmacokinetic data were obtained from patients with breast cancer, lung cancer and non-Hodgkin's Lymphoma (NHL) (N=12 per group) who received SC tbo-filgrastim 5 µg/kg/day. Following the first tbo-filgrastim 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 patients, respectively. For the three groups combined, the median T_{max} was between 4 to 6 hours and the median $t_{½}$ 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.

Data on the excretion of XM02 was not provided in this submission. Although information about the excretion of a product helps in understanding the scientific basis for dose modifications under special conditions, this information was not required for approval. The information on XM02 clearance (which is a function of exposure and excretion) relied upon for approval is based on studies conducted by the applicant.

No gender-related differences were observed in the pharmacokinetics of XM02 following a SC 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.

Information on chronic dosing of 5 µg/kg SC daily in breast cancer trial (XM02-02-INT) characterized the multiple dose PK of the product. No accumulation of XM02 was observed in phase 3 trials XM02-03-INT and XM02-04-INT.

The pharmacodynamics (PD) of XM02 was studied in both healthy subjects and in cancer patients. In healthy subjects who received a single SC dose of 5 or 10 µg/kg XM02, a transient decrease in the absolute neutrophil count (ANC) occurred during the first hour, followed by an increase in ANC. Following subcutaneous administration of 5 µg/kg (N=61), the mean maximum ANC was

$22x10^9$/L; the median time to peak ANC was 12 hours. After subcutaneous administration of 10 µg/kg (N=58), the mean maximum ANC was $26x10^9$/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), 5 µg/kg XM02 was administered SC daily starting 24 hours after the completion of chemotherapy until an ANC of $10x10^9$/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. ECGs were monitored in clinical trials at times when tbo-filgrastim was totally cleared from systemic circulation. The applicant provided a protocol, XM02-TQT-103 in the current submission to address this issue. Submission and evaluation of data from the completed thorough QT trial typically is not required prior to licensure given that XM02 is a supportive care product in the oncology setting. A post-marketing requirement to perform the thorough QT trial in accordance with the ICH E-14 guidelines is recommended.

The incidence of anti-XM02 antibody formation obtained in clinical studies is not considered reliable since the assessment did not use validated assay methods. Further, the impact of immunogenicity on XM02 PK generated could not be assessed because of the non-validated immunogenicity assay and because of XM02 PK data not collected in patients who tested positive for binding or neutralizing antibodies. A post-marketing requirement to conduct an assessment for the presence of anti-XM02 and anti-native human G-CSF binding antibodies using a validated assay in patients has been proposed.

Recommendation:

From the Clinical Pharmacology perspective, the XM02 (tbo-filgrastim) development program generated adequate data to characterize the PK and PD of XM02 and support the approval of this 351(a) BLA. The application is acceptable provided the Applicant and the Agency come to an agreement regarding the post-marketing requirements and language in the package insert.

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/s/

NAM ATIQUR RAHMAN
08/29/2012

OFFICE OF CLINICAL PHARMACOLOGY REVIEW

BLA: 125294\0\32	Submission Date(s): 2/29/2012
Brand Name	Neutroval®
Generic Name	Generic Name Pending
Reviewer	Joseph Grillo, Pharm.D.
Team Leader	Bahru Habtemariam, Pharm.D.
OCPB Division	DCP-5
ORM division	OND/ OHOP/DHP
Sponsor	Teva
Relevant IND(s)	N/A
Submission Type; Code	Resubmission of BLA (SDN 0/32), Standard Review
Formulation; Strength(s)	300 µg/0.5 mL and 480 µg/0.8 mL single use prefilled syringe
Indication	The reduction in the duration of severe neutropenia in patients with non-myeloid malignancies receiving myelo-suppressive anti-cancer drugs associated with a clinically significant incidence of febrile neutropenia

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1 EXECUTIVE SUMMARY

Neutroval is a human granulocyte colony-stimulating factor (G-CSF) produced by recombinant DNA technology in Escherichia coli (E coli). The original BLA for Neutroval with an indication for the reduction in the duration of severe neutropenia (DSN) in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a clinically significant incidence of febrile neutropenia (FN) was submitted on November 30, 2009. On September 29, 2010, FDA issued a complete response (CR) letter addressing deficiencies rated to data integrity, device safety and closure, reproductive toxicity, proposed proper name, microbial control, effects on QTc interval, anti-product antibody (ADA) assay validation and other CMC related issues.

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

1.1 Recommendation

From a clinical pharmacology perspective, this BLA application is acceptable provided that the applicant and the Agency come to a mutually satisfactory agreement regarding the PMR and language in the package insert.

1.2 Post Marketing Requirements

1.2.1 The sponsor should conduct a TQT assessment for Neutroval in accordance with the ICH E-14 guidelines.

Protocol submission Date: Draft protocol was submitted on 2/29/2012.
Submission Date: 12 months after FDA agreement to submitted protocol.
Final Study Report: 18 months after FDA agreement to submitted protocol.

1.3 Post Marketing Commitments

None

1.4 Comments to the Applicants

None

1.5 Summary of Important Clinical Pharmacology Findings from the original BLA review

Introduction: Neutroval, is a human granulocyte colony-stimulating factor (G-CSF) produced by recombinant DNA technology in E coli. The proposed indication for Neutroval is for the reduction in the duration of severe neutropenia (DSN) in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a clinically significant incidence of febrile neutropenia (FN). The selection of dose and dose regimen for the phase 3 trials were based on the data obtained in the phase 1 trials and historical clinical use with an FDA-approved product, Neupogen. To support approval for this indication, the sponsor conducted two phase 1 PK/PD trials in healthy subjects (N=176) and three phase 3 trials in patients with breast cancer (N=348), lung cancer (N=240), or non-Hodgkin lymphoma (NHL, N=92).

Pharmacokinetics Findings: The pharmacokinetics (PK) of Neutroval was studied in both healthy subjects and in cancer patients.

Healthy Subjects: Subjects in the phase 1 trials were assigned to receive single 5 pg/g or 10 μg/kg iv or SC doses of Neutroval or European Neupogen. The absolute bioavailability of 5 and 10 μg/kg SC Neutroval was 33% and 45%, respectively. After single dose SC administration of 5 μg/kg Neutroval (N=33), the geometric mean (CV%) of serum C_{max} was 18 ng/mL (41%) and of AUC_{0-48h} was 158 ng*h/mL (37%). The median T max was 6 hours and the median half-life (t½) was 8.9 hours. Increasing the dose of Neutoval from 5 to 10 μg/kg resulted in an approximately 3-fold increase in both C_{max} and AUC_{0-48h}.

Cancer Patients: PK data were obtained from patients with breast cancer, lung cancer and NHL (N=12 per group) who received SC Neutroval 5 μg/kg/day. Following the 1st Neutroval dose in cycle 1, the geometric mean (CV%) of serum C_{max} and AUC_{0-48h} 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 t½ 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 Neutroval following a SC administration. Mild renal impairment (creatinine clearance 60-89 mL/min; N=l1) had no clinical meaningful effect on Neutroval 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 Neutroval and the lack of relationship between the incidence of the major adverse event (bone pain) and degree of renal impairment, an Neutroval dosage adjustment would not be clinically warranted. The pharmacokinetic profile in patients with hepatic impairment has not been studied.

Pharmacodynamic Findings: The pharmacodynamics (PD) of Neutroval was studied in both healthy subjects and in cancer patients.

Healthy Subjects: In healthy subjects who received a single SC dose of 5 or 10 μg/kg Neutroval, a transient decrease in the ANC occurred during the first hour, followed by an increase in ANC. Following subcutaneous 5 μg/kg (N=61), the mean maximum ANC was 22 x 10^9/L; the median time to peak ANC was 12 hours. After subcutaneous 10 μg/kg (N=58), the mean maximum ANC was 26 x 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.

Cancer Patients: In cancer patients receiving various chemotherapies (N=361), SC 5 μg/kg Neutroval was administered daily starting 24 hours after the completion of chemotherapy until an ANC of 10 x 10^9/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.

Efficacy: All three phase 3 trials were multi-national, multi-center, randomized and controlled studies assessing efficacy and safety of XM02 as compared to placebo (breast cancer only) or European Neupogen. In all three trials, XM02 and Neupogen were administered at doses of 5 μg/kg/day SC for 5 to 14 days in each cycle of chemotherapy (CTX), starting the day after the end of CTX within a cycle and stopping when an ANC ≥ 10 x 10^9/L after nadir was reached. The dose and dose regimen for these

trials were based on the data obtained in the phase 1 trials and historical clinical use with an FDA-approved product, Neupogen.

- Breast cancer trial: 348 CTX-naïve patients with high risk stage II, III, or IV breast cancer needing CTX were enrolled. Patients were randomized 2:2:1 to Neutroval, European Neupogen, or placebo during cycle 1; those patients initially randomized to the placebo group in cycle 1, received Neutroval in all subsequent CTX cycles. Patients were administered 4 cycles of CTX (doxorubicin IV 60 mg/m2 and docetaxel IV 75 mg/m^2) on day 1 of each 3-week cycle for a total of 4 cycles.
- Lung cancer trial: 240 patients with small cell lung cancer (SCLC) or advanced non-small cell lung cancer (NSCLC) having received no more than 1 prior CTX cycle were enrolled. During cycle 1, patients received either Neutroval or European Neupogen and in all subsequent cycles patients received XM02. CTX regimens consisted of any myelosuppressive platinum-based CTX in a 3- or 4-week cycle for up to 6 cycles.
- Non-Hodgkin Lymphoma trial: 92 CTX-naïve patients with aggressive NHL treated with CHOP regimen (Cyclophosphamide IV 750 mg/m^2, Doxorubicin IV 50 mg/m^2, Vincristine IV 1.4 mg/m^2, Prednisolone 100 mg/day one to five days) were enrolled. During cycle 1, patients received either Neutroval or European Neupogen and in all subsequent cycles, up to 6 cycles, patients received Neutroval.

Results of the phase 3 trials showed that treatment with Neutroval reduced the duration of severe neutropenia (DSN) in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a clinically significant incidence of febrile neutropenia (FN). In the breast cancer trial, Neutroval efficacy was demonstrated as compared to placebo in reducing DSN and preventing the incidence of FN in patients with malignant disease undergoing CTX. Safety Profile: In clinical trials, the most frequent adverse reaction attributable to Neutroval 5 μg/kg/day SC is bone pain. In the breast cancer trial, the overall incidence of bone pain in cycle 1 was 14.2% for Neutroval, 17.9% for placebo, and 19.0% for Neupogen.

QT/QTc Evaluation: The potential effects of Neutroval on the QTc interval were not adequately evaluated in clinical trials included in the BLA since ECGs were monitored at times when Neutroval was totally cleared from systemic circulation. A post-marketing requirement to perform a QTc study in either healthy subjects or patients at the highest dose tested is recommended. Protocol XM02-TQT-103 was provided by the applicant in this submission to address this issue. Clinical pharmacology and the FDA Interdisciplinary Review Team (IRT) provided comments regarding the proposed protocol to the applicant on 5/25/2012.

Immunogenicity: The incidence of anti- Neutroval 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: Less than 1 % (5 out of 677) of patients treated with XM02 tested positive for binding antibodies during study treatment; 4 of the 5 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.

Conclusion: In conclusion, Neutroval provides a reduction in 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 with an acceptable safety profile.

Signatures

Joseph Grillo, Pharm.D.
Clinical Pharmacology Reviewer
Division of Clinical Pharmacology 5

Bahru Habtemariam, Pharm.D.
Clinical Pharmacology Acting Team Leader
Division of Clinical Pharmacology 5

Nam Atiqur Rahman, Ph.D.
Division Director
Division of Clinical Pharmacology 5

2 QUESTION BASED REVIEW

2.1 General Attributes

See the original BLA review by Dr. Schrieber on August 9, 2010.

2.2 General Clinical Pharmacology

See the original BLA review by Dr. Schrieber on August 9, 2010. In the September 29, 2010, CR letter, FDA stated that the applicant must conduct and provide the 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). In its response to the CR the applicant was instructed to provide the protocol for the requested clinical trial and milestones. A protocol for a thorough QT/QTc trial was submitted in the current submission. The applicant intends to initiate the study approximately 6 months from the date of BLA approval, to be completed by approximately 1 year from the date of BLA approval. The final study report will be submitted to the Agency approximately 1.5 years from the date of BLA approval. Clinical pharmacology and the FDA Interdisciplinary Review Team (IRT) provided comments regarding the proposed protocol to the applicant on 5/25/2012. The clinical trial and milestones are acceptable.

2.3 Intrinsic Factors

See the original BLA review by Dr. Schrieber on August 9, 2010.

2.4 Extrinsic Factors

See the original BLA review by Dr. Schrieber on August 9, 2010.

2.5 General Biopharmaceutics

See the original BLA review by Dr. Schrieber on August 9, 2010.

2.6 Analytical Section

See the original BLA review by Dr. Schrieber on August 9, 2010.

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/s/

JOSEPH A GRILLO
08/01/2012

BAHRU A HABTEMARIAM
08/01/2012

NAM ATIQUR RAHMAN
08/02/2012

CLINICAL PHARMACOLOGY
FILING FORM/CHECKLIST FOR BLA

Office of Clinical Pharmacology

BLA Filing and Review Form

General Information About the Submission

	Information		Information
BLA Number	125294\0\32	Brand Name	Neutroval®
OCP Division (I, II, III, IV, V)	5	Generic Name	XM02
Medical Division	DHP	Drug Class	Human Granulocyte Colony-Stimulating Factor
OCP Reviewer	Joseph Grillo	Indication	The reduction in the duration of severe neutropenia in patients with non-myeloid malignancies receiving myelo-suppressive anti-cancer drugs associated with a clinically significant incidence of febrile neutropenia
OCP Team Leader	Julie Bullock	Dosage Form	300 µg/0.5 in and 480 µg /0.8 mL solution
Pharmacometrics Reviewer	N/A	Dosing Regimen	5 µg /kg SC once daily (b) (4) to start 24 hours after receiving chemotherapy
Date of Submission	2/29/2012	Route of Administration	Subcutaneous
Estimated Due Date of OCP Review	7/20/12	Sponsor	Teva
Medical Division Due Date	8/2/12	Priority Classification	Priority
PDUFA Due Date	8/30/12		

Clinical Pharmacology and Biopharmaceutics Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.				
Tabular Listing of All Human Studies				
HPK Summary				
Labeling				
Reference Bioanalytical and Analytical Methods				
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:				
multiple dose:				
Patients-				
single dose:				
multiple dose:				

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD -				
Phase 1:				
Phase 2/3:				
PK/PD -				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies				
Bio-waiver request based on BCS				
BCS class				
Dissolution study to evaluate alcohol induced dose-dumping				
III. Other CPB Studies				
Genotype/phenotype studies				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
ECG Monitoring	**X**	**1**		**Protocol only**
Biomarkers				
Immunogenicity Testing				
Total Number of Studies		**1**		

On **initial** review of the BLA application for filing:

	Content Parameter	Yes	No	N/A	Comment
Criteria for Refusal to File (RTF)					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?			**X**	
2	Has the applicant provided metabolism and drug-			**X**	

	Content Parameter	Yes	No	N/A	Comment
	drug interaction information?				
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?			X	
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?			X	
5	Has a rationale for dose selection been submitted?			X	
6	Is the clinical pharmacology and biopharmaceutics section of the BLA organized, indexed and paginated in a manner to allow substantive review to begin?			X	
7	Is the clinical pharmacology and biopharmaceutics section of the BLA legible so that a substantive review can begin?			X	
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?	X			
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?			X	
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			X	
11	Is the appropriate pharmacokinetic information submitted?			X	
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?			X	
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?			X	
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?			X	
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			X	
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			X	
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?			X	

	Content Parameter	Yes	No	N/A	Comment
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	**X**			**Single TQT study Submitted**
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?			**X**	

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE? _X_Yes __ No

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

Not applicable

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

None

Reviewing Clinical Pharmacologist Date

Team Leader/Supervisor Date

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/s/

JOSEPH A GRILLO
03/16/2012

JULIE M BULLOCK
03/16/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION	Office of Clinical Pharmacology Division of Clinical Pharmacology 5 Tracking/Action Sheet for Formal/Informal Consults

From: **Joseph A. Grillo, Pharm.D.**	**To: DOCUMENT ROOM (LOG-IN & LOG-OUT)** **Please log-in this consult and review action for the specified IND/NDA submission**

Date: **5/25/12**	IND No.: Serial No.: SDN:	BLA No. **125-294** Serial No.: SDN: **32**	Document ID: **N**	Date of Document: **2/29/12**

Name of Drug **NEUTROVAL™ (XM02)**	Priority Consideration ☐ Yes ☐ No ☒ N/A	DARRTS Categories/Subcategories:

Name of Sponsor: **Teva**

TYPE OF SUBMISSION

CLINICAL PHARMACOLOGY RELATED ISSUE

☐ PRE-IND	☐ BA/BE STUDIES	☐ IN-VIVO WAIVER REQUEST
☐ ORIGINAL IND	☐ ORGAN IMPAIRMENT STUDIES	☐ CMC RELATED
☐ RESPONSE TO COMMENTS	☒ QT	☐ CORRESPONDENCE
☐ RESPONSE TO HOLD/REACTIVATION	☐ FORMULATION	☐ IN-VITRO METABOLISM
☒ NEW PROTOCOL	☐ PK/PD- POPPK ISSUES	☐ ADVERSE REACTION REPORT
☐ PROTOCOL CHANGE	☐ PHASE IV RELATED	☐ ANNUAL REPORTS
☐ PHASE 2 PROTOCOL	☐ DOSING REGIMEN CONSULT	☐ INVESTIGATORS BROCHURE
☐ PHASE 3 PROTOCOL	☐ PEDIATRICS	☒ OTHER *(SPECIFY BELOW)*:
☐ SPECIAL PROTOCOL ASSESMENT	☐ MEETING PACKAGE ( )	**PMR issue**

REVIEW ACTION

☐ NAI (No action indicated)	☐ Oral communication with Name: [ ]	☒ Formal Review/Memo (attached)
☐ E-mail comments to:	☐ Comments communicated in meeting/Telecon.	☒ See comments below
☐ Medical ☐ Chemist ☐ Pharm-Tox ☐ Micro ☐ Pharmacometrics ☐ Others (Check as appropriate and attach e-mail)	see meeting minutes dated: [ ]	☐ See submission cover letter ☐ OTHER *(SPECIFY BELOW)*: [ ]

Purpose: This review outlines a protocol (XM02-TQT-103) for Neutroval™ (XM02) submitted as part of a response to a Complete Response (CR) action by the agency on 9/29/10.

Background:

Neutroval is a granulocyte colony-stimulating factor (G-CSF) that is being developed for the reduction in 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. In its 8/9/10 review of the original BLA application the clinical pharmacology reviewer provided a deficiency that recommended the applicant conduct a thorough QT study. In response to this deficiency the applicant submitted a protocol for the conduct of a Thorough QT/QTc (TQT) study to evaluate the effect of Neutroval on cardiac repolarization in healthy volunteers as part of its response to the CR action. The applicant also states that it intends to initiate the study approximately 6 months from the date of BLA approval, to be completed by approximately 1 year from the date of BLA approval. The final study report will be submitted to the Agency approximately 1.5 years from the date of BLA approval. This issue will likely be a PMR.

Previous Relevant Regulatory History:

- 8/9/10 review of the original BLA application recommended TQT as a deficiency in the CR letter.

Pharmacokinetic Parameters

Pharmacokinetics

In healthy subjects, the absolute bioavailability of 5 mcg/kg subcutaneous Neutroval was 33%. After single dose subcutaneous administration of 5 mcg/g Neutroval (N=33), the geometric mean (CV%) of serum Cmax was 18 ng/mL (41 %) and of AUC0-48h was 158 ng•h/mL (37%). The median Tmax was 6 hours and the median half-life (t½) was 8.9 hours (48 hour sampling). Increasing the dose of Neutroval from 5 to 10 mcg/kg resulted in an approximately 200% increase in both Cmax and AUC0-48h. In patients with breast cancer, lung cancer and non-Hodgkin lymphoma (NHL) (N=12 per group) who received subcutaneous Neutroval 5 mcg/kg/day the AUC and Cmax was greater and more variable compared to healthy volunteers receiving the same dose. For the 3 cancer groups combined, the median Tmax was between 4 to 6 hours and the median t½ was between 3.2 to 3.8 hours (24 hour sampling). Accumulation was not observed in these cancer groups after repeated dosing.

Drug Interactions

No formal drug interaction studies between Neutroval and other drugs have been performed.

Special Populations

Age: The impact of age on the pharmacokinetics of Neutroval was not evaluated

Gender: No gender-related differences were observed in the pharmacokinetics of Neutroval following subcutaneous administration.

Renal Impairment: Mild renal impairment (creatinine clearance 60 - 89 mL/min) had no effect on Neutroval pharmacokinetics (N=11). The pharmacokinetic profile in patients with moderate and severe renal impairment has not been assessed.

Hepatic Impairment: The pharmacokinetic profile in patients with hepatic impairment has not been assessed.

Pharmacodynamics

In healthy subjects who received a, single subcutaneous dose of 5 or 10 mcg/kg Neutroval "a transient decrease in the ANC occurred during the first hour, followed by an increase in ANC. Following subcutaneous 5 mcg/g (N=61), the mean maximum ANC was 22 x 10^9/L; the median time to peak ANC was 12 hours. After subcutaneous 10 mcg/g (N=58), the mean maximum ANC was 26 x 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), subcutaneous 5 mcg/kg Neutroval was administered daily starting 24 hours after the completion of chemotherapy until an ANC of 10 x 10^9/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.

QT Prolongation

No clinical studies of the effects of Neutroval on the cardiac QT interval have been performed in human subjects.

Proposed Protocol

(b) (4)

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(b) (4)

Recommendation:

- The Office of Clinical Pharmacology, Division of Clinical Pharmacology 5, has reviewed this protocol from a clinical pharmacology perspective and has no comments at this time. We agree with the IRT comments above and agree they should be communicated to the sponsor.

Signatures:

Joseph A. Grillo, Pharm.D. Reviewer Division of Clinical Pharmacology 5	Bahru Habtemariam, Pharm.D. Acting Team Leader Division of Clinical Pharmacology 5

Cc: DDOP: CSO - **L Akinsanya;** MTL - **A Deisseroth**; MO - **T Herndon**
DCP-5: Reviewer - **J Grillo;** TL - **B Habtemariam;** Deputy DD - **B Booth;** DD - **A Rahman**

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/s/

JOSEPH A GRILLO
05/25/2012

BAHRU A HABTEMARIAM
05/25/2012

Clinical Pharmacology Review

BLA	125294 / 0
Submission Date:	30 November 2009
PDUFA Date:	30 September 2010
Brand Name:	Neutroval®
Generic Name:	(XM02) To be proposed
Formulation:	300 µg/0.5 mL and 480 µg/0.8 mL solution
Sponsor:	Teva
Submission Type; Code:	Original BLA; 000
Dosing regimen:	5 µg/kg SC once daily (b) (4) , to start 24 hours after receiving chemotherapy
Proposed Indication:	The reduction in the duration of severe neutropenia (DSN) in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a clinically significant incidence of febrile neutropenia (FN)
OND Division:	Division of Biologic Oncology Products
OCP Reviewer:	Sarah J. Schrieber, Pharm.D.
OCP Team Leader:	Hong Zhao, Ph.D.
OCP Division:	Division of Clinical Pharmacology 5

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1 EXECUTIVE SUMMARY

XM02, Neutroval®, is a human granulocyte colony-stimulating factor (G-CSF) produced by recombinant DNA technology in *Escherichia coli* (*E coli*). The current submission is an original BLA for XM02 with an indication for the reduction in the duration of severe neutropenia (DSN) in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a clinically significant incidence of febrile neutropenia (FN). The selection of dose and dose regimen for the phase 3 trials were based on the data obtained in the phase 1 trials and historical clinical use with an FDA-approved product, Neupogen®. To support approval for this indication, the sponsor conducted two phase 1 PK/PD trials in healthy subjects (N=176) and three phase 3 trials in patients with breast cancer (N=348), lung cancer (N=240), or non-Hodgkin lymphoma (NHL, N=92).

1.1 RECOMMENDATIONS

From a Clinical Pharmacology perspective, the application is acceptable provided that the Sponsor and the Agency come to a mutually satisfactory agreement regarding the PMR and language in the package insert.

1.2 POST MARKETING REQUIREMENTS / COMMITMENTS

- Conduct a thorough QT study to evaluate the potential of Neutroval to prolong the QTc interval as a PMR.

1.3 CLINICAL PHARMACOLOGY SUMMARY

Introduction: XM02, Neutroval®, is a human granulocyte colony-stimulating factor (G-CSF) produced by recombinant DNA technology in *E coli*. The proposed indication for Neutroval is for the reduction in the duration of severe neutropenia (DSN) in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a clinically significant incidence of febrile neutropenia (FN). The selection of dose and dose regimen for the phase 3 trials were based on the data obtained in the phase 1 trials and historical clinical use with an FDA-approved product, Neupogen®. To support approval for this indication, the sponsor conducted two phase 1 PK/PD trials in healthy subjects (N=176) and three phase 3 trials in patients with breast cancer (N=348), lung cancer (N=240), or non-Hodgkin lymphoma (NHL, N=92).

Pharmacokinetics Findings: The pharmacokinetics (PK) of Neutroval was studied in both healthy subjects and in cancer patients.

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®. The absolute bioavailability of 5 and 10 µg/kg SC Neutroval was 33% and 45%, respectively. After single dose SC administration of 5 µg/kg Neutroval (N=33), the geometric mean (CV%) of serum C_{max} was 18 ng/mL (41%) and of AUC_{0-48h} was 158 ng*h/mL (37%). The median T_{max} was 6 hours and the median half-life ($t_{½}$) was 8.9 hours. Increasing the dose of Neutroval from 5 to 10 µg/kg resulted in an

approximately 3-fold increase in both C_{max} and AUC_{0-48h}.

Cancer Patients: PK data were obtained from patients with breast cancer, lung cancer and NHL (N=12 per group) who received SC Neutroval 5 µg/kg/day. Following the 1st Neutroval 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 $t_{½}$ 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 a SC 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.

Pharmacodynamic Findings: The pharmacodynamics (PD) of XM02 was studied in both healthy subjects and in cancer patients.

Healthy Subjects: In healthy subjects who received a single SC dose of 5 or 10 µg/kg XM02, a transient decrease in the ANC occurred during the first hour, followed by an increase in ANC. Following subcutaneous 5 µg/kg (N=61), the mean maximum ANC was $22x10^9$/L; the median time to peak ANC was 12 hours. After subcutaneous 10 µg/kg (N=58), the mean maximum ANC was $26x10^9$/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 5 µg/kg XM02 was administered daily starting 24 hours after the completion of chemotherapy until an ANC of $10x10^9$/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.

Efficacy: All three phase 3 trials were multi-national, multi-center, randomized and controlled studies assessing efficacy and safety of XM02 as compared to placebo (breast cancer only) or European Neupogen®. In all three trials, XM02 and Neupogen® were administered at doses of 5 µg/kg/day SC for 5 to 14 days in each cycle of chemotherapy (CTX), starting the day after the end of CTX within a cycle and stopping when an ANC $\geq 10x10^9$/L after nadir was reached. The dose and dose regimen for these trials were based on the data obtained in the phase 1 trials and historical clinical use with an FDA-approved product, Neupogen®.

- Breast cancer trial: 348 CTX-naïve patients with high risk stage II, III, or IV breast cancer needing CTX were enrolled. Patients were randomized 2:2:1 to XM02, European Neupogen®, or placebo during cycle 1; those patients initially randomized to the placebo group in cycle 1, received XM02 in all subsequent CTX cycles. Patients were administered 4 cycles of CTX (doxorubicin IV 60 mg/m^2 and docetaxel IV 75 mg/m^2) on day 1 of each 3-week cycle for a total of 4 cycles.
- Lung cancer trial: 240 patients with small cell lung cancer (SCLC) or advanced non-small cell lung cancer (NSCLC) having received no more than 1 prior CTX cycle were enrolled. During cycle 1, patients received either XM02 or European Neupogen® and in all subsequent cycles patients received XM02. CTX regimens consisted of any myelosuppressive platinum-based CTX in a 3- or 4-week cycle for up to 6 cycles.
- Non-Hodgkin Lymphoma trial: 92 CTX-naïve patients with aggressive NHL treated with CHOP regimen (Cyclophosphamide IV 750 mg/m^2, Doxorubicin IV 50 mg/m^2, Vincristine IV 1.4 mg/m^2, Prednisolone 100 mg/day one to five days) were enrolled. During cycle 1, patients received either XM02 or European Neupogen® and in all subsequent cycles, up to 6 cycles, patients received XM02.

Results of the phase 3 trials showed that treatment with XM02 reduced the duration of severe neutropenia (DSN) in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a clinically significant incidence of febrile neutropenia (FN). In the breast cancer trial, XM02 efficacy was demonstrated as compared to placebo in reducing DSN and preventing the incidence of FN in patients with malignant disease undergoing CTX.

Safety Profile: In clinical trials, the most frequent adverse reaction attributable to XM02 5 µg/kg/day SC is bone pain. In the breast cancer trial, the overall incidence of bone pain in cycle 1 was 14.2% for XM02, 17.9% for placebo, and 19.0% for Neupogen.

QT/QTc Evaluation: 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 totally cleared from systemic circulation. A post-marketing requirement to perform a QT study in either healthy subjects or patients at the highest dose tested is recommended.

Immunogenicity: 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: Less than 1% (5 out of 677) of patients treated with XM02 tested positive for binding antibodies during study treatment; 4 of the 5 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.

Conclusion: In conclusion, XM02 provides a reduction in 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 with an acceptable safety profile.

1.4 SIGNATURES

Sarah Schrieber Date: 8/9/10

Primary Reviewer: Sarah J. Schrieber, Pharm.D.

Division of Clinical Pharmacology 5

Hong Zhao Date: 8/9/10

Secondary Reviewer: Hong Zhao, Ph.D.

Division of Clinical Pharmacology 5

NAM Atiqur Rahman Date: 08/09/2010

Dvision Director: NamAtiqur Rahman, Ph.D.

Division of Clinical Pharmacology 5

Cc: DBOP: CSO – Jeff Summers; MTL – Suzanne Demko; MO – Thomas Herndon
DCP-5: Reviewers S Schrieber, H Zhao
DDD - B Booth; DD - A Rahman

2 QUESTION BASED REVIEW

2.1 GENERAL ATTRIBUTES

2.1.1 What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product as they relate to clinical pharmacology and biopharmaceutics review?

XM02 is a recombinant methionyl human granulocyte-colony stimulating growth factor (r-metHuG-CSF) manufactured by recombinant DNA technology using the bacterial strain *E 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 (NH_2)-terminal end that is not present on endogenous human G-CSF. Neutroval is a sterile, clear, colorless, preservative-free solution containing XM02, glacial acetic acid, sorbitol, polysorbate 80, and Water for Injection. Neutroval will be provided as 300 µg/0.5 mL and 480 µg/0.8 mL solution prefilled syringes.

2.1.2 What are the proposed mechanisms of action and therapeutic indications?

XM02, Neutroval®, is a human granulocyte colony-stimulating factor (G-CSF). Colony-stimulating factors are proteins that act on hematopoietic cells by binding to specific cell surface receptors and stimulating proliferation, differentiation commitment, and some end-cell functional activation. The proposed indication of XM02 is for the reduction in the duration of severe neutropenia (DSN) in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a clinically significant incidence of febrile neutropenia (FN).

2.1.3 What are the proposed dosage and route of administration?

The proposed dose of XM02 is 5 µg/kg administered subcutaneously (SC) once daily (b) (4) to start 24 hours after receiving chemotherapy.

2.2 GENERAL CLINICAL PHARMACOLOGY

2.2.1 What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?

Clinical Pharmacology Studies

Results of clinical and clinical pharmacology studies were submitted to support the clinical pharmacology of XM02 for patients with cancer (Table 1).

Table 1. Studies in Healthy Subjects and Patients with Cancer.

Study	Study population	Design
XM02-01-LT	Healthy, Caucasian, male volunteers	Phase 1, randomized, double-blind, active-controlled, single-dose
XM02-05-DE	Healthy, Caucasian, male and female volunteers	Phase 1, randomized, double-blind, active-controlled, single-dose
XM02-02-INT	CTX-naive patients with high-risk stage II, or with stage III or IV breast cancer needing CTX	Phase 3, randomized, double-blind, placebo-controlled, active-controlled
XM02-03-INT	Lung cancer patients	Phase 3, randomized, active-controlled
XM02-04-INT	Non-Hodgkin Lymphoma (NHL)	Phase 3, randomized, active-controlled

Clinical Endpoints

The clinical efficacy of XM02 in patients with established myelosuppressive chemotherapy for cancer has been demonstrated in one phase 3 trial (XM02-02-INT), and was supported by two phase 3 safety trials (XM02 -03-INT, -04-INT) and two phase 1 PK/PD trials in healthy volunteers (XM02 -01-LT, -05-DE). The phase 3 trial designs were multicenter, randomized, active-controlled. However, trial XM02-02-INT also included a placebo control comparison. The primary endpoint was DSN in cycle 1. Other endpoints included: incidence of febrile neutropenia (FN) and mortality, depth of absolute neutrophil count (ANC) nadir, and time to ANC recovery.

What is the clinical efficacy and safety in cancer patients?

Breast Cancer (XM02-02-LT): This was a phase 3, multicenter, active-controlled, randomized trial in patients with high-risk stage II, or with stage III or IV breast cancer needing chemotherapy (CTX) (N=350). Eligible patients were randomized in a 2:2:1 fashion to receive one of the following treatments:

- XM02 5 μg/kg/day SC (n=140)
- European Neupogen 5 μg/kg/day SC (n=140)
- Placebo (n=70).
    - Patients in the placebo group switched to XM02 after cycle 1.

Patients received a maximum of 4 CTX cycles (3 wks/cycle) with doxorubicin 60 mg/m^2 IV and docetaxel 75 mg/m^2 IV. Following CTX on Day 1 of a cycle, the patients received daily SC injections of 5 μg/kg/day of study drug treatment for 5 – 14 days, or until an ANC $\geq$10 x 10^9/L after nadir was documented.

The primary efficacy endpoint was DSN in cycle 1, defined as grade 4 neutropenia with an ANC <0.5 x 10^9/L. Secondary endpoints were: incidence of FN per cycle and across all cycles, DSN in cycles 2 to 4, depth of ANC nadir in cycles 1 to 4, times to ANC recovery in cycles 1 to 4, mortality, incidence of adverse events (AEs), changes of safety laboratory parameters, and immunogenicity.

Prostate Cancer (XM02-03-INT): This was a phase 3, international, multicenter, randomized (1:1), controlled safety study in patients with small-cell or non-small-cell lung cancer receiving platinum-based chemotherapy (N=240). Eligible patients were randomized in a 1:1 fashion to receive one of the following treatments:

- XM02 5 µg/kg/day SC (n=160)
- European Neupogen 5 µg/kg/day SC in the CTX cycle 1 (n=80)
    - In the subsequent cycles, all patients received XM-02.

CTX regimens in this trial consisted of any myelosuppressive platinum-based CTX, in 3-week or 4-week cycles, depending on the CTX protocol. Up to 6 CTX cycles were applied. Following CTX on Day 1 of a cycle, the patients received daily SC injections of 5 µg/kg/day of study drug treatment for 5 – 14 days, or until an ANC $\geq 10 \times 10^9$/L after nadir was documented.

This was a safety trial to evaluate the incidence of AEs, changes of safety laboratory parameters, and immunogenicity. Secondary efficacy endpoints were incidence of FN per cycle and across all cycles, the DSN in cycles 1 and 4, depth of ANC nadir in cycles 1 and 4, times to ANC recovery in cycles 1 and 4, and mortality.

Non-Hodgkin-Lymphoma (XM02-04-INT): This was a phase 3, international, multicenter, randomized (2:1), controlled safety trial in patients with chemotherapy (CTX) naïve aggressive Non-Hodgkin-Lymphoma (NHL) (allowed subtypes: diffuse large B cell lymphoma, mediastinal large B cell lymphoma, follicular lymphoma grade 3, anaplastic large cell lymphoma) needing CTX (N=92). Eligible patients were randomized in a 1:1 fashion to receive one of the following treatments:

- XM02 5 µg/kg/day SC (n=63)
- European Neupogen 5 µg/kg/day SC in the CTX cycle 1 (n=29)
    - In the subsequent cycles, all patients received XM-02.

The CTX regimen in this study was according to the CHOP protocol: Cyclophosphamide IV 750 mg/m^2, doxorubicin IV 50 mg/m^2, vincristine IV 1.4 mg/m^2 (maximum 2 mg) on Day 1 of each cycle, and prednisolone 100 mg/day orally from Days 1 – 5. Patients on CHOP could receive rituximab (stratification criterion). Up to 6 CTX cycles could be used. Following CTX on Day 1 of a cycle, the patients received daily SC injections of 5 µg/kg/day of study drug treatment for 5 – 14 days, or until an ANC $\geq 10 \times 10^9$/L after nadir was documented.

This was a safety trial to evaluate the incidence of AEs, changes of safety laboratory parameters, and immunogenicity. Secondary efficacy endpoints were incidence of FN per cycle and across all cycles, the DSN in cycles 1 and 4, depth of ANC nadir in cycles 1 and 4, times to ANC recovery in cycles 1 and 4, and mortality.

Summary of Clinical Efficacy

XM02 was efficacious compared to placebo. Table 2 presents Cycle 1 efficacy results from the three Phase 3 trials. In XM02-02-INT, the mean DSN 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% confidence interval -3.2 days, -2.2 days). The incidence of FN was lower in the XM02 group compared to the placebo group (12.1% vs. 36.1%). Patients in the Neupogen arm had a mean DSN of 1.1 days; the 95% confidence interval between the XM02 and the Neupogen arms was -0.26 days, 0.33 days.

XM02 and Neupogen had comparable effects in reducing DSN and preventing the incidence of FN in patients with malignant disease undergoing CTX.

Table 2. Summary of Efficacy Endpoint Results Across Trials for Cycle 1.

Trial / Parameter	Breast Cancer XM02-02-INT			Lung Cancer XM02-03-INT		NHL XM02-04-INT	
	XM02 (N=140)	Neupogen (N=136)	Placebo (N=72)	XM02 (N=160)	Neupogen (N=80)	XM02 (N=63)	Neupogen (N=29)
Mean DSN (days)	1.1	1.1	3.8	0.5	0.3	0.5	0.9
Incidence FN (%)	12.1	12.5	36.1	15.0	8.8	11.1	20.7
ANC nadir (days)	7	7	11	11	12	9	9
Mean ANC nadir (10^9/L)	0.7	0.7	0.2	2.1	2.9	1.7	1.1
Mean time to ANC (days)	8.0	7.8	14.0	6.3	4.5	6	6.7

Summary of Clinical Safety

Across all cycles and within each cycle, the adverse event profile was similar between the XM02 and Neupogen/XM02 groups. In XM02-02-INT, the most frequent treatment-emergent adverse event (TEAE) that occurred at a higher incidence in patients treated with XM02 compared with patients treated with placebo was bone pain (3.4% vs 1.4% in cycle 1). The most common TEAEs in patients treated with XM02 or Neupogen/XM02 were nausea (27.3% in cycle 1 and 46.2% overall) and alopecia (25.0% in cycle 1 and 33.8% overall). Other common TEAEs were neutropenia (16.1% in cycle 1 and 22.6% overall), diarrhea (13.0% in cycle 1 and 20.4% overall), asthenia (12.9% in cycle 1 and 28.7% overall), and vomiting (12.6% in cycle 1 and 25.6% overall).

In XM02-02-INT, the incidence of FN was higher in the placebo/XM02 group. Also, the incidence of stomatitis, pharyngitis, and pharyngolaryngeal pain were higher in the placebo/XM02 group compared to the other groups.

2.2.2 What is the basis for selecting the response endpoints or biomarkers and how are they measured in clinical pharmacology and clinical studies?

Biomarkers

- Absolute neutrophil count (ANC): The ANC refers to the total number of neutrophil granulocytes present in the blood.

In the healthy volunteer trials (XM02-01-LT and XM02-05-DE), the ANC pharmacodynamic (PD) parameters (C_{max}, AUC, T_{max}) were similar between the two trials and were comparable to Neupogen (Tables 3 and 4). XM02 and Neupogen after IV administration resulted in lower ANC AUC_{0-t}, and ANC_{max} values compared to that after SC administration with the same dose.

Table 3. Comparison of ANC Parameters at a 5 µg/kg SC and IV Doses in Healthy Subject Trials.

PD Parameter	XM02-01-LT		XM02-05-DE			
	5 µg/kg SC (N=28)		5 µg/kg SC (N=33)		5 µg/kg IV (n=31)	
	XM02	Neupogen	XM02	Neupogen	XM02	Neupogen
Geomean (CV%) ANC_{max} (10^9/L)	22.2 (14)	22.9 (24)	22.6 (24)	21.1 (28)	18.7 (27)	19.5 (25)
Geomean (CV%) ANC AUC_{0-t} (h*10^9/L)	906.2 (13)	901.8 (16)	956.9 (30)	983.1 (25)	738.4 (28)	776.7 (25)
Median ANC T_{max} (h)	12	12	12	12	12	12

Table 4. Comparison of ANC Parameters at a 10 µg/kg SC and IV Doses in Healthy Subjects Trials.

PD Parameter	XM02-01-LT		XM02-05-DE			
	10 µg/kg SC (n=28)		10 µg/kg SC (N=30)		10 µg/kg IV (N=30)	
	XM02	Neupogen	XM02	Neupogen	XM02	Neupogen
Geomean (CV%) ANC_{max} (10^9/L)	25.7 (26)	25.7 (24)	26.9 (25)	27 (27)	21.7 (26)	22.2 (26)
Geomean (CV%) ANC AUC_{0-t} (h*10^9/L)	1200.1 (17)	1172.5 (17)	1305.9 (28)	1245.2 (39)	917 (33)	958.9 (28)
Median ANC T_{max} (h)	14	16	18	20	16	16

Formal assessments such as ANC_{max}, ANC AUC_{0-t}, and ANC T_{max} were not done in the oncology clinical trials (XM02-02-INT, XM02-03-INT, and XM02-04-INT). Refer to Table 2 above for a summary of the ANC efficacy endpoint results across studies for Cycle 1.

- CD34+: CD23+ is an antigen expressed on human hematopoietic progenitor cells and CD34+ cells differentiate to mature neutrophils in response to G- CSF.

In the healthy volunteer trial #XM02-05-DE, baseline serum CD34+ concentrations were similar between treatment groups (N=30/cohort). Following single doses of Neupogen or XM02 maximum CD34+ concentrations were achieved around 72 hours post-dose and values appeared to return to baseline values after 336 hours.

Table 5. Comparison of CD34+ Parameters at 5 and 10 µg/kg SC Doses in Healthy Subjects.

PD Parameter	XM02-05-DE			
	5 µg/kg SC (N=33)		10 µg/kg SC (N=30)	
	XM02	Neupogen	XM02	Neupogen
Geomean (CV%) CD34+ C_{max} (/µL)	8.42 (43)	8.78 (46)	12.23 (55)	13.29 (55)
Geomean (CV%) CD34+ AUC_{0-t} (h*/µL)	1462.6 (39)	1448.6 (43)	1860.8 (46)	2063.9 (48)
Median CD34+ T_{max} (h)	72.1	72.3	72.1	74.9

Table 6. Comparison of CD34+ Parameters at 5 and 10 µg/kg IV Doses in Healthy Subjects.

PD Parameter	XM02-05-DE			
	5 µg/kg IV (N=31)		10 µg/kg IV (N=30)	
	XM02	Neupogen	XM02	Neupogen
Geomean (CV%) CD34+ C_{max} (/µL)	8.56 (58)	8.79 (52)	10.43 (59)	9.68 (76)
Geomean (CV%) CD34+ AUC_{0-t} (h*/µL)	1451.4 (44)	1448.6 (40)	1644.9 (65)	1525.6 (67)
Median CD34+ T_{max} (h)	73	72.4	72.1	71.8

2.2.3 Are the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?

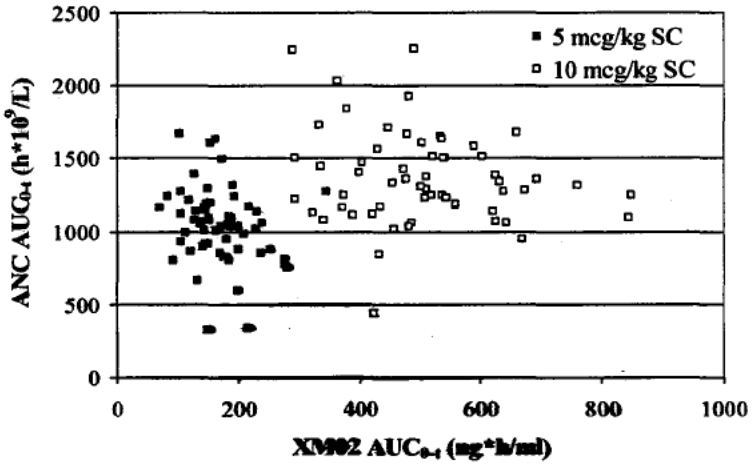
Yes. Analysis of r-MetHuG-CSF concentrations in blood serum was performed using a method based on the enzyme-linked immunosorbent assay (ELISA) kit (Quantikine®, R&D Systems, USA) at (b) (4). The assay standard curve range is 39 – 2500 pg/ml. However, the determination of G-CSF in human serum is more reliable within 50 – 1800 pg/ml. Refer to Section 2.6 Analytical for detailed information.

2.2.4 Exposure-response

2.2.4.1 What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for efficacy?

As described in Section 2.2.2 above, absolute neutrophil count (ANC) is the PD marker used for G-CSF products. In the healthy volunteer PK/PD trials (XM02-01-LT and XM02-05-DE), less than dose proportional increases in the ANC_{max} and ANC AUC_{0-t} were observed between the 5 and 10 µg/kg SC dose levels (Tables 3 – 4, Figure 1). Doubling the XM02 SC dose from 5 to 10 µg/kg resulted in a 16-19% increase in the ANC_{max} and a 33-36% increase in $ANCAUC_{0-t}$.

Figure 1. XM02 Exposure-Response Relationship.



Formal assessments such as ANC_{max}, ANC AUC_{0-t}, and ANC T_{max} were not done in the three oncology phase 3 clinical trials (XM02-02-INT, XM02-03-INT, and XM02-04-INT) which only studied the XM02 5 µg/kg SC dose. Additionally, only 12 patients from each phase 3 oncology

trials had XM02 PK data collected. Therefore, the exposure-response relationships for efficacy were not able to be explored.

2.2.4.2 What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for safety?

In the healthy volunteer trials (XM02-01-LT and XM02-05-DE), the most common adverse event related to drug was headache (25 – 29% of all AEs). No apparent relationship between exposure or dose and safety were evident.

In the three oncology phase 3 clinical trials, across all cycles and within each cycle, the adverse event profile was similar between the XM02 and Neupogen/XM02 groups. In XM02-02-INT, the most frequent treatment-emergent adverse reaction that occurred at a higher incidence in patients treated with XM02 compared with patients treated with placebo was bone pain (3.4% vs 1.4% in cycle 1). The most common treatment emergent adverse events in patients treated with XM02 or Neupogen/XM02 in Cycle 1 were nausea (27.3%) and alopecia (25.0%). Only 12 patients from the phase 3 clinical trials had PK data collected. Therefore, the exposure-response relationships for safety were not able to be explored.

2.2.4.3 Does this drug prolong the QT or QTc interval?

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 totally cleared from systemic circulation. In the two phase 1 trials (XM02-01-LT (N=56), XM02-05-DE (n=144)) in healthy volunteers, 12-lead ECGs were monitored at screening and at follow-up (14 days post-dose). No significant changes in QT were observed in either study. XM02 has not been associated with cardiac adverse events.

Since XM02 was granted marketing authorization in Europe on September 2008, Teva also provided a summary of its post-marketing safety reports to support the lack of QTc prolongation signal. As indicated in the March 31, 2010 European Periodic Safety Update Report, the post-marketing safety data collected includes (b)(4) daily XM02 doses. The sponsor searched this database for all events potentially related to QT prolongation, cardiac arrhythmia and any possibly related events. 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.

Since Neutroval is submitted under PHS Act 351(a), a post-marketing requirement to perform a thorough QT (TQT) trial is recommended. The TQT trial may be designed as a single-dose, 3-way crossover (XM02, moxifloxacin, placebo) trial in healthy volunteers with the highest XM02 SC dose tested (10 µg/kg). The sponsor should propose the appropriate sample size for this trial.

2.2.4.4 Is the dose and dosing regimen selected by the sponsor consistent with the known relationship between dose-concentration-response, and are there any unresolved dosing or administration issues?

After SC administration, there was a greater than proportional (3-fold) increase in AUC_{0-t} and C_{max} of G-CSF with a 2-fold increase in dose from 5 to 10 µg/kg for both XM02 and Neupogen. However, there was a dose proportional increase in AUC_{0-t} and C_{max} of G-CSF after IV

administration. In general, IV administration resulted in distinctly larger AUC and higher C_{max} values compared to SC administration. The selection of dose and dose regimen for the phase 3 trials were based on the data obtained in the phase 1 trials and historical clinical use with an FDA-approved product, Neupogen®, Amgen.

2.2.5 Pharmacokinetic characteristics of the drug and its major metabolites

2.2.5.1 What are the single dose and multiple dose PK parameters?

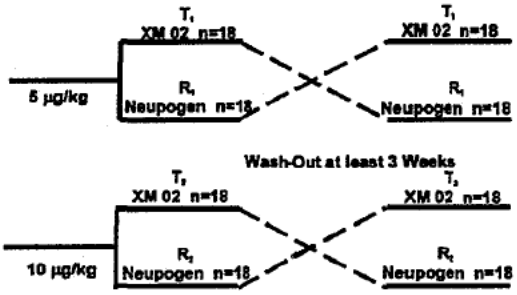
Phase 1 – Healthy volunteers

The sponsor conducted two single dose trials in healthy volunteers (XM02-01-LT, XM02-05-DE).

- XM02-01-LT was a randomized, single-blind, 2-period crossover, 2-arm, single dose PK and PD study in healthy male subjects (N=56). XM02 or European Neupogen 5 µg/kg or 10 µg/kg were administered as single SC doses.

Group	Treatment Period	
	First	Second
A	T_1 or R_1	R_1 or T_1
B	T_2 or R_2	R_2 or T_2

- XM02-05-DE was a single blind, randomized, 2-period, 2-way crossover, 8 treatments and 2 sequences with at least 3 weeks wash-out carried out in 4 groups of ~36 subjects each (N=144). XM02 or Neupogen® 5 µg/kg or 10 µg/kg were administered as single doses SC or IV.



PK blood samples were obtained at the following times for the SC and IV dose cohorts:

- SC: 0 (pre-dose), and 0.5, 1. 1.5, 2, 3, 4, 6, 8, 10, 12, 24 and 48 hours after the injection.
- IV: 0 (pre-dose), 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 16, 24 and 48 hours after start of IV infusion

For study XM02-05-DE, in both the XM02 and Neupogen groups receiving 5 or 10 µg/kg SC or IV doses, mean G-CSF serum concentrations rapidly increased, reached a median Tmax around 6 hours for the SC doses and around 0.75 hours for the IV doses. The G-CSF serum concentrations decreased to pre-dose values at 24 hours after SC or IV doses. Based on the serum levels measured up to 48 hours, the median $t_{½}$ was between 5.2 – 9.4 hours following SC or IV administration at either dose. The absolute bioavailability of 5 and 10 mcg/kg SC XM02 was 33% and 45%, respectively. Increasing the SC dose of XM02 from 5 to 10 µg/kg resulted in an approximately 3-fold increase in C_{max} and AUC_{0-t}. However, after IV administration there was a dose-proportional increase of C_{max} and AUC_{0-t} from 5 to 10 µg/kg. The PK parameter data are summarized in Tables 7 and 8. Figure 2 depicts the concentration vs. time profile for the 5 µg/kg

SC (Panel A) and 5 µg/kg IV (Panel B) dose cohorts.

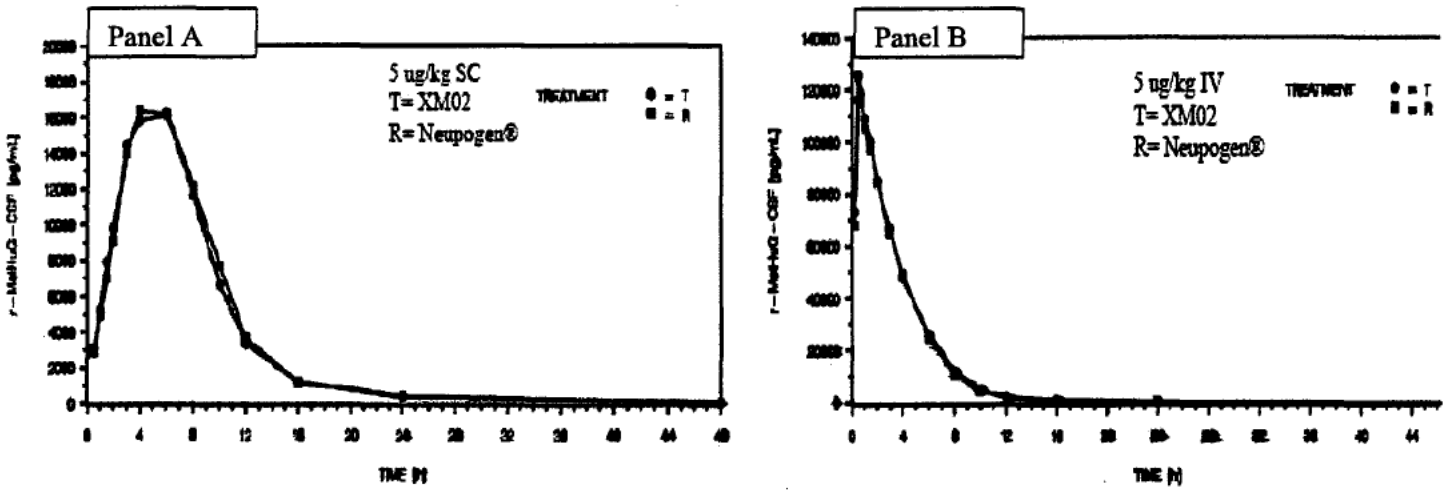
Table 7. Trial XM02-05-DE: Summary of Single Dose XM02 SC Pharmacokinetic Parameters in Healthy Subjects.

Parameter	5 µg/kg SC (N=33)		10 µg/kg SC (N=30)	
	XM02	Neupogen	XM02	Neupogen
AUC_{0-t} (ng*h/mL)	157.6 (37.1)	159.4 (36.4)	471.2 (24.9)	430.7 (18)
C_{max} (ng/mL)	18 (41.1)	18.4 (43.5)	46.2 (30.2)	43.1 (37.1)
T_{max} (hr)	6.0	4.1	6.0	6.0
t ½ (hr)	8.9	9.4	5.2	5.2
Data are presented as Geometric mean (CV%) AUC_{0-t} and C_{max} and median T_{max} and t½.				

Table 8. Trial XM02-05-DE: Summary of Single Dose XM02 IV Pharmacokinetic Parameters in Healthy Subjects.

Parameter	5 µg/kg IV (N=31)		10 µg/kg IV (N=30)	
	XM02	Neupogen	XM02	Neupogen
AUC_{0-t} (ng*h/mL)	480.2 (22.2)	470.4 (21.5)	1056.5 (22.9)	991.0 (23.9)
C_{max} (ng/mL)	129.8 (18.7)	126.1 (16.2)	231.1 (16.7)	221.6 (18.6)
t ½ (hr)	9.4	9.4	7.2	7.3
Data are presented as Geometric mean (CV%) AUC and Cmax and median t½.				

Figure 2. Trial XM02-05-DE: Mean Serum Concentration-Time Profile of G-CSF Following a Single 5 µg/kg SC (Panel A) or 5 µg/kg IV (Panel B) Injection of XM02 or Neupogen in Healthy Subjects.



Phase 3 –Cancer Patients

In the three Phase 3 clinical studies in cancer patients, breast cancer: #XM02-02-INT (N=348), lung cancer: #XM02-03-INT (N=240), and NHL: #XM02-04-INT (N=92), up to 12 patients per treatment group from each trial had XM02 concentration time profiles determined. XM02 or Neupogen SC 5 µg/kg/day was administered starting 24 hours after chemotherapy for at least 5

days and a maximum of 14 days in each cycle. The pharmacokinetic results are listed in Table 9. For the 3 trials combined, the median Tmax was between 4 to 6 hours and the median t½ was between 3.2 to 3.8 hours, which was shorter than that observed in healthy volunteers in trial XM02-05-DE. However, the $t_{½}$ was based on serum levels measured up to 24 hours, as compared to up to 48 in the healthy volunteer trial XM02-05-DE. A large variability in the pharmacokinetics of XM02 was observed between the 3 patient populations studied, including breast cancer, lung cancer and NHL. No accumulation after repeated dosing was observed.

Table 9. Summary of XM02 PK Parameters after SC Administration of 5 μg/kg/day during Cycle 1.

Parameter	XM02-02-INT		XM02-03-INT		XM02-04-INT	
	XM02	Neupogen	XM02	Neupogen	XM02	Neupogen
$AUC_{0\text{-}24h}$ (ng*h/mL)	305 (35)	259 (47)	273 (61.4)	240 (30.9)	184 (23.2)	188 (63.4)
C_{max} (ng/mL)	36.1 (40.6)	28.9 (52.6)	25.2 (59.6)	23.7 (33.3)	20.1 (24.2)	18.8 (56.9)
T_{max} (hr)	4	4	6	6	6	5
t½ (hr)	3	3.2	3.5	3.3	3.2	3.8
Data are presented as Geometric mean (CV%) $AUC_{0\text{-}24h}$ and C_{max} and median T_{max} and $t_{½}$.						

2.2.5.2 How does the PK of the drug and its major active metabolites in healthy volunteers compare to that in patients?

The XM02 (AUC and C_{max} in the patient populations appear greater compared to healthy volunteers after receiving the same dose (Table 10). However, there was also greater variability in patients XM02 exposures compared to healthy volunteers (Figure 3). G-CSF undergoes neutrophil-mediated clearance (see section 2.2.5.7). Given that XM02 PK samples were collected in patients following chemotherapy treatment in the trials, it is expected that the patients will have decreased neutrophil counts due to chemotherapy, compared to healthy volunteers, and therefore greater XM02 exposures. Tumor type may be the other factor that may contribute to the variability between patient populations.

Figure 3. XM02 Exposures in Patients 24h Post-Chemo vs. Exposures in Healthy Volunteers.

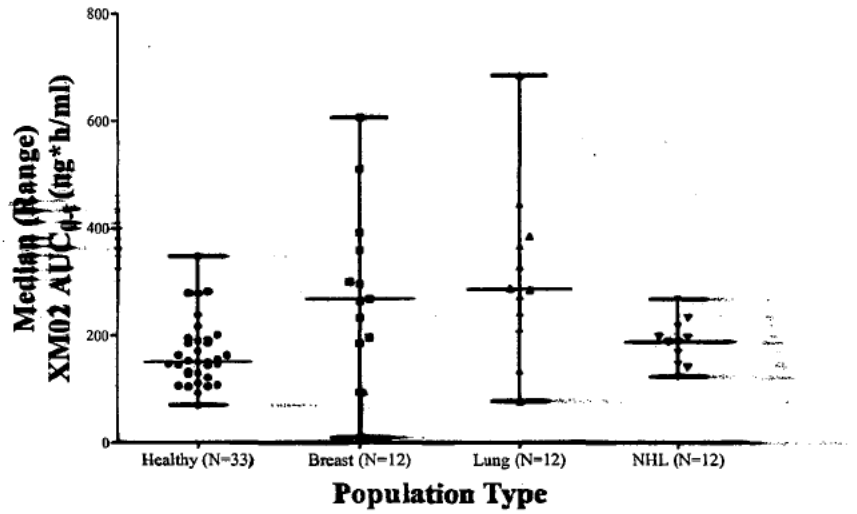


Table 10. Summary of PK Parameters for Phase 1 and Phase 3 Trials in the BLA.
Geometric Means of AUC and Cmax and Median of Tmax and $t_{½}$ of G-CSF Following Injection of XM02 or Neupogen to Healthy Subjects and Cancer Patients.

	Age [years]	Number of patients		AUC[a] [ng/mL*h]		Cmax [ng/mL]		tmax [hours]		t1/2 [hours][b]	
	Median (range)	XM02	Neupogen®	XM02	Neupogen®	XM02	Neupogen®	XM02	Neupogen®	XM02	Neupogen®
XM02-01-LT (Healthy Male Volunteers)											
5 µg/kg s.c.	21.5 (19 to 40)	24		158.45	143.10	23.54	21.23	4	4	2.10	2.00
10 µg/kg s.c.		26		473.91	475.20	55.74	56.28	6	6	2.75	2.66
XM02-05-DE (Healthy Male and Female Volunteers)											
5 µg/kg s.c.	32.5 (18 to 45)	33		157.585	159.426	17.976	18.416	6	4	8.93	9.36
10 µg/kg s.c.		30		471.148	430.717	46.239	43.145	6	6	5.15	5.21
5 µg/kg i.v.		31		480.201	470.373	129.786	126.124	0.5	0.75	9.38	9.35
10 µg/kg i.v.		30		1056.472	990.996	231.142	221.562	0.75	0.75	7.15	7.30
XM02-02-INT (Breast Cancer Patients)											
5 µg/kg s.c.	57 (35 to 74)	14	13	305.299	258.499	36.148	28.985	4	4	3.04	3.225
XM02-03-INT (Lung Cancer Patients)											
5 µg/kg s.c.	59 (35 to 78)	13	12	272.481	240.127	25.223	23.664	6	6	3.53	3.34
XM02-04-INT (Non-Hodgkin Lymphoma Patients)											
5 µg/kg s.c.	53 (22 to 76)	11	4	183.495	118.119	20.116	18.833	6	5	3.16	3.84

[a] AUC0-t in phase I studies, where t = 48 hours; AUC0-24, in phase III studies, # Mean (range)

[b] The differences in $t_{½}$ among studies are due to varying length of sampling duration in these studies. However, using same sampling scheme within each study, the $t_{½}$ is similar for XM02 and Neupogen.

Note.: in phase III studies, results are from first injection in first chemotherapy cycle

2.2.5.3 What are the characteristics of drug absorption?

XM02 is administered via SC route. Intravenous pharmacokinetic data are available in humans. The phase 1 study, XM02-05-DE determined that the absolute bioavailability of SC XM02 was 33% and 45% for the 5 µg/kg and 10 µg/kg dose, respectively.

2.2.5.4 What are the characteristics of drug distribution?

No drug distribution study has been conducted for XM02. XM02 is a biologic product. Drug distribution studies are not generally performed for biologic products because they are proteins which are degraded into amino acids that then recycled into other proteins.

2.2.5.5 Does the mass balance study suggest renal or hepatic as the major route of elimination?

No mass balance study has been conducted for XM02. XM02 is a biologic product. Mass balance studies are not generally performed for biologic products because they are proteins which are degraded into amino acids that are then recycled into other proteins.

2.2.5.6 What are the characteristics of drug metabolism?

No drug metabolism study has been conducted for XM02. XM02 is a biologic product. Drug metabolism studies are not generally performed for biologic products because they are proteins which are degraded into amino acids that are then recycled into other proteins.

2.2.5.7 What are the characteristics of drug excretion?

When neutrophil-mediated clearance (CL) is saturated by high G-CSF concentrations or is diminished by neutropenia, the linear clearance pathway predominates and the pharmacokinetics appears linear. (Neupogen®, Roche New Zealand July 2009 Package Label and Neulasta®, Amgen U.S. February 2010 Package Label).

A population PK model was recently published which demonstrate that a receptor-mediated model adequately describes filgrastim serum concentrations and quantifies the role of receptor binding in Neupogen®, Amgen GmbH, Munich, Germany clearance (Wiczling P., et al. *Clin Pharmacokinet.* 2009;48:817-826). The model predicted that filgrastim CL is initially mostly through the binding of filgrastim to G-CSF receptors. Subsequently, the CL slows down because of the saturation of binding sites, and occurs mostly via the linear (renal) pathway. Finally, for filgrastim concentrations lower than the K_d of 0.308 ng/ml, target-mediated CL dominates.

2.2.5.8 Based on PK parameters, what is the degree of linearity or non-linearity based in the dose-concentration relationship?

Increasing the SC dose of XM02 from 5 to 10 µg/kg resulted in an approximately 3-fold increase in C_{max} and AUC_{0-t}. However, after IV administration there was a dose-proportional increase of C_{max} and AUC_{0-t} from 5 to 10 µg/kg. The PK parameter data are summarized above in Tables 7 and 8. Also refer to Figure 2 above, which depicts the concentration vs. time profiles for the 5 µg/kg SC (Panel A) and the 5 µg/kg IV (Panel B) dose cohorts.

2.2.5.9 How do the PK parameters change with time following chronic dosing?

After XM02 5 µg/kg SC daily dosing for 9 to 11 days in the breast cancer trial (XM02-02-INT), the geometric mean AUC_{0-24h} was slightly lower than that after the first injection. A trend of accumulation was not observed in the other two phase 3 trials XM02-03-INT and XM02-04-INT.

When neutrophil-mediated clearance is saturated by high filgrastim concentrations or is diminished by neutropenia, the linear clearance pathway predominates and the pharmacokinetics appear linear. (Wiczling P., et al. *Clin Pharmacokinet.* 2009;48:817-826; Neupogen®, Roche New Zealand July 2009 Package Label; Neulasta®, Amgen U.S. February 2010 Package Label).

2.2.5.10 What is the inter- and intra-subject variability of PK parameters in volunteers and patients, and what are the major causes of variability?

The observed variability (CV%) in PK parameters (C_{max} and AUC) following XM02 5 µg/kg SC dosing in healthy volunteers was ~40% (Table 7 above), in breast cancer was ~35%, in lung cancer was ~60%, and in NHL was ~23% (Table 9 above). Not enough data were gathered to determine causes of variability in patients because PK data were collected in only ~12 patients in each cancer type.

2.3 INTRINSIC FACTORS

2.3.1 What intrinsic factors (age, gender, race, weight, height, disease, genetic polymorphism, pregnancy, and organ dysfunction) influence exposure (PK usually) and/or response, and what is the impact of any differences in exposure on efficacy or safety responses?

Based on data from 124 Caucasian, healthy volunteers in trial XM02-05-DE, gender did not appear to alter the PK or PD of XM02 following SC dosing (Table 11). However, following XM02 IV administration, both AUC and C_{max} appeared to be reduced in females as compared to males. ANC parameter values appeared similar between males and females regardless of XM02 dose or administration route. CD34+ AUC and C_{max} values appeared to be slightly less in females compared to males regardless of XM02 dose or administration route. See Appendix 4.2.2 for the XM02-05-DE individual study report and complete gender analysis results.

Table 11. Trial 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)
Cmax (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)
ANCmax ($10^9/L$)	22.9 (28)	22.3 (20)	27.2 (21)	26.7 (27)

Not enough data were gathered to determine an effect of other intrinsic factors such as race.

2.3.2 Based upon what is known about exposure-response relationships and their variability and the groups studied, healthy volunteers vs. patients vs. specific populations, what dosage regimen adjustments, if any, are recommended for each of these groups? If dosage regimen adjustments are not based upon exposure-response relationships, describe the alternative basis for the recommendation.

2.3.2.1 Pediatric patients

A pediatric deferral has been requested by the sponsor at this time since adult efficacy trials were complete. Teva proposes to conduct a singe, open-label study (N=50) to evaluate the safety, efficacy, as well as sparse pharmacokinetic sampling of XM02 in solid tumors without bone marrow involvement.

- Age groups: Infants: 1m-24m, Children: 2-12y, Adolescents: 12-18y.
- Dose: 5 µg/kg/d SC
- Populations to be studied are from the following who are receiving myelotoxic chemotherapy: lymphomas bone and soft tissue sarcomas (e.g., Osteosarcoma, Ewings Sarcoma), kidney tumors, brain tumors, other solid tumors (gonadal and germ cell tumors, malignant melanoma, retinoblastoma, liver tumors, and miscellaneous tumors).

Clinical pharmacology has the following comments to the sponsor:

1. The sponsor's 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). The sponsor may also refer to the November 1998 FDA Clinical Pharmacology Pediatric Pharmacokinetic Study Draft Guidance to Industry, which may be found at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072114.pdf.
2. 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 the sponsor proposed.
3. The pharmacodynamic (absolute neutrophil count) profile should also be evaluated in patients so that exposure-response relationships may be evaluated.

2.3.2.2 Geriatric Patients

Among 677 cancer patients enrolled in clinical trials of Neutroval, a total of 111 patients were 65 years of age and older. No overall differences in safety or effectiveness were observed between patients age 65 and older and younger patients. There were an insufficient number of geriatric patients with PK data available to assess the impact of age on the PK of XM02.

2.3.2.3 Renal impairment

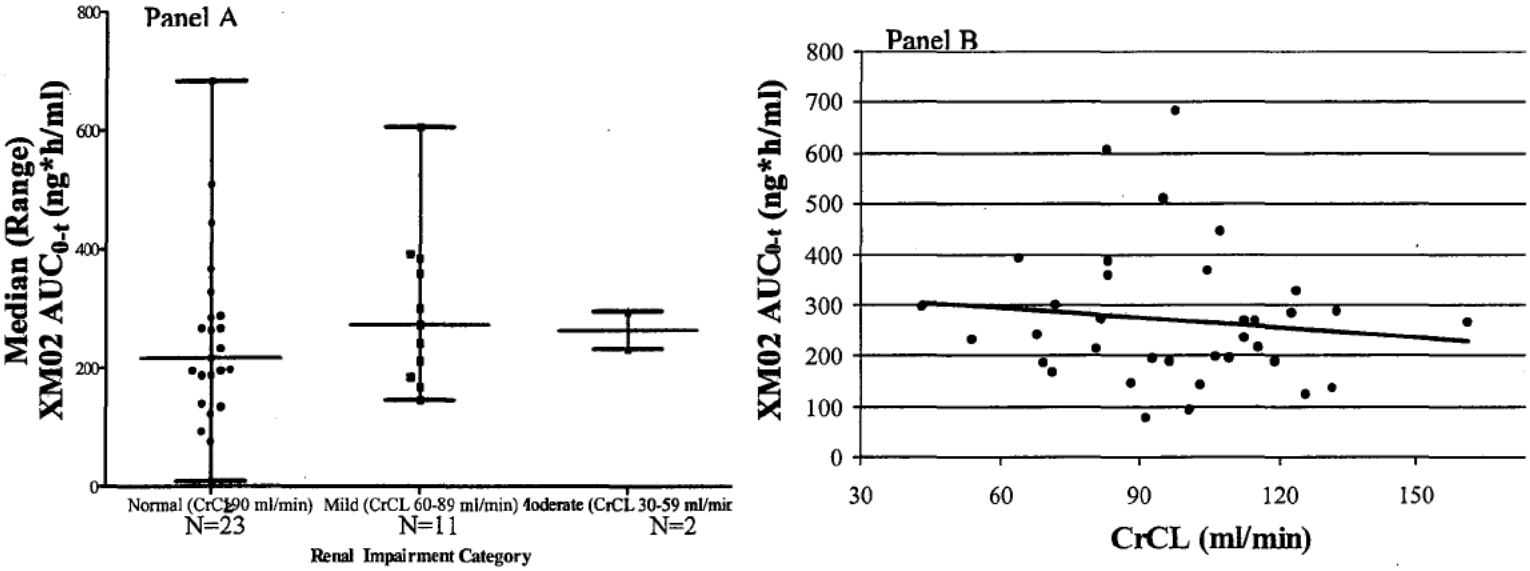
Renal impairment PK/PD studies were not conducted. In the three phase 3 oncology clinical trials, renal impairment was defined as a baseline serum creatinine > 2 mg/dl; only 1 patient enrolled in XM02-04-INT (NHL trial) was identified with renal impairment. However, creatinine clearance (CrCL) was retrospectively calculated using the Cockcrof-Gault formula in all patients enrolled in the three phase 3 trials. Based on the retrospective CrCL analysis, additional patients with renal impairment were identified in the BLA submission (Table 12). Of the patients with 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). Figure 4A depicts the median (range) XM02 exposures achieved in these patient groups. Figure 4B depicts the correlation between individual CrCL and exposure.

Table 12. Number of Patients with Renal Impairment Enrolled in the Phase 3 Trials.

Trial	Treatment	Renal Function Category (CrCL, ml/min)		
		Normal (>89)	Mild (60 - 89)	Molderate (30 - 59)
XM02-02-INT	XM02 (N=140)	77	52	11
	EU Neupogen® (N=136)	81	50	5
XM02-03-INT	XM02 (N=158)	75	72	11
	EU Neupogen® (N=79)	47	24	8

XM02-04-INT	XM02 (N=60)	40	20	0
	EU Neupogen® (N=28)	12	16	0
TOTALS	XM02 (N=358)	192	144	22
	EU Neupogen® (N=243)	140	90	13
OVERALL TOTAL	(N=601)	332	234	35

Figure 4. XM02 Exposure Data in Patients with Renal Impairment from the Phase 3 trials (Panel A) and XM02 Exposure-CrCL relationship (Panel B).



Bone pain was the most prominent and specific adverse event known to be related to Neupogen treatment. Therefore, any change in G-CSF blood concentrations would potentially change the incidence of bone pain. The incidence of bone pain following the chemotherapy Cycle 1 is presented in Table 13, and is calculated from data recorded in Table 12. Although the number of patients in each group is small, it does not appear that renal impairment induced an increase in the incidence of bone pain.

Table 13. Incidence (number) of Patients with Bone Pain in Patients with Renal Impairment.

Trial	Treatment	Incidence, (N) of Bone Pain*		
		Normal (>89)	Mild (60 - 89)	Molderate (30 - 59)
XM02-02-INT	XM02	7.8% (6)	3.8% (2)	-
	EU Neupogen®	11% (9)	8% (4)	-
XM02-03-INT	XM02	4% (3)	5.6% (4)	-
	EU Neupogen®	4.3% (2)	-	-
XM02-04-INT	XM02	10.8% (4)	9.5% (2)	-
	EU Neupogen®	-	-	-

*Incidence is calculated based on N for each category listed in Table 12.

The recommended dose of XM02 is 5 µg/kg administered by SC injection once daily. XM02 is dosed 24-h post-chemotherapy daily until the expected neutrophil nadir is passed and the neutrophil count has reached ≥10 x 10^9/L [redacted] (b) (4) Given the safety margin of XM02, Neutroval dosage adjustments for renal impairment would not be warranted from a clinical perspective. Therefore, no additional PK studies will be requested in severe or end-stage renal disease.

2.3.2.4 Hepatic impairment

Hepatic impairment PK/PD studies were not conducted. There were 4 hepatic impairment patients identified in trial XM02-02-INT, 4 in trial XM02-03-INT, and 2 in trial XM02-04-INT. Hepatic impairment was defined as having a baseline ALT > 3 times the upper normal limit or baseline AST > 3 times the upper normal limit. None of the patients identified to have hepatic impairment had PK data available.

2.3.2.5 What pregnancy and lactation use information is there in the application?

As with all human G-CSF products produced by recombinant DNA technology, there are no clinical data on the safety of XM02 in pregnancy, or on the development of the fetus. Preclinical studies on reproductive and developmental toxicity have not been performed. There are reports in the literature in which transplacental passage of filgrastim in pregnant women has been demonstrated. The potential risk for humans is unknown.

Nonteratogenic Effects: As with all filgrastim products, there are no adequate and well-controlled studies in pregnant women. The safe use of XM02 in pregnancy has not been studied and should not be used during pregnancy.

Filgrastim and human G-CSF products are poorly secreted in breast milk and G-CSF is not orally absorbed by neonates. Caution should be exercised when administered to a nursing woman.

2.3.3 Immunogenicity

2.3.3.1 What is the incidence (rate) of the formation of the anti-product antibodies (APA), including the rate of pre-existing antibodies, the rate of APA formation during and after the treatment, time profiles and adequacy of the sampling schedule?

The assays used to test the development of antibodies to XM02 was not validated. Therefore, the incidence of anti-XM02 antibody formation obtained in clinical studies is not considered reliable.

Immunogenicity sample collection times in the three Phase 3 trials: Blood samples for testing of binding antibodies and neutralizing antibodies (NAB) against G-CSF were collected at the screening visit, within 24 hours before each cycle, at end-of study (day 85), and at the 180 day follow-up visit.

Overall, the incidence rate of developing binding antibodies from the un-validated assay was 0.7% (5 of 677) in XM02-treated subjects in the studies included in this BLA (Table 14).

Samples for immunogenicity to assess for anti-product antibody formation were collected at early onset, during study, and during study follow-up and are considered adequate time points. Out of the 5 subjects that were positive for binding antibodies at any time in the studies, 4 were positive for neutralizing antibody formation at any time in the study (Table 15). In summary, the G-CSF immunogenicity incidence appears low and not associated with any clinical consequence. However, development of antibodies to XM02 was not assessed using a validated assay method so the incidence of anti-XM02 antibody formation obtained is not considered reliable.

Table 14. Percentage of Patients with Binding Antibodies in the Three Phase 3 Oncology Trials Combined.

	XM02 only (N=356)		Neupogen® only (N=134)		Neupogen®/ XM02 (N=115)		Placebo/XM 02 (N=72)		Overall (N=677)	
	n	%	n	%	n	%	n	%	n	%
Positive for binding antibody at any time in the study	4	1.1	0	0.0	0	0.0	1	1.4	5	0.7
Positive for binding antibody during study follow-up	1	0.3	1	0.7	2	1.7	2	2.8	6	0.9

Table 15. Percentage of Patients with Neutralizing Antibodies in the Three Phase 3 Oncology Trials Combined.

	XM02 only (N=356)		Neupogen® only (N=134)		Neupogen®/ XM02 (N=115)		Placebo/XM 02 (N=72)		Overall (N=677)	
	n	%	n	%	n	%	n	%	n	%
Positive for neutralizing antibody at any time in the study	4	1.1	0	0.0	0	0.0	0	0.0	4	0.6
Positive for neutralizing antibody during study follow-up	2	0.6	2	1.5	0	0.0	2	2.8	6	0.9

2.3.3.2 Does the immunogenicity affect the PK and/or PD of the therapeutic protein?

None of the six patient who tested positive for binding antibodies had pharmacokinetic data available. Evidence of altered pharmacodynamics (ANC values) has not been observed in patients who tested positive for binding antibodies.

2.3.3.3 Do the anti-product antibodies have neutralizing activity?

The assay used to test the development of neutralizing antibodies to XM02 was not validated. Therefore, the incidence of neutralizing XM02 antibody formation obtained in clinical studies is not considered reliable.

Using the un-validated assay, neutralizing antibodies were detected in 4 of 677 (0.6%) XM-02-treated patients in all three phase 3 cancer trials. None of the six patient who tested positive for neutralizing antibodies had pharmacokinetic data available. Evidence of altered pharmacodynamics (ANC values) has not been observed in patients who tested positive for neutralizing antibodies

2.3.3.4 What is the impact of anti-product antibodies on clinical efficacy?

The XM02 immunogenicity incidence was low and did not appear to be associated with any clinical efficacy consequences (e.g. no effect on DSN).

2.3.3.5 **What is the impact of anti-product antibodies on clinical safety? (e.g. infusion-related reactions, hypersensitivity reactions, cross-reactivity to endogenous counterparts, etc.)**

No evidence [illegible] has been observed in subjects who tested positive for [illegible] or binding and/or neutralizing antibodies.

2.4 EXTRINSIC FACTORS

2.4.1 **What extrinsic factors (drugs, herbal products, diet, smoking, and alcohol use) influence dose-exposure and/or response and what is the impact of any differences in exposure and response?**

There were no specific studies or analyses designed to evaluate the effects of factors such as herbal products, diet, smoking or alcohol use on the PK and PD of [illegible].

2.4.2 Drug-drug interactions

It has been established in the literature that G-CSF has minimal effect on the major CYP enzymes. The delay in effect of a few days on major enzymes due to an indirect effect mechanism combined with a 24-hour delay in G-CSF dosing relative to chemotherapy reduces the potential for interactions. Therefore, there appears to be minimal potential for DDI with G-CSF and concomitant medications.

2.4.2.1 **Is there an in vitro basis to suspect in vivo drug-drug interactions?**

Gallin et al., reported that the CYP mediated monooxygenase activity of human hepatocytes treated with G-CSF at 300 U/ml for 48 hours, decreased by 20% for CYP1A2 and CYP2E6, [illegible]% for CYP2A6 and 13% for CYP3A4 (Table 6). The peak of the decrease in CYP1A2 activity was observed 48 hours after incubating the cultured hepatocytes with G-CSF (Figure 5B).

Table 6. CYP-dependent Monooxygenase Activities of Human Hepatocytes treated with Various Cytokines.

Treatment[b]	CYP1A2	Activity[a] CYP2B6	CYP2A6	CYP3A4
Control	[illegible]	[illegible]	[illegible]	[illegible]
CNTF	[illegible]	[illegible]	[illegible]	[illegible]
IL-6	[illegible]	[illegible]	[illegible]	[illegible]
LIF	[illegible]	[illegible]	[illegible]	[illegible]
IL-11	[illegible]	[illegible]	[illegible]	[illegible]
OSM	[illegible]	[illegible]	[illegible]	[illegible]
G-CSF	[illegible]	[illegible]	[illegible]	[illegible]

[a] [illegible]
[b] [illegible]

Gallin M. et al. *J Pharmacol Exp Ther.* [illegible]

Figure 5. Dose Response (Panel A) and Time-Course Effects (Panel B) of Cytokines on the CYP1A2 Activity.

(Guillen M.I., et al. J Pharmacol Exp Ther. 1998;285:127-134).

G-CSF exhibits minimal inhibition of activity of CYP enzymes in primary cultures of human hepatocytes and is considered unlikely to have significant clinical effects.

2.4.2.2 Is the drug a substrate of CYP enzymes? Is metabolism influenced by genetics?

Generally, protein products are not substrates of CYP P450 substrates.

2.4.2.3 Is the drug an inhibitor and/or an inducer of CYP enzymes?

See 2.4.2.1.

2.4.2.4 Is the drug a substrate and/or an inhibitor of P-glycoprotein transport processes?

See 2.4.2.1.

2.4.2.5 Are there other metabolic/transporter pathways that may be important?

See 2.4.2.1.

2.4.2.6 Does the label specify co-administration of another drug and, if so, has the interaction potential between these drugs been evaluated?

No. Chemotherapy is administered 24 hours prior to XM02 dosing. In the phase 3 breast cancer clinical trial XM02-02-INT, doxorubicin IV 60 mg/m^2 and docetaxel IV 75 mg/m^2 were administered. The half-lives of these chemotherapy agents range from 11 to 48 hours.

2.4.2.7 Are there any in vivo drug-drug interaction studies that indicate the exposure alone and/or exposure-response relationships are different when drugs are co-administered?

No. There is no reason to suspect clinically meaningful drug-drug interactions between G-CSF and chemotherapy agents based on the 24 hour dosing space the *in vitro* experimental results of G-CSF on the activity of CYP enzymes.

2.5 GENERAL BIOPHARMACEUTICS

2.5.1 Based on BCS principles, in what class is this drug and formulation? What solubility, permeability and dissolution data support this classification?

Not applicable.

2.5.2 What is the composition of the to-be-marketed formulation?

Neutroval is a sterile, clear, colorless, preservative-free solution containing XM02, glacial acetic acid, sorbitol, polysorbate 80, and Water for Injection. See the Table 17 for the 0.5 and 0.8 ml prefilled syringe product compositions. The to-be-marketed product is the same as the clinical trial product.

Table 17. Neutroval Formulation

	300 mcg/0.5 ml Syringe	480 mcg/0.8 ml Syringe
Filgrastim	300 µg	480 µg
Glacial Acetic Acid	0.3 mg	0.48 mg
Sorbitol	25 mg	40 mg
Polysorbate 80	0.0275 mg	0.044 mg
Sodium Hydroxide	q.s. to pH 4.2	q.s. to pH 4.2
Water for Injection	q.s. to 0.5 ml	q.s. to 0.8 ml

2.5.3 What moieties should be assessed in bioequivalence studies?

The active moiety, G-CSF, should be assessed in any PK comparability studies.

2.5.4 What is the effect of food on the bioavailability (BA) of the drug from the dosage form? What dosing recommendation should be made, if any, regarding administration of the product in relation to meals or meal types?

Not applicable because XM02 is given via SC infusion.

2.5.5 Has the applicant developed an appropriate dissolution method and specification that will assure in vivo performance and quality of the product?

Not applicable.

2.6 ANALYTICAL SECTION

2.6.1 Were relevant metabolite concentrations measured in the clinical pharmacology and biopharmaceutics studies?

Not applicable.

2.6.2 Were the analytical procedures used to determine drug concentrations in this BLA acceptable?

Analysis of r-MetHuG-CSF concentrations in blood serum was performed using a method based on the enzyme-linked immunosorbent assay (ELISA) kit (Quantikine®, R&D Systems, USA) at (b) (4)

2.6.3 What bioanalytical methods are used to assess therapeutic protein concentrations? Briefly describe the methods and summarize the assay performance.

A monoclonal antibody specific for G-CSF has been pre-coated on a microplate. The G-CSF standards, XMO2 standards, XMO2 Run QC's, G-CSF QC Controls, and samples are dispensed into the wells. After washing away any unbound XM02 (or G-CSF), an enzyme-linked polyclonal antibody specific for human G-CSF (cross-reactive to XMO2) is added to the wells. Following washing to remove any unbound reagent, a substrate solution is added and color is allowed to develop. Optical densities are taken and are proportional to the quantity of bound XM02 or G-CSF. Refer to the review by Dr. Jee Chung, Product reviewer, on the technical validation of this assay.

The assay standard curve range is 39 – 2500 pg/ml. However, the determination of XM-02 in human serum is more reliable within 50 – 1800 pg/ml.

	Low (50 pg/ml)		Mid (600 pg/ml)		High (1800 pg/ml)	
	Accuracy (% Diff)	Precision (% CV)	Accuracy (% Diff)	Precision (% CV)	Accuracy (% Diff)	Precision (% CV)
Intra-assay	82.3	5.2	78.6	2.8	98.1	1.5
Inter-assay	96.1	9.5	79.0	4.6	92.7	7.3

	Low (100 pg/ml)		High (1000 pg/ml)	
	Accuracy (% Diff)	Precision (% CV)	Accuracy (% Diff)	Precision (% CV)
Quality Controls	95.2	5.3	92.3	7.7

2.6.4 What bioanalytical methods are used to assess the formation of the anti-product antibodies? Briefly describe the methods and assay performance including sensitivity, specificity, precision, cut point, interference and matrix, etc.

The assay methods used to evaluate the development of antibodies to XM02 are not acceptable because the assays have not been validated. See Appendix 4.1 for detailed assay methods and refer to the review by Dr. Laura Salazar-Fontana, Product reviewer, for the technical validation of all of these assays, including information on standardization, reference materials, assay validation, selectivity, specificity, and sensitivity.

Patient sera were first assessed for binding antibodies using dual screening with anti-XM02 (IgG) ELISA and anti-XM02 (IgG-IgM) Luminex assays. Samples testing as positive or questionable

were subjected further to IgG- and IgM-specific Western Blot confirmation assays. Western-Blot confirmed or questionable (equivocal) samples were further investigated using the 3 assays in parallel:

1. Luminex assay: This assay was used to determine concentrations of anti-XM02 IgG antibodies with the quantitative anti-XM02 (IgG) using polyclonal calibrator sera and relative assay units (RU-MFI IgG).
2. (b) (4) cell-based assay: This assay was used to test the samples for neutralizing antibodies (NAB), and further categorized as NAB positive or NAB negative, and concentrations in terms of percentage of neutralization were determined in case of a positive result.
3. Biacore® total antibody assay: This assay was used to test the samples for binding antibodies. The cutoff value was 14.4 RU.

The Day 180 samples collected in all patients were tested by the Biacore® (3rd screening assay) method in order to detect low-affinity antibodies.

2.6.4.1 What is the performance of the binding assay(s)?

ELISA assay: This assay was used as an indirect method to screen for the detection of anti-XM02 IgG antibodies. The cutoff value was determined to be 0.400 optical density (OD).

Table-4. Intra-Assay Precision

	Assay B	NCLT-2	NCTL-1	PCTL-1	PCTL-2
OD1	0,004	0,148	0,024	0,797	0,327
OD2	0,003	0,148	0,025	0,769	0,316
OD3	0,003	0,147	0,025	0,748	0,307
OD4	0,003	0,144	0,025	0,764	0,300
OD5	0,004	0,148	0,025	0,755	0,297
OD6	0,003	0,141	0,026	0,749	0,294
OD7	0,004	0,144	0,023	0,763	0,294
OD8	0,003	0,146	0,025	0,764	0,311
Mean	0,003	0,146	0,025	0,764	0,306
SD	0,000	0,002	0,001	0,015	0,012
CV (%)	11,1	1,6	2,8	2,0	3,9
Minus blank	0,000	0,142	0,021	0,760	0,302

Table-5. Summary of Inter-Assay Precision

	Run-1		Run-2		Run-3		Mean	SD	CV(%)
PCTL-1	0,763	0,752	0,762	0,760	0,708	0,748	0,749	0,021	2,8
PCTL-2	0,335	0,321	0,297	0,302	0,253	0,270	0,296	0,031	10,4
NCTL-2	0,115	0,144	0,158	0,142	0,152	0,156	0,145	0,016	10,9
NCTL-1	0,018	0,019	0,023	0,021	0,028	0,027	0,023	0,004	18,2
Positions	Beg	End	Beg	End	Beg	End	n/a		

PCTL-1 Positive control-1, 1:200 diluted monkey Anti-XM02_101_day84
PCTL-2 Positive control-2, 1:1600 diluted monkey Anti-XM02_101 day 84
NCTL-1 Negative control-1, PNMS
NCTL-2 Negative control-2, PNHS

Luminex assay: This assay was used to determine concentrations of anti-XM02 IgG antibodies with the quantitative anti-XM02 (IgG) using polyclonal calibrator sera and relative assay units (RU-MFI IgG). The cutoff value was determined to be 146.5 Median fluorescent Intensity (MFI).

Table-5. Intra-Assay Precision

	Bead mix				
%CV of MFI / VQCs	hIgG	hIgM	mIgG	mIgM	XM02
Blank	1,3	1,4	2,5	2,8	≤100
HP-1(CTL-1)	1,3	3,7	1,8	2,9	3,2
LP-1 (CTL-2)	0,7	2,5	2,1	2,7	7,4
OP-3	0,9	3,1	3,3	2,1	15,9
OP-4	1,6	1,4	2,7	2,8	7,9
PNMS (NC-1)	2,5	1,4	4,4	2,7	≤100
PNHS (NC-2)	2,3	2,7	3,9	2,7	Index ≤1

PNHS Pooled normal human serum
NHS Normal human serum
PNMS Pooled naïve monkey serum
NMS Naïve Monkey serum

Table-6. Summary of Inter-Assay Precision

	Bead mix				
%CV of MFI / VQCs	hIgG	hIgM	mIgG	mIgM	XM02
Blank	0,3	2,8	2,6	2,5	≤100
HP-1 (CTL-1)	1,6	3,4	2,5	3,8	2,6
LP-2 (CTL-2)	0,1	1,9	3,1	2,6	13,2
OP-3	1,9	2,8	2,2	5,1	12,5
OP-4	0,7	2,9	2,5	1,5	15,3
PNMS	1,6	3,4	3,5	4,1	≤100
PNHS	1,6	3,5	4,7	2,3	Index ≤1

%CV of MFI calculated from grand mean of three independent experiments.

Biacore® total antibody assay: This assay was used to test the samples for binding antibodies. The cutoff value was 14.4 RU.

Table-15. Intra-assay precision of the validation QCs

Intra-assay	Rat (5ug/ml) RU	Rat (0.625ug/ml) RU	Monkey(1:40) RU	Monkey (1:160) RU
Mean	119	24	208	52
SD	5.8	1.5	3.1	1.1
CV (%)	4.9	6.4	1.5	2.5

Table-16. Inter-assay precisions of validation QCs

Inter-Assay	Ratmab [1]		Monkey (pAB)[2]		BMP (1:10)
	5 ug/ml	0.625ug/ml	1:40	1:160	
Mean of RU three runs	120	22	191	53	2
SD	2.2	2.0	14.5	2.1	0.7
CV (%)	1.8	9.3	7.6	4.0	28.0

1. Ratmab: rat anti-human G-CSF. 2. Monkey (pAB): monkey anti-XM02_101_day84

Table-18. Assay recovery and Precision

Nominal Conc. (ug/ml)	RU		Mean	SD	CV (%)	Detected conc. (ug/ml)	Bias (%)
	Inject-1	Inject-2					
Spiked 7	105	110	108	3.5	3.3	6.1	12.5
Spiked 0.7	19	13	16	3.8	23.9	0.5	22.8
Control 7	116	121	118	3.3	2.7	6.8	3.1
Control 0.7	14	16	15	1.6	10.7	0.5	30.2

Note: the %bias for the control-0.7 is more than 30%. It will not have impact on the conclusion of this study.

The Day 180 samples collected in all patients were tested by the Biacore® (3rd screening assay) method in order to detect low-affinity antibodies.

2.6.4.2 What is the performance of the neutralizing assay(s)?

The human anti-XM02 neutralizing antibody (NAB) assay was based on a G-CSF specific cell proliferation assay with a cell line (b) (4)) for which growth relies on human G-CSF (XM02) in a dose dependent manner. Antibodies raised against human G-CSF and monkey anti-XM02 positive serum were able to deplete human G-CSF (XM02) induced cell proliferation, and the degree of the neutralization is dependent on the quantity and quality of the antibodies in the serum samples. NABs in a serum sample were determined by comparing human G-CSF induced proliferating response to that induced by human G-CSF pre-incubated with these serum samples. The presence of anti-XM02 NAB was determined according to the cutoff and the percentage of neutralization of XM02 (NP) was calculated according to the following formula: $NP = (1-((OD_S-OD_{BL}) / (OD_{NC}-OD_{BL}))) \times 100$, Where:

1) OD_S is the mean optical density of tested samples (A+S1 and etc)
2) OD_{NC} is the mean optical density of (A+NC) triplicates
3) OD_{BL} is the mean optical density of blank, i.e., cells without G-CSF (B+NC)
4) Cells with 95-100% neutralization should be diluted at 1:40 and retested

The cutoff formula is as follows: $OD_{cutoff} = OD_{NC} - 3SD$, Where:

1) OD_{NC} is the mean optical density (A+NC) of triplicate
2) SD is the standard deviation.

Table-6. Intra-Assay Precision: Parameters Validated

Parameters	Human	Monkey
ODpc/ODnc	0,6	0,7
$OD_{(A+B)}$-($OD_{(B+NC)}$+$OD_{(B+PC)}$)	0,4	0,5
OD_{A+B}/OD_{B+NC}	3,0	3,3
OD_{A+B}/OD_{B+PC}	3,0	3,3
Neutralization (%)	57,7 (PC-1)	43,0 (PC-2)
Cutoff	1,004	0,894

Table-7. Inter-Assay Precision

Validated Parameters	05.06.30	05.07.21	05.07.28	05.09.29	Mean	SD	CV (%)
1).ODpc1/ODnc2	0,6	0,6	0,7	0,7	0,6	0,033	5,1
2).ODpc2/ODnc1	0,7	0,7	0,7	0,8	0,7	0,054	7,5
3).$OD_{(A+B)}$-($OD_{(B+NC)}$+$OD_{(B+PC)}$)_human	0,4	0,6	0,7	0,6	0,6	0,121	21,4
	excluded	0.6	0.7	0.6	0.6	0.076	12.3
4).$OD_{(A+B)}$-($OD_{(B+NC)}$+$OD_{(B+PC)}$)_Monkey	0,5	0,7	0,7	0,6	0,6	0,112	18,1
5).OD_{A+B}/OD_{B+NC}_Human	3,0	2,9	3,8	3,4	3,3	0,411	12,6
6).OD_{A+B}/OD_{B+PC}_Human	3,0	3,6	3,3	3,1	3,3	0,271	8,3
7).OD_{A+B}/OD_{B+NC}_Monkey	3,3	3,7	3,6	3,5	3,5	0,196	5,6
8).OD_{A+B}/OD_{B+PC}_Monkey	3,3	3,5	3,6	3,1	3,4	0,246	7,3
9).Neutralization (%)for positive PC-1	57,7	61,5	47,5	46,0	53,2	7,576	14,2
10). Neutralization (%) for positive PC-2	43,0	45,6	41,2	34,8	41,2	4,595	11,2
11).Cutoff_Human	1,004	1,208	1,204	1,365	1,195	0,148	12,4
12).Cutoff_Monkey	0,894	1,363	1,400	1,355	1,253	0,240	19,2

Table-10. Sensitivity of the Assay

Concentration (ug/ml)	Reduction of cell growth (%)		Mean	SD	CV (%)
	05.07.28	05.07.29			
5	39,3	51,6	45,42	8,676	19,1
2.5	37,3	41,3	39,32	2,851	7,3
1,25	31,1	29,9	30,48	0,856	2,8
0,625	27,8	25,6	26,74	1,539	5,8
0,3125	16,1	11,5	13,80	3,322	24,1

Table-15. Determination of the Range of the Cutoff

Validated Parameters	Mean	SD	CV	Mean +2SD	Mean-2SD
Cutoff (Human) [1]	1.144	0.255	22.3	1.655	0.633
Cutoff (Monkey)	1,133	0,216	19,1	1,565	0,700

3 DETAILED LABELING RECOMMENDATIONS

Only relevant clinical pharmacology sections are included.

(b) (4)

7 Pages of Draft Labeling Have Been Withheld In Full As b4 (CCI/TS) Immediately Following This Page

4.2 INDIVIDUAL STUDY REVIEWS

4.2.1 Study# XM02-01-LT: Pharmacokinetics – Single Dose

Study #	XM02-01-LT
Investigator	Gintautas Gumbrevičius, M.D., Ph.D.
Study Sites	The 2nd Clinical Hospital of Kaunas, Josvainių str. 2, Kaunas, Lithuania.
Study Period	November 11, 2003 – February 23, 2004

Title: Comparative study of pharmacodynamic and pharmacokinetic parameters of XM02 and Filgrastim when formulations are given to healthy volunteers.

Objectives

Primary: Comparison of the PD parameters (ANCmax, ANC AUC, ANC tmax) of XM02 and filgrastim formulations after SC administration of 5 μg/kg or 10 μg/kg of product in healthy male subjects.

Secondary:

- Comparison of the PK parameters (Cmax, AUC, Tmax, t½, λz) of XM02 and filgrastim formulations after SC administration of 5 μg/kg or 10 μg/kg of product in healthy male subjects.
- Collection of tolerability and safety data.
- Calculation of the relative bioavailability (F) of XM02 preparation vs filgrastim.
- Comparison of PD and PK parameters of 5 μg/kg and 10 μg/kg SC doses of XM02.

Study Rationale (Per Applicant)

The study was designed in order to obtain a valid description of the *in vivo* performance of XM02, to assess comparability of PD & PK between test and reference products, its bioavailability, and to characterize safety and tolerability.

Test Drug

- XM-02 single use pre-filled syringes (480 μg/0.8 ml), manufactured by (b) (4) (Batch No. P-03-058).
- Filgrastim single use pre-filled syringes (300 μg/0.5 ml), manufactured by (b) (4) (Batch No. B 1032).

Study Design

A randomized, single-blind, 2-period crossover, 2-arm, single dose PK and PD study in healthy male subjects (N=56). Group A received 5 μg/kg and Group B received 10 μg/kg of both XM02 and filgrastim in a randomly assigned crossover sequence. A two-week washout period was used between the treatments.

- Treatment T1: XM02 5 μg/kg SC
- Treatment T2: XM02 10 μg/kg SC
- Treatment R1: Filgrastim 5 μg/kg SC
- Treatment R2: Filgrastim 10 μg/kg SC

Group	Treatment Period	
	First	Second
A	T_1 or R_1	R_1 or T_1
B	T_2 or R_2	R_2 or T_2

Sampling times
Pharmacokinetic blood samples were drawn at pre-dose and 0.5, 1. 1.5, 2, 3, 4, 6, 8, 10, 12, 24 and 48 hours after the injection.

Pharmacodynamic blood samples were drawn at pre-dose and 0.5, 1. 1.5, 2, 3, 4, 6, 8, 10, 12, 16, 24, 32, 40, 48, 72 and 96 hours after the injection.

Immunogenicity samples were not collected in this trial.

Assay Method
Pharmacokinetics: Analysis of r-MetHuG-CSF concentrations in blood serum was performed using a GLP validated method based on the enzyme-linked immunosorbent assay (ELISA) kit (Quantikine®, R&D Systems, USA) at (b) (4). The assay LLOQ is 39 ng/ml and the ULOQ is 2500 pg/ml.

Pharmacodynamics: A differential automated haematology analyser (Beckman/Coulter AcT) was used at (b) (4) for the determination of ANC in blood.

Pharmacodynamic & Pharmacokinetic Analysis
PK parameters for r-MetHuG-CSF were calculated using non-compartmental procedures. Descriptive statistics was calculated for the blood ANC and G-CSF concentrations in serum at each sampling time and for the PK/PD parameters of active moiety for the test and the reference formulations. ANOVA with 90% CI was assessed on the basis of test to reference ratio of log-transformed ANC AUC_{0-t}, ANC $AUC_{0-\infty}$, ANC_{max}, AUC_{0-t}, $AUC_{0-\infty}$, and C_{max} data. The statistical comparability of non log-transformed ANC Tmax and Tmax, $t½$, λz parameters were also tested.

Results
Subject Disposition: Fifty-six subjects (n=28/cohort) were enrolled. However, only 50 subjects completed the trial (Group A (5 µg/kg SC): N=24; Group B (10 µg/kg SC): N=26). All subjects were Caucasian males.

Summary of Patient Demographics. Values in the Table are presented as mean (SD).

	Age (yrs)	Weight (kg)	BMI (kg/m^2)
Group A (N=28): 5 µg/kg SC	22.86 (4.36)	72.86 (7.11)	22.99 (1.99)
Group B (N=28): 10 µg/kg SC	23.64 (5.70)	74.29 (8.68)	22.60 (2.03)

Pharmacokinetic Results:

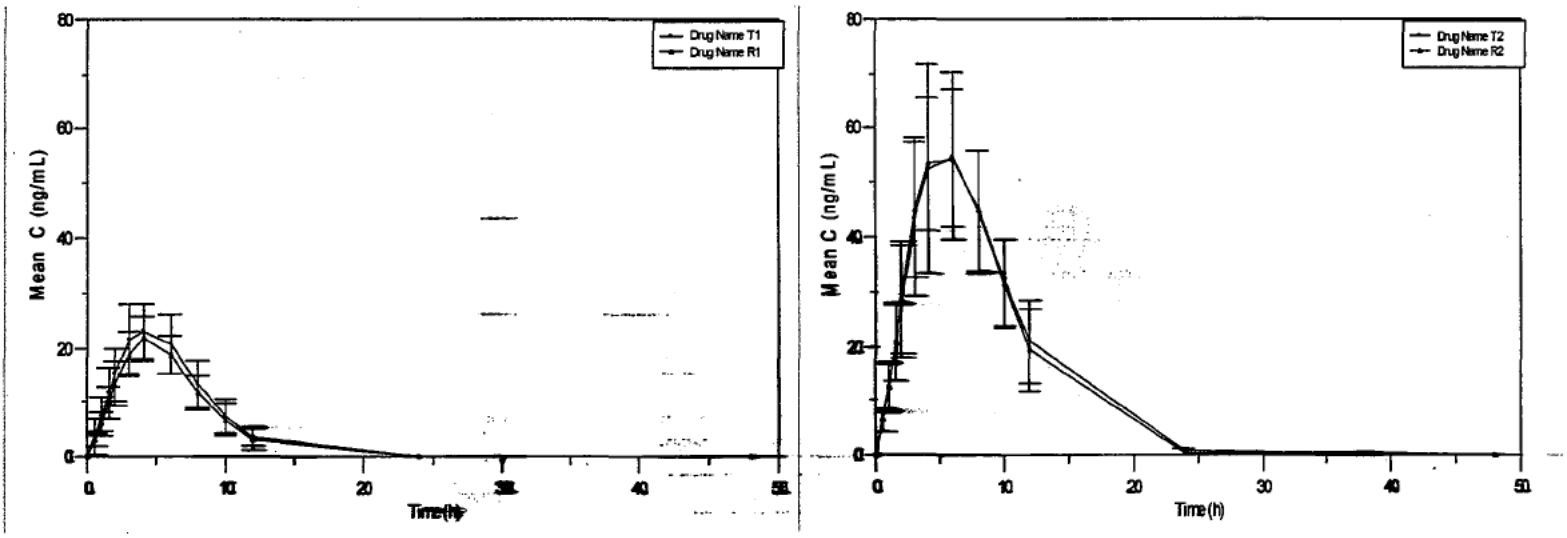
Group A (5 µg/kg SC):

Treatment	Descriptive Statistic	C_{max} (ng/ml)	AUC_{0-t} (hr*ng/ml)	$AUC_{0-\infty}$ (hr*ng/ml)	T_{max} (hr)	t½ (hr)
XM02 (N=25)	GeoMean	23.46	159.37	170.13	3.89	2.12
	SD	5.79	37.84	41.53	1.16	0.46
	Median	22.72	171.54	176.74	4	2.11
	Range	15.07 – 33.05	80.97 – 234.48	83.22 – 252.79	1.5 – 6	1.52 – 3.31
Filgrastim (N=27)	GeoMean	21.42	145.69	156.35	3.95	2.09
	SD	3.99	26.99	33.26	0.68	0.71
	Median	21.16	141.35	156.11	4	2.01
	Range	14.82 – 33.48	97.67 – 208.3	98.62 – 231.56	3 – 6	1.28 – 3.97

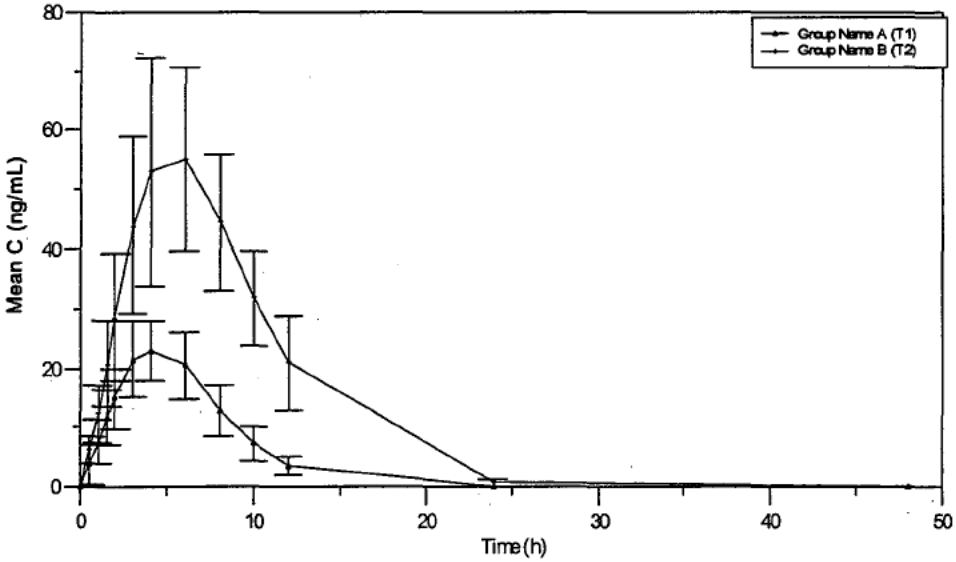
Group B (10 µg/kg SC):

Treatment	Descriptive Statistic	C_{max} (ng/ml)	AUC_{0-t} (hr*ng/ml)	$AUC_{0-\infty}$ (hr*ng/ml)	T_{max} (hr)	t½ (hr)
XM02 (N=25)	GeoMean	55.37	473.92	528.59	5.01	3.03
	SD	17.13	146.71	124.57	1.20	1.22
	Median	54.45	454.16	511.03	6.00	2.72
	Range	34.85 – 111.99	275.92 – 844.59	334.55 – 847.88	3 – 8	1.66 – 5.91
Filgrastim (N=27)	GeoMean	56.45	478.80	513.78	5.27	2.72
	SD	12.37	123.98	107.48	1.50	0.66
	Median	54.43	475.68	501.65	6.00	2.7
	Range	39.73 – 90.76	323.45 – 769.38	377.19 – 771.48	3 – 8	1.57 – 4.43

Mean G-CSF concentration-time profiles for 5 µg/kg (left panel) and 10 µg/kg (right panel) SC.



Mean XM02 5 µg/kg (bottom curve) and 10 µg/kg (top curve) SC concentration-time profiles.Pharmacokinetic Comparison of Group A and B Treatments.



Parameter	Point estimate	90% CI	Intra-subject CV (%)
Group A (5 µg/kg)			
AUC_{0-t}	110.5	102.7-119	14.92
$AUC_{0-\infty}$	109.9	101.9-118.6	15.34
C_{max}	110.8	102.2-120.1	16.33
Group B (10 µg/kg)			
AUC_{0-t}	99.7	93.9-105.9	12.64
$AUC_{0-\infty}$	103.8	97.9-110.1	12.34
C_{max}	99.0	92.1-106.5	15.42

The pharmacokinetic parameters (AUC and Cmax) of both 5 µg/kg and 10 µg/kg doses of XM02 and filgrastim are equivalent in both dose groups.

Relative bioavailability (F) of the test formulations was calculated comparing the extent of absorption of 5 µg/kg and 10 µg/kg doses with respect to appropriate doses of the reference formulations.

$$F_{relative} = \frac{AUC_{test}^{0-\infty}[(ng/ml)*h)\times dose_{reference}(\mu g)]}{AUC_{reference}^{0-\infty}[(ng/ml)*h)\times dose_{test}(\mu g)]}$$

Data for only those subjects' who completed both study periods was included in calculation of relative bioavailability (F).

Mean received dose, AUC and relative bioavailability (F) in Group A (5 µg/kg).

XM-02 5 µg/kg		Filgrastim 5µg/kg	
Mean received dose (µg)±SD	365.50±37.57	Mean received dose (µg)±SD	364.96±38.39
Mean $AUC_{0-\infty}$ [(ng/ml)*h]±SD	173.43±41.45	Mean $AUC_{0-\infty}$ [(ng/ml)*h]±SD	155.29±28.34
Relative bioavailability (F): 1.12			
Mean dose and AUC0-∞ were calculated for the 24 subjects, who completed both study periods.			

Mean received dose, AUC and relative bioavailability (F) in Group B (10 µg/kg).

XM-02 10 µg/kg		Filgrastim 10 µg/kg	
Mean received dose (µg)±SD	741.69±94.81	Mean received dose (µg)±SD	741.46±96.47
Mean $AUC_{0-\infty}$ [(ng/ml)*h]±SD	544.36±126.35	Mean $AUC_{0-\infty}$ [(ng/ml)*h]±SD	521.43±108.86
Relative bioavailability (F): 1.04			
Mean dose and AUC were calculated for the 26 subjects, who completed both study periods.			

The extent of absorption of the XM02 appears slightly higher than that of filgrastim at both doses. However, there is no apparent pharmacokinetic significant difference.

Pharmacodynamic Results:

Group A (5 µg/kg SC): While difficult to see in the figure below, there was a drop in ANC below baseline at approximately 0.5 – 1hr after administration for both the test (XM02) and reference (filgrastim) formulation. Then, ANC exceeded the baseline by 1.5hr. The ANCmax ranged from 17.0 x 10^9/L to 29.1 x 10^9/L for XM02 and from 15.3 x 10^9/L to 33.9 x 10^9/L for filgrastim. The ANC T_{max} ranged from 10 – 16 hr for both the test and reference formulations. The increase in ANC for all subjects was reversible and returned to the baseline values after 96 hr.

Parameter	Analysis	XM02	Neupogen®	90% CI [%]	Point estimate [%]
ANC AUC_{0-t} [h*10^9/L]	LS mean	899.69	898.52	97.8-102.5	100.1
	Geometric Mean	901.68	901.57		
	CV% intra-subject	4.66			
ANC $AUC_{0-\infty}$ [h*10^9/L]	LS mean	1042.00	1015.61	99.7-105.6	102.6
	Geometric Mean	1046.22	1016.30		
	CV% intra-subject	5.85			
ANC_{max} [10^9/L]	LS mean	22.30	22.64	93.6-103.6	98.5
	Geometric Mean	22.23	22.91		
	CV% intra-subject	10.22			

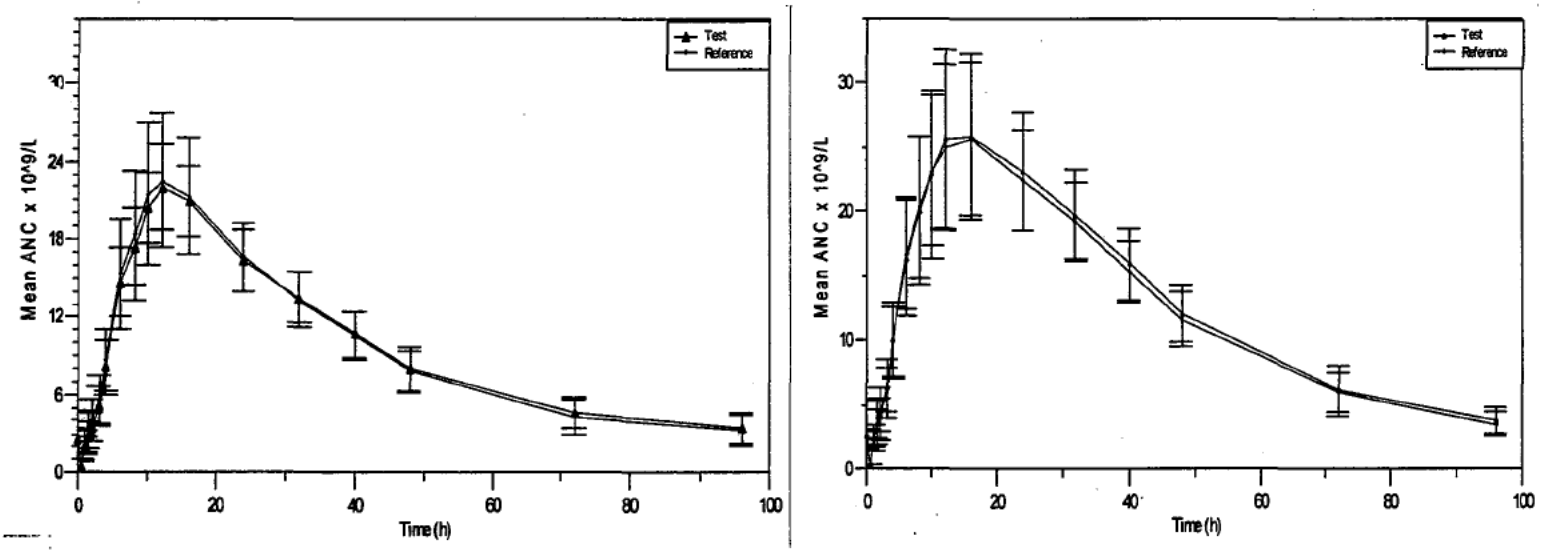
Parameter		XM02	Neupogen®	Non-parametric point estimator of difference	Non-parametric 90% CI of difference	Bio-equivalence interval
ANC t_{max} [hours]	Minimum	10	10	0	[-1; 0]	[-2.4; 2.4]
	Maximum	16	16			
	Median	12	12			

Group B (10 µg/kg SC): As was seen in Group A, in Group B the ANC/time profiles of XM02 and filgrastim formulations were similar. ANC fell below baseline at approximately 0.5 – 1hr after administration for both the test (XM02) and reference (filgrastim) formulation. Then, ANC exceeded the baseline by 1.5hr.

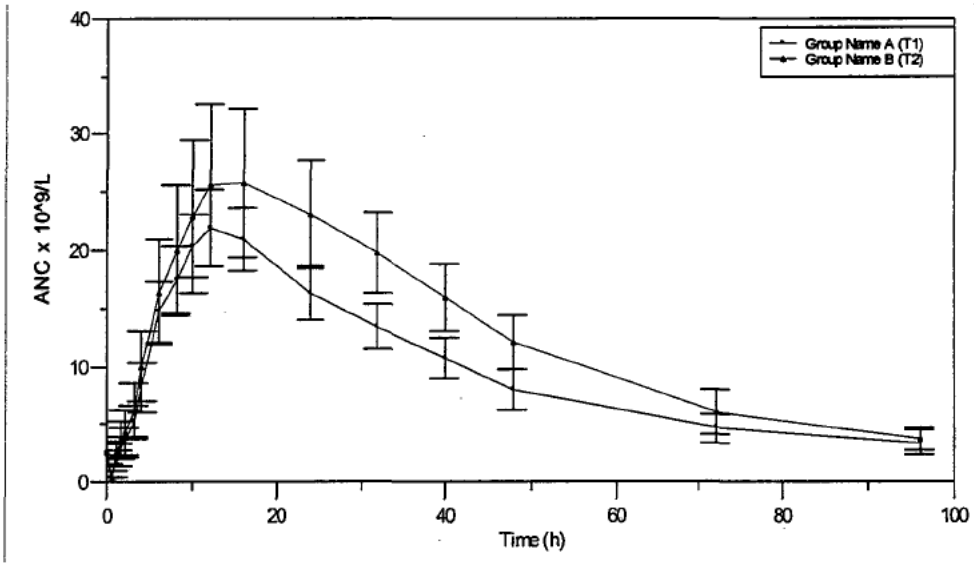
Parameter	Analysis	XM02	Neupogen®	90%CI [%]	Point estimate [%]
ANC AUC_{0-t} [$h*10^9/L$]	LS mean	1199.67	1187.85	97.2-104.9	101.0
	Geometric Mean	1199.66	1187.85		
	CV% intra-subject	8.05			
ANC $AUC_{0-\infty}$ [$h*10^9/L$]	LS mean	1345.54	1325.57	97.9-105.2	101.5
	Geometric Mean	1345.54	1325.57		
	CV% intra-subject	7.54			
ANC_{max} [$10^9/L$]	LS mean	25.79	25.96	94.5-104.5	99.4
	Geometric Mean	25.79	25.96		
	CV% intra-subject	10.64			

Parameter		XM02	Neupogen®	Non-parametric point estimator of difference	Non-parametric 90% CI of difference	Bio-equivalence interval
ANC t_{max} [hours]	Minimum	10	12	2	[0; 4]	[-3.2; 3.2]
	Maximum	24	24			
	Median	14	16			

Mean ANC/time profiles for 5 µg/kg (left panel) and 10 µg/kg (right panel) SC dose.



Mean ANC XM02 5 μg/kg (blue) and 10 μg/kg (red) SC concentration-time profiles.



The pharmadynamic parameters (ANC AUC, ANCmax) of both 5 μg/kg and 10 μg/kg doses of XM02 and filgrastim are equivalent in both dose groups.

Safety (Per Applicant)

Single doses of 5 μg/kg or 10 μg/kg of XM02 or filgrastim were safe and well tolerated. In total, 75 AEs were reported in 31 subjects (55.4% of the total number of subjects).

- Group A (5 μg/kg SC): 37 AEs in 16 subjects (57.1%)
- Group B (10 μg/kg SC): 38 AEs in 15 subjects (53.6%)

The most common AE related to drug was headache, total 22 AEs (Group A: 10 AEs; Group B: 12 AEs). Other frequent AEs were erythrocyturia (9 AEs), and myalgia (6 AEs).

In total, 40 AEs (53.3% of total number of AEs) were reported as possibly and probably related to investigational product. AEs related to investigational product were mild (Group A: 10; Group B: 14) and moderate (Group A: 8; Group B: 8) in intensity.

- Group A:
  - 10 subjects in Group A experienced 18 AEs (48.6% of AEs in Group A)
  - 6 AEs related to investigational product were reported after the T_1 and 9 after the R_1 treatment.
  - 3 AEs related to investigational product occurred in Group A at the follow-up period.
- Group B:
  - 12 subjects in Group B experienced 22 AEs (57.8% of AEs in Group B).
  - 13 AEs related to investigational product were reported after the T_2 and 7 after the R_2 treatment.
  - 2 AEs related to investigational product occurred in Group B at the follow-up period.

No serious AEs and unexpected adverse drug reactions were reported. No clinically relevant changes in the laboratory parameters, ECG, vital signs or ultrasonic spleen examination were detected at the follow-up. XM02 and filgrastim were comparable with respect to their safety profile. No relevant difference in the AEs was reported between Group A and B.

ECG: ECGs were performed at screening and follow-up (14 days post-dose) in 56 healthy volunteers. The ECG measurements were within normal limits for all subjects.

Conclusions

- The PK results are similar for XM02 and filgrastim.
  - The increases in AUC and C_{max} observed with an increase in dose, from 5 μg/kg to 10 μg/kg, were similar between XM02 and filgrastim XM-02 was determined to be bioequivalent to filgrastim at 5 μg/kg and 10 μg/kg SC for AUC and C_{max}.
  - The t½ ranged from 1.39 – 5.91 hours.
  - Relative bioavailability (F) of XM02 vs filgrastim was estimated to be 1.12 in Group A and 1.04 in Group B.
- The PD results are similar for XM02 and filgrastim
  - The PD response on ANC for XM02 was equivalent for AUC and C_{max} to filgrastim in doses of 5 μg/kg and 10 μg/kg SC.
  - Peaks in ANC value were observed between 10 - 24 hours and returned to baseline after 96 hours.
- Single dose XM02 or filgrastim SC at doses of either 5 μg/kg or 10 μg/kg were well tolerated without significant differences between treatment groups.

4.2.2 Study#XM02-05-DE: Pharmacokinetics – Single Dose

Study #	XM02-05-DE
Investigator	Dr. M. Grossmann
Study Sites	Institut für Klinische Pharmakologie Bobenheim
Study Period	April 3, 2006 – August 25, 2006

Title: 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.

Objectives

Primary: To compare r-MetHuG-CSF PK concentration-time parameter AUC_{0-t} to demonstrate equivalence of XM02 and Neupogen® after single 5 µg/kg or 10 µg/kg dose IV or SC in healthy subjects.

Secondary: To compare r-MetHuG-CSF

- PK parameters (AUC_{0-inf}, C_{max}, T_{max}, and t½) to demonstrate equivalence of XM02 and Neupogen® after single 5 µg/kg or 10 µg/kg dose IV or SC in healthy subjects.
- PD marker ANC parameters ($ANCAUC_{0-t}$, ANC_{max}, $ANCt_{max}$) to demonstrate equivalence of XM02 and Neupogen® after single 5 µg/kg or 10 µg/kg dose IV or SC in healthy subjects.
- PD marker CD34+ cell count parameters ($CD34+AUC_{0-t}$, CD34+max, $CD34+t_{max}$) to demonstrate equivalence of XM02 and Neupogen® after single 5 µg/kg or 10 µg/kg dose IV or SC in healthy subjects.
- PK or PD parameters of 5 µg/kg and 10 µg/kg doses of XM02 after IV or SC administration.
- Collect tolerability and safety data.

Study Rationale

To demonstrate bioequivalence between XM02 and Neupogen® in directed by the EMEA/ CHMP product-specific guidance on biosimilar medicinal products containing rG-CSF.

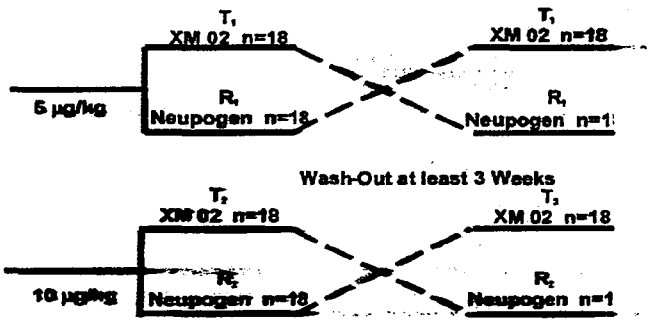
Test Drug

- XM02 0.8 ml PFS (Batch#P-05-003/2)
- Neulasta 0.5 ml PFS (Batch#N1100AK)

Study Design

Single dose, single blind, randomized, 2 period, 2-way crossover, 8 treatments and 2 sequences with at least 3 weeks wash-out carried out in 4 groups of ~36 subjects each. XM02 or Neupogen® 5 µg/kg or 10 µg/kg were administered as single doses SC or IV.

- Group 1: 5 µg/kg of XM02 and 5 µg/kg of Neupogen® IV (n=36)



- Group 2: 10 µg/kg of XM02 and 10 µg/kg of Neupogen® IV (n=35)
- Group 3: 5 µg/kg of XM02 and 5 µg/kg of Neupogen® SC (n=35)
- Group 4: 10 µg/kg of XM02 and 10 µg/kg of Neupogen® SC (n=34)

Sampling times

Pharmacokinetic blood samples were drawn for r-MetHuG-CSF concentration at:

- IV: 0 (pre-dose), 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 16, 24 and 48 hours after start of IV infusion
- SC: 0 (pre-dose), 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 16, 24 and 48 hours after SC injection.

Pharmacodynamic blood samples were drawn at the following time points:

- ANC: 0 (pre-dose), 0.5, 1, 2, 4, 6, 8, 10, 12, 16, 20, 24, 32, 48, 72 and 96 hours after dosing.
- CD34+ cell count: 0 (pre-dose), 24, 48, 72, 96, 120, 144, 168 (Day 8), 240 (Day 11), and 336 hours (Day 15) after dosing.

Immunogenicity: Blood samples for antibody analyses were not collected in this trial.

Assay Method

Pharmacokinetics: Analysis of r-MetHuG-CSF concentrations in blood serum was performed using a GLP validated method based on the enzyme-linked immunosorbent assay (ELISA) kit (Quantikine®, R&D Systems, USA) at [redacted] (b) (4) The assay LLOQ is 39 ng/ml and the ULOQ is 2500 pg/ml.

Pharmacodynamics:

- A differential automated haematology analyser (Beckman/Coulter AcT) was used at [redacted] (b) (4) for the determination of ANC in blood.
- Flow cytometry on a Coulter Epics XL-MCL instrument (Beckman/Coulter) equipped with an argon-ion laser tuned at 488 nm was performed. CD34+ cell count was determined by flow cytometry using a validated CD34+ Cells Enumeration Kit (DakoCytomation Denmark A/S) by [redacted] (b) (4)

Pharmacokinetic Analysis

Pharmacokinetic parameters for r-MetHuG-CSF were calculated using non-compartmental procedures. Descriptive statistics (number of observations, mean, standard deviation, minimum, Q1, median, Q3, maximum) were calculated for the r-MetHuG-CSF concentrations. Geometric mean and geometric standard deviation were also computed. ANOVA point estimates with 90% confidence intervals were calculated to determine bioequivalent between test/reference ratios of the AUC and Cmax.

Pharmacodynamic Analysis

The PD characteristics for ANC and CD34+ following single dose IV or SC administrations of 5 or 10 µg/kg XM02 solution or Neupogen® solution were calculated using non-compartmental procedures. Descriptive statistics (number of observations, mean, standard deviation, minimum,

Q1, median, Q3, maximum) were calculated. Geometric mean and geometric standard deviation were also computed. ANOVA point estimates with 90% confidence intervals were calculated to determine bioequivalent between test/reference ratios for both ANC and CD34+.

Results

Subject Disposition: One hundred and four-four (144) healthy male and female Caucasian subjects were enrolled. One hundred and twenty-four (124) subjects (male, 53% and female, 47%) completed both treatment periods in the trial without major protocol deviations; data in the table are presented as mean (SD), min/max values.

	Age [years]	**Body height [cm]**	**Body weight [kg]**	**BMI [kg/m^2]**
Subgroup 1 (n = 31)	35.2 (6.73) 22/45	173.4 (9.56) 155/189	73.56 (11.40) 52/94	24.36 (2.36) 20.3/31
Subgroup 2 (n = 30)	30.4 (8.73) 18/45	170.8 (7.07) 158/186	71.6 (11.17) 56/92	24.50 (2.97) 19.8/31
Subgroup 3 (n = 33)	31.9 (8.06) 18/45	174.1 (9.63) 152/193	74.3 (10.43) 54.5/92	24.50 (2.74) 19.5/30
Subgroup 4 (n = 30)	32.3 (7.67) 20/45	171.5 (8.80) 153/188	70.27 (10.10) 53.0/93	23.86 (2.88) 19.4/30
Total (n = 124)	32.5 (7.92) 18/45	172.5 (8.85) 152/193	72.50 (10.771) 52.0/94	24.31 (2.72) 19.4/31

*Group 1 & 2 refers to 5 and 10 µg/kg IV doses, respectively. Group 3 & 4 refers to 5 and 10 µg/kg SC doses, respectively.

Summary of Demographic data within the PK/PD population by Gender (N=124)

	Gender	
	Male	Female
Subgroup 1: 5 µg/kg IV (N=31)	18	13
Subgroup 2: 10 µg/kg IV (N=30)	15	15
Subgroup 3: 5 µg/kg SC (N=33)	18	15
Subgroup 4: 10 µg/kg SC (N=30)	15	15
SubTotal	66	58
Total	124	

Pharmacokinetic Results: There were no statistically significant period or sequence effects ($p>0.05$) for AUC_{0-t}, AUC_{0-inf}, C_{max} and t½. The PK results are similar for XM02 and Neupogen®. After XM-02 IV administration there was a dose-proportional increase of AUC_{0-t} and C_{max} from 5 µg/kg to 10 µg/kg dose. After SC administration there was approximately a 3-fold increase of AUC_{0-t} and C_{max} from 5 µg/kg to 10 µg/kg dose of XM-02. The increases in AUC_{0-t} and C_{max} observed with an increase in dose, from 5 µg/kg to 10 µg/kg, were similar between XM02 and Neupogen®. The t½ ranged from 5.2 - 9.4 hours. The absolute

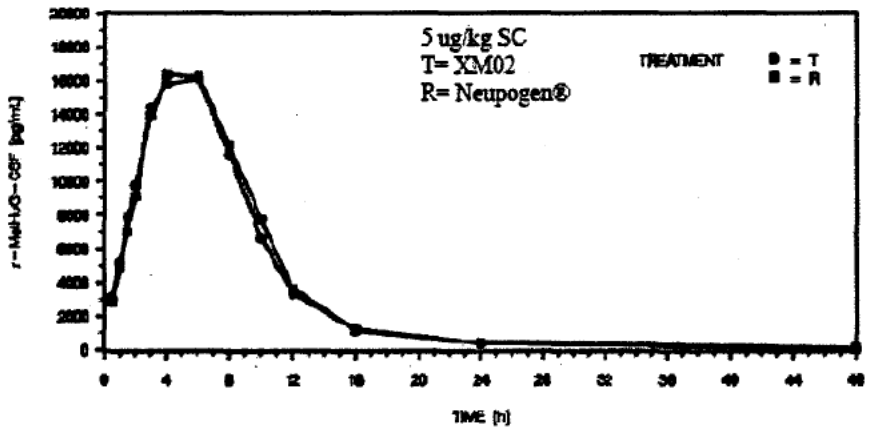
bioavailability of SC XM02 was 33% and 45% for the 5 µg/kg and 10 µg/kg dose, respectively.

Geometric means of AUC_{0-t} and C_{max} and median T_{max} and t½ of G-CSF following XM02 or Neupogen® to Healthy Volunteers. N=33 for 5 µg/kg SC, N=30 for 10 µg/kg SC, N=31 for 5 µg/kg IV, and N=30 for 10 µg/kg IV.

	Dose Level 5 µg/kg s.c.		Dose Level 10 µg/kg s.c.	
Parameter	**XM02**	**Neupogen®**	**XM02**	**Neupogen®**
AUC_{0-t} [ng/mL*h]	157.58	159.43	471.15	430.72
$AUC_{0-\infty}$ [ng/mL*h]	158.98	160.78	472.24	431.86
C_{max} [ng/mL]	17.98	18.42	46.24	43.14
t_{max} [h]	6.00	4.12	6.00	6.00
$t_{1/2}$ [h]	8.93	9.36	5.15	5.21

	Dose Level 5 µg/kg i.v.		Dose Level 10 µg/kg i.v.	
Parameter	**XM02**	**Neupogen®**	**XM02**	**Neupogen®**
AUC_{0-t} [ng/mL*h]	480.20	470.37	1056.47	991.00
$AUC_{0-\infty}$ [ng/mL*h]	481.10	471.43	1057.42	991.89
C_{max} [ng/mL]	129.79	126.12	231.14	221.56
t_{max} [h]	0.50	0.75	0.75	0.75
$t_{1/2}$ [h]	9.38	9.35	7.15	7.30

Subgroup 3 (SC 5 µg/kg): Geometric mean concentrations of r-MetHuG-CSF vs. time profile.



XM02 was bioequivalent, in terms of AUC_{0-t}, to Neupogen® at both doses (5 and 10 µg/kg) and following both IV and SC routes of administration (see Table below). The study also demonstrated bioequivalence for the secondary pharmacokinetic parameters AUC_{0-inf}, Cmax, and t½ for all 4 subgroups.

the primary target parameter $AUC_{(0-t)}$ for the four different subgroups

Subgroup	Dose, mode of administration	Point estimate [T/R] (90% confidence interval)	90% confidence interval for $AUC_{(0-t)}$ within 80-125%
Subgroup 1 (n = 31)	5 µg/kg, i.v.	101.65 (96.55 – 107.01)	yes
Subgroup 2 (n = 30)	10 µg/kg, i.v.	106.62 (102.14 – 111.30)	yes
Subgroup 3 (n = 33)	5 µg/kg, s.c.	98.63 (92.05 – 105.66)	yes
Subgroup 4 (n = 30)	10 µg/kg, s.c.	109.39 (104.02 – 115.03)	yes

Pharmacokinetic data summarized by Gender: Gender does not appear to alter XM02 PK following SC administration. However, following XM02 IV administration, both AUC and Cmax appear to be reduced in females as compared to males.

Parameter	5 µg/kg SC			
	Male (N=18)		Female (N=15)	
	XM02	Neupogen	XM02	Neupogen
Geomean AUC_{0-t} [ng/mL*h]	166	162	148	157
Geomean $AUC_{0-\infty}$ [ng/mL*h]	167	163	149	158
Geomean C_{max} [ng/mL]	18.7	17.8	17.2	19.2
Median t_{max} [h]	4	4.1	6	6.
Median $t_{1/2}$ [h]	10	9.4	7	9.4

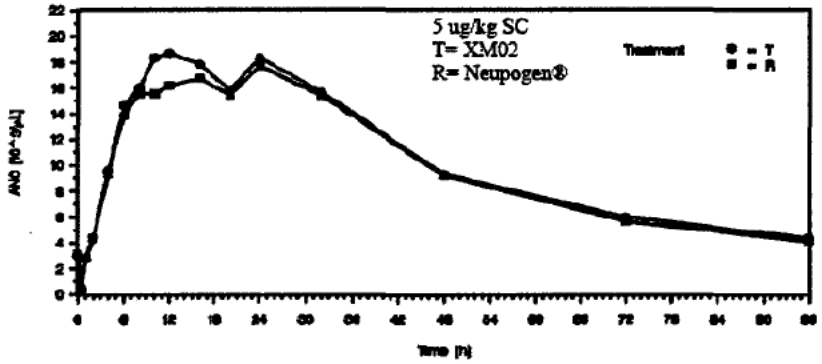
Parameter	10 µg/kg SC			
	Male (N=15)		Female (N=15)	
	XM02	Neupogen	XM02	Neupogen
Geomean AUC_{0-t} [ng/mL*h]	455	433	488	428
Geomean $AUC_{0-\infty}$ [ng/mL*h]	456	434	489	430
Geomean C_{max} [ng/mL]	43.3	41.5	49.4	44.9
Median t_{max} [h]	6	6	6	6
Median $t_{1/2}$ [h]	5.1	5.4	5.2	5.1

Parameter	5 µg/kg IV			
	Male (N=18)		Female (N=13)	
	XM02	Neupogen	XM02	Neupogen
Geomean AUC_{0-t} [ng/mL*h]	518	514	433	416
Geomean $AUC_{0-\infty}$ [ng/mL*h]	519	515	433	417

Geomean C_{max} [ng/mL]	140.5	135.2	116.3	114.6
Median t_{max} [h]	0.6	0.75	0.5	0.75
Median $t_{1/2}$ [h]	9.3	8.4	9.4	10

Parameter	10 µg/kg IV			
	Male (N=15)		Female (N=15)	
	XM02	Neupogen	XM02	Neupogen
Geomean AUC_{0-t} [ng/mL*h]	1128	1041	990	943
Geomean $AUC_{0-\infty}$ [ng/mL*h]	1129	1042	991	944
Geomean C_{max} [ng/mL]	247.5	228.7	215.9	214.7
Median t_{max} [h]	0.75	0.75	0.75	0.75
Median $t_{1/2}$ [h]	4.7	4.4	7.6	7.5

Pharmacodynamic Results: Geomean ANC time profiles following a single SC injection of XM02 or Neupogen® are presented for the 5 µg/kg dose. In both treatment groups (T and R), ANC peaks were observed between 12 - 24 hours and returned to baseline values after 96 hours.



ANOVA demonstrated equivalence of XM02 and Neupogen® with regard to ANC in both the 5 µg/kg and 10 µg/kg dose group after both single SC injection and IV infusion. The ANC data for the SC and IV dose groups are presented in the tables below.

Geometric Mean of ANC AUC_{0-t} and ANC_{max} and Median of ANC T_{max} Following a Single SC Injection of 5 and 10 µg/kg XM02 or Neupogen® to Healthy Male and Female Subjects

	Dose Level 5 µg/kg s.c. n=33				
Parameter	**XM02**	**Neupogen®**	**ANOVA CV [%]**	**Point estimate Test/Ref. ratio**	**90% Confidence interval**
ANC AUC_{0-t} [$h*10^9/L$]	956.93	983.14	24.47	97.58	88.23 - 107.92
ANC_{max} [$10^9/L$]	22.58	21.14	10.70	107.27	102.60 - 112.16
ANC t_{max} [h]	12.03	12.00		0.94	-1.03 – 2.97
	Dose Level 10 µg/kg s.c. n=30				
	XM02	**Neupogen®**	**ANOVA CV [%]**	**Point estimate Test/Ref. ratio**	**90% Confidence interval**
ANC AUC_{0-t} [$h*10^9/L$]	1305.93	1245.18	32.58	104.88	91.22 - 120.58
ANC_{max} [$10^9/L$]	26.94	26.98	8.70	99.84	96.10 - 103.72
ANC t_{max} [h]	18.03	20.00		0.07	-0.27 – 2.07

ANOVA and 90% confidence intervals for (log-transformed) pharmacodynamic parameters

Geometric Mean of ANC AUC_{0-t} and ANC_{max} and Median of ANC T_{max} Following a Single IV Injection of 5 and 10 µg/kg XM02 or Neupogen® to Healthy Male and Female Subjects

Parameter	**Dose Level 5 µg/kg i.v. n=31**				
Parameter	**XM02**	**Neupogen®**	**ANOVA CV [%]**	**Point estimate Test/Ref. ratio**	**90% Confidence interval**
ANC AUC_{0-t} [$h*10^9/L$]	738.37	776.67	24.83	97.25	87.47 - 108.13
ANC_{max} [$10^9/L$]	18.73	19.46	12.40	98.21	93.08 - 103.61
ANC t_{max} [h]	12.00	12.00		0.01	-0.94 – 1.00
	Dose Level 10 µg/kg i.v. n=30				
	XM02	**Neupogen®**	**ANOVA CV [%]**	**Point estimate Test/Ref. ratio**	**90% Confidence interval**
ANC AUC_{0-t} [$h*10^9/L$]	916.96	958.90	44.55	96.56	80.07 - 116.45
ANC_{max} [$10^9/L$]	21.71	22.21	15.74	98.97	92.39 - 106.03
ANC t_{max} [h]	16.00	16.00		-1.99	-3.00 – 0.00

ANOVA and 90% confidence intervals for (log-transformed) pharmacodynamic parameters

ANC data summarized by Gender:

ANC parameter values appear similar between gender regardless of XM02 dose or administration route.

Parameter	Dose Level 5 µg/kg SC (N=33)				Dose Level 10 µg/kg SC (N=30)			
	XM02		Neupogen		XM02		Neupogen	
	male	female	male	female	male	female	male	female
Geomean ANC AUC_{0-t} [$h*10^9/L$]	968.9	942.8	970.8	998.2	1385.9	1230.6	1183.4	1310.5
Geomean ANC_{max} [$10^9/L$]	22.9	22.3	20.3	22.2	27.2	26.7	26.3	27.7
Median ANC T_{max} [h]	12	12	12	12	20	16	20	16

Parameter	Dose Level 5 µg/kg IV (N=31)				Dose Level 10 µg/kg IV (N=30)			
	XM02		Neupogen		XM02		Neupogen	
	male	female	male	female	male	female	male	female
Geomean ANC AUC_{0-t} [$h*10^9/L$]	690.9	809.6	734.3	839.5	893.7	940.8	912.5	1007.6
Geomean ANC_{max} [$10^9/L$]	18.2	19.5	17.1	23.2	19.9	23.7	21.6	22.8
Median ANC T_{max} [h]	12	10	12	12	16	16	16	16

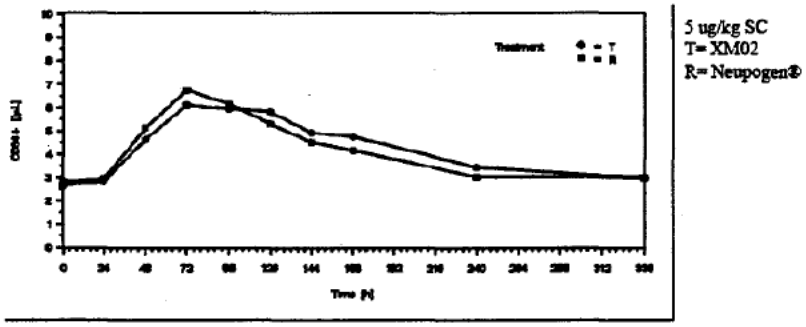
Mean CD34+ count time profiles following a single 5 µg/kg SC injection of XM02 or Neupogen® are presented in the figure below. In both groups, a peak was observed around 72 hours after dosing. Values appear to return to baseline values after 336 hours. Similar findings were observed in the SC 10 µg/kg dose cohort, as well as the IV cohorts (data not shown). The comparability range for the CD34+ parameters was defined as 70–143%; ANOVA demonstrated equivalence of XM02 and Neupogen® in both the 5 µg/kg and 10 µg/kg dose group after both single SC and IV (see tables below). Data are depicted as geometric mean of CD34+ AUC0-t and CD34+ Cmax and median of CD34+ tmax following a single SC or IV injections of 5 and 10 µg/kg XM02 or Neupogen® to healthy male and female subjects.

	Dose Level 5 µg/kg s.c. n=33				
Parameter	**XM02**	**Neupogen®**	**ANOVA CV [%]**	**Point estimate Test/Ref. ratio**	**90% Confidence interval**
$CD34^+$ AUC_{0-t} [$h*/\mu L$]	1462.63	1448.61	19.09	100.96	93.29 – 109.26
$CD34^+C_{max}$ [$/\mu L$]	8.42	8.78	27.11	95.67	85.60 - 106.92
$CD34^+$ t_{max} [h]	72.05	72.30		-10.49	-23.51 – 11.76
	Dose Level 10 µg/kg s.c. n=30				
	XM02	**Neupogen®**	**ANOVA CV [%]**	**Point estimate Test/Ref. ratio**	**90% Confidence interval**
$CD34^+$ AUC_{0-t} [$h*/\mu L$]	1860.82	2063.90	14.04	90.16	84.79 – 95.87
$CD34^+C_{max}$ [$/\mu L$]	12.23	13.29	25.58	92.05	82.42 – 102.81
$CD34^+$ t_{max} [h]	72.09	74.94		-10.97	-12.28 – 0.03

ANOVA and 90% confidence intervals for (log-transformed) pharmacodynamic parameters

Parameter	Dose Level 5 µg/kg i.v. n=31				
Parameter	**XM02**	**Neupogen®**	**ANOVA CV [%]**	**Point estimate Test/Ref. ratio**	**90% Confidence interval**
$CD34^+$ AUC_{0-t} [h*/µL]	1451.35	1545.21	17.37	93.77	87.02 – 101.05
$CD34^+C_{max}$ [/µL]	8.56	8.79	26.04	96.78	86.61 – 108.15
$CD34^+$ t_{max} [h]	72.97	72.38		-11.73	-35.82 – 12.05
	Dose Level 10 µg/kg i.v. n=30				
	XM02	**Neupogen®**	**ANOVA CV [%]**	**Point estimate Test/Ref. ratio**	**90% Confidence interval**
$CD34^+$ AUC_{0-t} [h*/µL]	1644.85	1525.62	13.84	107.71	101.37 – 114.44
$CD34^+C_{max}$ [/µL]	10.43	9.68	21.67	107.09	97.46 – 117.68
$CD34^+$ t_{max} [h]	72.06	71.83		-0.08	-12.01 – 11.86

ANOVA and 90% confidence intervals for (log-transformed) pharmacodynamic parameters



Study XM02-05-DE: Geometric Mean Concentration-Time Profile of $CD34^+$ Count Following a Single Subcutaneous Injection of 5 µg/kg of XM02 or Neupogen® to Healthy Male and Female Subjects

CD34+ data summarized by Gender: CD34+ AUC and Cmax values appear to be slightly less in females compared to males regardless of XM02 dose or administration route.

Parameter	Dose Level 5 µg/kg SC (N=33)				Dose Level 10 µg/kg SC (N=30)			
	XM02		Neupogen		XM02		Neupogen	
	male	female	male	female	male	female	male	female
Geomean CD34+ AUC_{0-t} [h*/µL]	1647	1268	1545	1341	2190	1581	2477	1720
Geomean CD24+ C_{max} [/µL]	9.3	7.5	9.9	7.6	14.7	10.2	17.5	10.1
Median CD34+ T_{max} [h]	72	72	72	72	72	72	72	77

Parameter	Dose Level 5 µg/kg IV(N=31)				Dose Level 10 µg/kg IV (N=30)			
	XM02		Neupogen		XM02		Neupogen	
	male	female	male	female	male	female	male	female
Geomean CD34+ AUC_{0-t} [h*/µL]	1511	1372	1617	1451	1781	1519	1668	1395
Geomean CD24+ C_{max} [/µL]	9.6	7.4	9.1	8.3	11.7	9.3	10.4	9
Median CD34+ T_{max} [h]	72	96	72	96	72	72	72	72

Safety (Per Applicant)

No specific definitions for the safety population were made in the protocol, so the safety analysis was done on the "full analysis data set". Of the 140 subjects who received either XM-02 or Neulasta®, 98 subjects experienced a total of 297 treatment-emergent AEs. Two subjects experienced only two baseline AEs. Forty subjects experienced no AEs.

The most frequently reported AEs were headache (75; 25% of all AEs), myalgia (41; 14% of all AEs) and back pain (41; 14% of all AEs), see Table. Headache, myalgia, and back pain observed in this study were mostly mild; except for that of 1 subject, who experienced severe back pain ~1 minute before the end of infusion and had to be subsequently withdrawn. Other AEs reported included dizziness, bone pain, fatigue, and nausea. Laboratory measurements showed no clinically significant alterations. No deaths or other serious adverse events occurred during this study.

Table. Adverse events of special interest stratified by subgroup and treatment. T, Test (XM-02); R, Reference (Neulasta®).

	T			R		
	E	N	%	E	N	%
Subgroup 1						
Headache	8	8	22.9	10	9	28.1
Myalgia	5	5	14.3	3	3	9.4
Back pain	2	2	5.7	6	6	18.8
Bone pain	-	-	-	1	1	3.1
Subgroup 2						
Headache	6	5	14.3	9	9	28.1
Myalgia	8	7	20.0	1	1	3.1
Back pain	2	2	5.7	7	7	21.9
Bone pain	-	-	-	-	-	-
Subgroup 3						
Headache	12	11	32.4	11	10	29.4
Myalgia	10	7	20.6	5	5	14.7
Back pain	7	7	20.6	3	3	8.8
Bone pain	-	-	-	1	1	2.9
Subgroup 4						
Headache	10	9	28.1	9	9	27.3
Myalgia	6	6	18.8	3	3	9.1
Back pain	8	8	25.0	6	6	18.2
Bone pain	3	3	9.4	2	2	6.1

E = number of AEs, N = number of subjects with AEs, % = percentage of subjects with AEs

ECG: ECGs were performed at screening and follow-up (14 days post-dose). The ECG measurements were within normal limits for all but 32 subjects. These 32 subjects exhibited 14 borderline QTc prolongations, 11 short PQ intervals, 6 QTc prolongations, 5 incomplete right bundle branch blocks, 3 primary atrioventricular blocks, 3 non-specific QRS configurations, 1 respiratoric arrhythmias, 2 atrial premature complexes, 1 sinus tachycardia, 1 sinus bradycardia, 1 sinus arrhythmia, and 1 ventricular premature complex either at screening or follow-up. All were judged as not clinically significant. The majority (40 out of 49 findings) of the ECG findings were present at screening.

Conclusions

- The PK results are similar for XM02 and Neupogen®. The t½ ranged from 5.2 - 9.4 hours. The increases in AUC_{0-t} and C_{max} observed with an increase in dose, from 5 μg/kg to 10 μg/kg, were similar between XM02 and Neupogen®. XM-02 was determined to be bioequivalent to Neupogen® at 5 μg/kg and 10 μg/kg when given IV or SC for AUC_{0-t}.
- The PD response on ANC and CD34+ for XM02 was equivalent for AUC_{0-t} and C_{max} to Neupogen® in doses of 5 μg/kg and 10 μg/kg after IV or SC dosing.
    - Peaks in ANC value were observed between 12 - 24 hours and returned to baseline after 96 hours.
    - A peak in CD34+ count was observed around 72 hours after dosing and values appear to return to baseline after 336 hours.
- Single dose XM02 or Neupogen® administered via IV or SC routes at doses of either 5 μg/kg or 10 μg/kg were well tolerated.
    - The safety results showed comparability between XM02 and Neupogen® in terms of number of AEs and number of subjects with those respective AEs.

4.2.3 Study# XM02-02-INT: Phase 3 trial –Breast cancer

Study #	XM02-02-INT
Investigator	Multi-center
Study Sites	Faculdade de Medicina, Departamento de Oncologia, Brazil
Study Period	December 30, 2004 – September 26, 005

Title: Efficacy and Safety of XM02 compared to Filgrastim in patients with breast cancer receiving chemotherapy: A multinational, multicentre, randomized, controlled study.

Objectives

Primary:

- Confirmation of assay sensitivity with respect to duration of severe neutropenia (DSN) by comparing XM02 vs. placebo in cycle 1.
- Demonstration of equivalence of XM02 and Filgrastim (Neupogen®, Amgen) in patients with breast cancer during the first cycle of chemotherapy (CTX) with respect to the primary endpoint, DSN in cycle 1, defined as grade 4 neutropenia with an absolute neutrophil count (ANC) $<0.5 \times 10^9$/L. after showing superiority of XM02 over placebo with respect to DSN.

Secondary:

- Demonstration of efficacy and safety of XM02 in comparison to filgrastim in patients with breast cancer under CTX, based on the secondary endpoints (incidence of febrile neutropenia, DSN Cycles 2 – 4, ANC).
- Evaluation of PK properties of XM02 in comparison to filgrastim (N=12 patients/group).

Study Rationale (Per Applicant): The aim of the phase 3 study is to show equivalence of XM02 and filgrastim with respect to efficacy and safety in patients with breast cancer receiving CTX.

Test Drug

XM02 Batch numbers and expiry dates:

- P-04-024 Apr 2006 (initially Jul 2005)
- P-04-025 May 2006 (initially Aug 2005)
- P-05-002 Nov 2006

Filgrastim (Neupogen®, Amgen, German trade ware) Batch numbers and expiry dates:

- N0856AA Jan 2006
- N0875AA Mar 2006
- N0911AA Apr 2006
- N1005AA Apr 2007

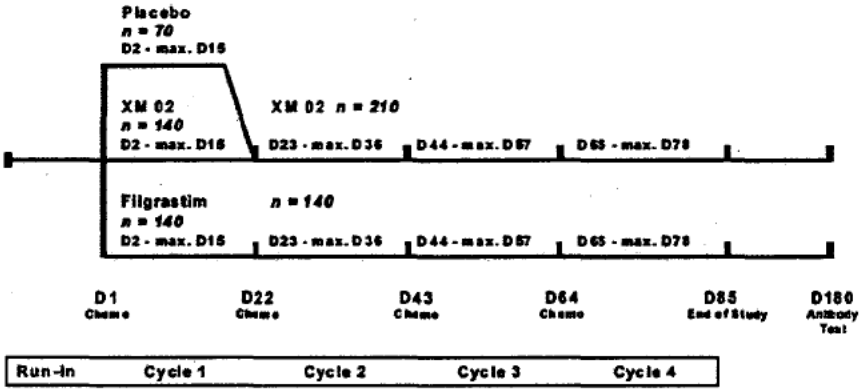
Placebo Batch number and expiry date:

- 4181C35 Mar 2007

Study Design

This was a multinational, multicentre, randomized (2:2:1), controlled Phase 3 trial (N=350). Patients with high-risk stage II, or with stage III or IV breast cancer needing CTX were randomized to treatment with either XM02 (n=140), filgrastim (n=140) or placebo (n=70). Patients received a maximum of 4 CTX cycles (3 wks/cycle) with doxorubicin 60 mg/m^2 and docetaxel mg/m^2. Following CTX on Day 1 of a cycle, the patients received daily SC injections of 5 µg/kg/day of either XM02 (n=140), filgrastim (n=140), or placebo (n=70) for 5 – 14 days, or until an ANC ≥10 x 10^9/L after nadir was documented. Patients in the placebo group switched to XM02 after cycle 1.

Figure 1: Study Design and Plan



Sampling times

Pharmacokinetic blood samples for the determination of serum concentrations of XM02, filgrastim, or endogenous G-CSF were taken in CTX cycle 1 and cycle 4 on Day 2 of a cycle (first profile), and on the day the ANC had reached ≥2 x 10^9/L after nadir (second profile). On the 4 PK days, samples were collected at pre-dose and 1, 2, 3, 4, 6, 12, and 24 h post-dose.

Pharmacodynamic blood samples were drawn Cycles 1 – 4 for ANC: predose Day 1, then predose daily on Days 5 – 15, or longer until the patient's ANC reached ≥2.0 x 10^9/L.

Immunogenicity samples were collected for both XM02 and filgrastim at:

- Screening
- 24h before each cycle
- End of study visit (Day 85)
- Follow-up visit (Day 180)

ECG samples were not collected.

Assay Method

Pharmacokinetics: Analysis of r-MetHuG-CSF concentrations in blood serum was performed using a GLP validated method based on the enzyme-linked immunosorbent assay (ELISA) kit (Quantikine®, R&D Systems, USA) at [redacted] (b) (4). The assay

LLOQ is 39 ng/ml and the ULOQ is 2500 pg/ml.

Pharmacodynamics: A differential automated haematology analyser (Beckman/Coulter AcT) was used at [redacted] (b) (4) for the determination of ANC in blood.

Pharmacokinetic Analysis: PK parameters (AUC, C_{max}, T_{max}, t½) were calculated by non-compartmental methods, using WinNonlin 3.3. AUC was calculated using the linear trapezoidal method. Derived PK parameters are summarized via descriptive statistics (including geometric mean (CV%) per day and treatment group.

Results

Subject Disposition:

A total of 378 patients in 52 study sites in 10 countries (Belarus, Slovenia, South Africa, Brazil, Chile, Russia, Hungary, Lithuania, Romania, and Poland) were enrolled into the study. Thirty (30) patients were not eligible to continue to baseline, thus, 348 patients were randomized (XM02 = 140, filgrastim = 136, and placebo/XM02 = 72), and received CTX and study drug in cycle 1. A total of 333 (95.7%) patients completed the entire course of the study. The treatment groups were similar with regard to the demographic characteristics; overall, 86.2% of randomized patients were Caucasian and 99.4% were women.

Summary of Baseline Patient Demographics.

	XM02 (N=140)	Filgrastim (N=136)	Placebo (N=72)	Overall (N=348)
Age (yr), mean (SD)	51 (9.7)	51.4 (10.7)	49.5 (10.3)	50.9 (10.2)
Weight (kg), mean (SD)	71.9 (16.1)	73.2 (15.0)	72.3 (18.0)	72.5 (16.1)
BMI (kg/m^2), mean (SD)	27.77 (6.11)	28.20 (5.70)	27.42 (6.02)	27.87 (5.93)

Efficacy Results

Primary Endpoint (Full analysis): Mean DSN in cycle 1 was 1.1, 1.1, and 3.8 days in the XM02, filgrastim, and placebo group, respectively. DSN ranged from 0 to 5 days in the XM02 and filgrastim groups, and from 0 to 9 days in the placebo group. More patients in the XM02 and filgrastim group had a DSN of 0 days (43.6% and 43.4%, respectively) than in the placebo group (11.1%).

Equivalence: DSN in Cycle 1 - ANCOVA for XM02 vs. Filgrastim – PP and FA Set

				Least square means		Estimate and 2-sided 95% CI for difference XM02 - Filgrastim		
Source of variation	DF	F	2-sided p-value	XM02	Filgrastim	Estimate	Lower bound	Upper bound
PP Set								
Baseline ANC	1	0.24	0.6245	-	-	-	-	-
Country	9	2.77	0.0042	-	-	-	-	-
Therapy	1	0.09	0.7583	-	-	-	-	-
Treatment	1	0.05	0.8305	1.119	1.087	0.032	-0.262	0.325
FA Set								
Baseline ANC	1	0.60	0.4400	-	-	-	-	-
Country	9	2.83	0.0034	-	-	-	-	-
Therapy	1	0.66	0.4183	-	-	-	-	-
Treatment	1	0.04	0.8508	1.148	1.120	0.028	-0.261	0.316

Note: Equivalence can be concluded, if the 2-sided 95% CI for XM02 minus Filgrastim lies entirely in the equivalence range [-d, d]. The comparison is based primarily on the PP Set.

Secondary Endpoint (Full analysis):

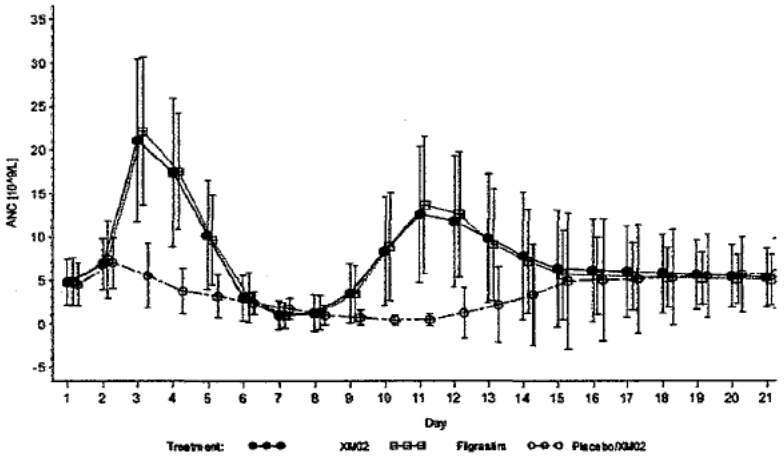
Febrile Neutropenia (FN): In cycle 1, the incidence of observed or protocol defined FN was 12.1% in the XM02 group, 12.5% in the filgrastim group, and 36.1% in the placebo/XM02 group. Across all cycles, the incidence of observed or protocol defined FN was 20.7% in the XM02 group, 22.1% in the filgrastim group, and 41.7% in the placebo/XM02 group. All observed FNs occurred in cycle 1. There were no significant differences with regard to FN incidence between the XM02 and filgrastim groups.

DSN: The mean DSN in cycles 2 – 4 was similar in all treatment groups. The majority of patients had a DSN of 0 days. Overall, DSN ranged from 0 to 6 days. In the XM02, filgrastim, and placebo/XM02 group, respectively, mean DSN was:

- Cycle 2: 0.7, 0.7, and 0.5 days
- Cycle 3: 0.6, 0.7, and 0.6 days
- Cycle 4: 0.7, 0.7, and 0.6 days

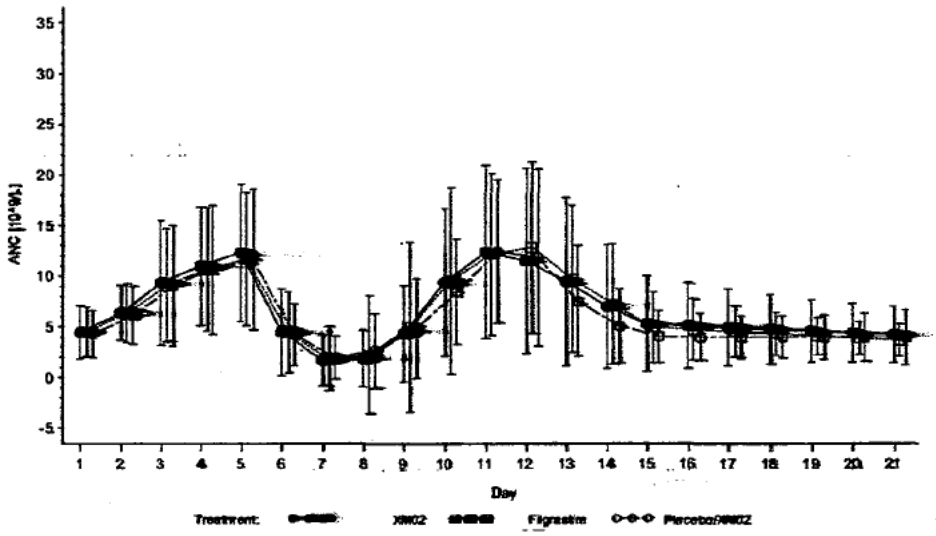
Absolute Neutrophil Count Over Time: In cycle 1 in the placebo group, mean ANC values decreased after Day 2 and reached a nadir on Day 11, whereas in the XM02 and Filgrastim groups, mean values achieved a maximum on Day 3, and then decreased to a nadir on Day 7. Then, mean values in the active treatment groups increased again, reaching a maximum on Day 11. On Day 21, mean values returned to values as observed on Day 1 in all treatment groups. The figure displays the mean ANC values in cycle 1 per treatment group for the full analysis set.

: Mean (± SD) of Absolute Neutrophil Counts in Cycle 1 – FA Set



In cycle 4 patients received XM02 or filgrastim, and the course over time was similar in all treatment groups. Mean ANC values increased after Day 1, reaching a maximum on Day 5, and then decreased to a nadir on Day 7. Then, mean values increased again, reaching a maximum on Day 11. On Day 21, mean values returned to values as observed on Day 1.

Mean (± SD) of Absolute Neutrophil Counts in Cycle 4 – FA Set



Depth of ANC Nadir in Cycles 1 to 4: ANC nadir in a given cycle was defined as the lowest ANC value after start of CTX in the given cycle. In cycle 1, the mean ANC nadir was deeper in the placebo group (0.163 x 109/L) compared to the XM02 and Filgrastim groups (0.655 x 10^9/L and 0.651 x 10^9/L, respectively). In cycles 2, 3, and 4, the mean ANC nadir was not as deep as in cycle 1 and was similar across treatment groups with a mean value of approximately 1.0 x 10^9/L.

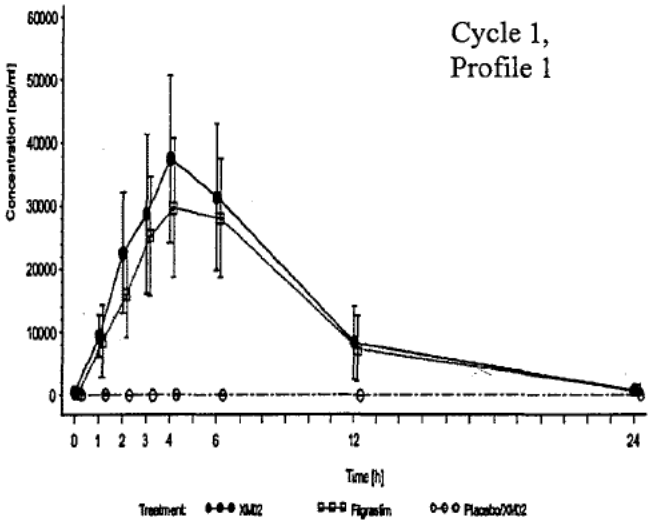
Time to ANC Recovery in Cycles 1 to 4: Time to ANC recovery was defined as the time in days from CTX administration until the patient's ANC increased to $\geq$2.0 x 10^9/L after the expected nadir. In cycle 1, the median time to ANC recovery was shorter in the XM02 and Filgrastim groups (8.0 and 8.0 days) compared to the placebo group (15.0 days). In cycles 2, 3, and 4, the median time to ANC recovery was similar in all treatment groups with a median of 8.0 days.

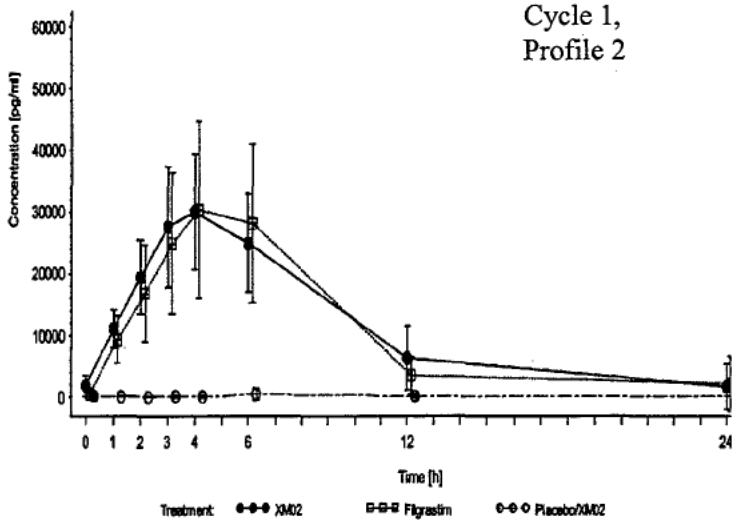
Body Temperature Over Time: In cycle 1, mean body temperature values over time remained fairly constant in the course of the study in the XM02 and filgrastim groups, whereas in the placebo/XM02 group, there was a slight increase of mean body temperature values reaching a maximum on Day 11. In cycle 4, mean body temperature values over time were similar in both XM02 and filgrastim groups.

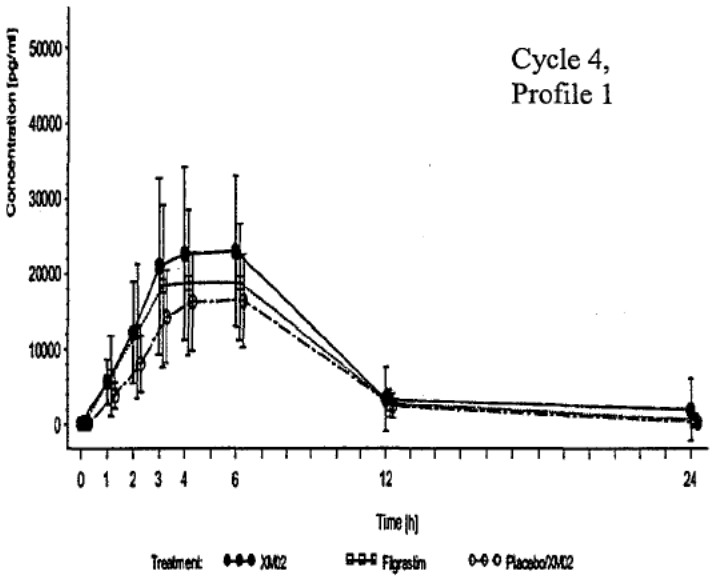
Mortality: Mortality rates up to the End of Study visit (Day 85) were compared between XM02 (only patients randomised to XM02 in cycle 1) and filgrastim by means of Fisher's exact test. In the observation period until Day 85, 3 patients died. There were no significant differences between patients treated with XM02 or filgrastim with respect to the mortality rate.

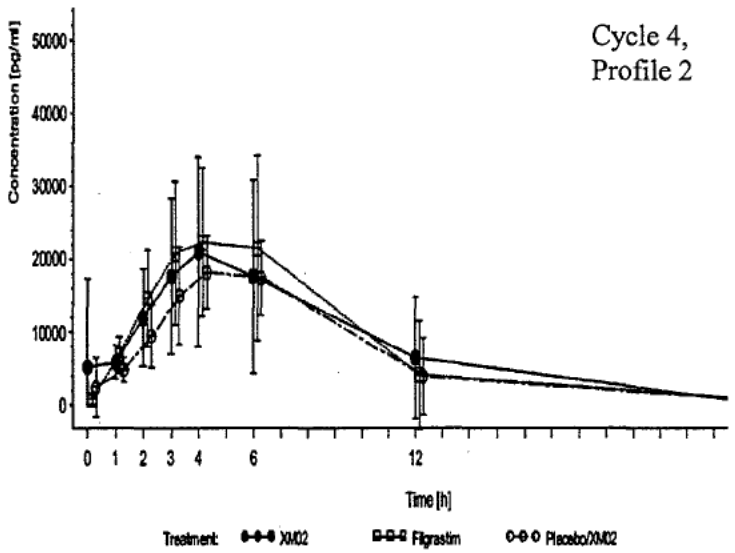
Pharmacokinetic Results:
All 37 patients in the PK set were female. The majority were Caucasian (86.5%); 8.1% were Hispanics, and 5.4% Blacks. Only patients providing profiles for each of the 4 PK profiles is summarized (XM02 N=9 of 14, Filgrastim N=10 of 13, placebo/XM02 N=6 of 10). Geometric mean (CV%) PK parameters are presented in the table for those patients providing all 4 PK profiles. No accumulation after repeated dosing was observed. Mean serum concentrations were lower in cycle 4 than in cycle 1, and this was not related to antibody formation.

The PK profile for breast cancer patients that received either XM02 or Neupogen® during Cycle 1 and Cycle 4 is presented in the figure. In cycle 1 and cycle 4 in both profiles, mean serum concentrations of XM02 and Neupogen® increased, achieving T_{max} at 4 to 6 hrs post-dose, and returned to pre-dose values by 24 hrs.









	Cycle 1				Cycle 4					
	First Profile		Second Profile		First Profile			Second Profile		
Parameter	XM02	Neupogen	XM02	Neupogen	XM02	Neupogen	Placebo /XM02	XM02	Neupogen	Placebo /XM02
AUC_{0-24} (ng/ml*h)	305.3 (35)	258.5 (47)	276.03 (29.7)	229.53 (51.6)	180.01 (41.3)	153.35 (56.6)	136.94 (32.1)	179.26 (75)	173.5 (64.1)	162.14 (32.9)
C_{max} (ng/ml)	36.15 (40.6)	28.98 (52.6)	29.63 (36.5)	28.36 (46.5)	22.59 (53.5)	18.27 (71.5)	17.1 (38.9)	21.25 (75.2)	21.78 (52.6)	18.35 (33.2)
T_{max} (h)*	4 (4, 6)	4 (3, 6)	4 (3, 6)	4 (4, 6)	4 (3, 6)	5 (3, 6)	4 (3, 6)	4 (0, 6)	4 (4, 6)	5 (3, 6)
t½ (h)	3.2 (23.2)	6.6 (32.7)	4.2 (114.8)	4.0 (66.7)	3.7 (20.8)	4.1 (44.4)	3.4 (24)	3.8 (28.3)	3.9 (32.7)	3.9 (53.5)

Note: First profile was on Day 2 of cycle 1; second profile was on the day the ANC $\geq 2 \times 10^9$/L after nadir in cycle 1.
*** For Tmax, median (range) is given.**

Pharmacodynamic Results: See Secondary efficacy results above for ANC results.

Safety (Per Applicant)

In the course of the study, 329 (94.5%) patients experienced a total of 3,268 treatment emergent adverse events (TEAEs). In 112 (32.2%) patients, a total of 294 TEAEs were considered as possibly study drug related. In cycle 1, the most frequent treatment-emergent adverse reaction that occurred at a higher incidence in patients treated with XM02 (or filgrastim) compared with patients treated with placebo was bone pain (14.2% XM02, 19.0% filgrastim, 9.1% placebo). Across all cycles, the AE profile was similar between the XM02 and filgrastim groups with exception of the incidence of possibly study drug related treatment emergent adverse events (TEAEs) (filgrastim: 39.7% of patients, XM02: 25.7% of patients (p=0.0149)). The same trend was observed in every cycle.

- Most commonly reported possibly drug related TEAEs were bone pain (10.3%), asthenia (7.8%), myalgia (6.3%), and diarrhea (5.2%).
- Most commonly reported TEAEs (preferred term) were nausea (49.4% of patients), alopecia (48.0%), and asthenia (36.5%); the treatment groups were similar with regard to the incidence of most commonly reported TEAEs.

Injection Site Reactions: Overall, there were 6 cases of injection site reactions during the study (2 in the XM02 group, 3 in the filgrastim group, and 1 in the placebo/XM02 group). After Cycle 1, any reaction was observed in 3 patients (1 in the XM02 group and 2 in the filgrastim group). The number of patients with injection site reactions remained low in the subsequent cycles, and was 0 at the end of study visit. There did not appear to be differences between the treatment groups with regard to the incidence of injection site reactions.

Immunogenicity: No evidence of an effect of the presence of anti-filgrastim antibodies or neutralizing antibodies on safety, efficacy, or pharmacokinetic profiles was observed.

Anti-Antibodies & Neutralizing Antibodies: There were no patients who developed either binding antibodies or neutralizing antibodies during the study treatment. However, 4 (2.1%) patients in the XM02 group were positive for binding antibodies at the 180 day follow-up visit and 3 (1.5%) were positive for neutralizing antibodies at the 180 day follow-up visit. However, for positive samples with the BIAcore assay, both corresponding ELISA and Luminex screening samples of the Day 180 follow-up visit were negative.

		XM02* N=195	Neupogen® N=124
Binding Antibodies	Positive for binding antibody at any time in the study	0	0
	Positive for binding antibody during study follow-up	4 (2.1%)	3 (2.4%)
Neutralizing Antibodies	Positive for neutralizing antibody at any time in the study	0	0
	Positive for neutralizing antibody during study follow-up	3 (1.5%)	2 (1.6%)

* Includes patients who received placebo in the first cycle and XM02 during subsequent cycles

Conclusions

- XM02 and Filgrastim are significantly more effective than placebo in reducing the DSN in cycle 1 of CTX in patients with breast cancer.
- XM02 is equally effective as filgrastim in reducing the DSN in cycle 1 of CTX in patients with breast cancer.
- XM02 and Filgrastim have a similar effect on the incidence of febrile neutropenia, and the time to ANC recovery.
- XM02 and Filgrastim have similar PK profiles.
- XM02 and Filgrastim have similar safety profiles.
- Immunogenicity of XM02 and filgrastim was similar over all 4 CTX cycles and after 6 months of follow-up.

4.2.4 Study# XM02-03-INT: Phase 3 trial – Lung Cancer

Study #	XM02-03-INT
Investigator	Multi-center
Study Sites	Faculdade de Medicina, Departamento de Oncologia, Brazil
Study Period	December 28, 2004 – December 17, 2005

Title: Safety and Efficacy of XM02 in patients with small-cell or non-small-cell lung cancer receiving platinum-based chemotherapy: a multinational, multicenter, randomized, controlled study.

Objectives

Primary: Demonstration of safety of XM02 when administered for up to a maximum of 6 cycles of chemotherapy (CTX) in patients with lung cancer.

Secondary:

- Demonstration of efficacy of XM02 (in the 1st cycle compared to filgrastim) in patients with lung cancer.
- Evaluation of PK properties of XM02 in comparison to filgrastim.

Study Rationale (Per Applicant): The aim of this study was to demonstrate that XM02 is safe and effective in patients with lung cancer receiving CTX.

Test Drug

XM02 Batch numbers and expiry dates:

- P-04-024 Apr 2006 (initially Jul 2005)
- P-04-025 May 2006 (initially Aug 2005)
- P-05-002 Nov 2006

Filgrastim (Neupogen®) Batch numbers and expiry dates:

- N0856AA Jan 2006
- N0875AA Mar 2006
- N0911AA Apr 2006
- N1005AA Apr 2007

Study Design

This was a multinational, multicenter (47 study centers) in 11 countries (Belarus, Slovenia, Portugal, Brazil, Chile, Russia, Hungary, Lithuania, Canada, Romania, and Poland), randomized (2:1), controlled phase 3 trial in patients with small cell lung cancer (SCLC) or non-small cell lung cancer (NSCLC) requiring CTX (N=240).

- Patients were randomized to treatment with either XM02 (n=160) or Filgrastim (n=80) in the CTX cycle 1. In the subsequent cycles, all patients received XM-02. Filgrastim or XM-02 was administered daily starting 1 day after CTX as SC 5 μg/kg injection for 5 – 14 days in each cycle.

- CTX regimens in this study consisted of any myelosuppressive platinum-based CTX, in 3-week or 4-week cycles, depending on the CTX protocol. Up to 6 CTX cycles were applied.
- PK properties of XM02 and Neupogen® were examined in up to 12 patients per treatment group (XM02 and Neupogen®/XM02) in a parallel-group design.

Sampling times

Pharmacokinetic blood samples for the determination of serum concentrations of XM02, filgrastim, or endogenous G-CSF were taken in CTX cycle 1 and cycle 4 on Day 2 of a cycle (first profile), and on the day the ANC had reached ≥2 x 10^9/L after nadir (second profile). On the 4 PK days, samples were collected at pre-dose and 1, 2, 3, 4, 6, 12, and 24 h post-dose.

Pharmacodynamic blood samples were drawn pre-dose for the determination of ANC:

- In cycle 1: within 24 hours before CTX and then daily until Day 15, or longer until the patient's ANC reached ≥2.0 x 10^9/L.
- In cycle 4, within 24 hours before CTX, and then daily starting on Day 5 until Day 15, or longer until the patient's ANC reached ≥2.0 x 10^9/L.

Immunogenicity samples were collected for both XM02 and filgrastim at:

- Screening
- 24h before each cycle
- End of study visit (Day 85)
- Follow-up visit (Day 180)

ECG samples were not collected.

Assay Method

Pharmacokinetics: Analysis of r-MetHuG-CSF concentrations in blood serum was performed using a GLP validated method based on the enzyme-linked immunosorbent assay (ELISA) kit (Quantikine®, R&D Systems, USA) at [redacted] (b) (4). The assay LLOQ is 39 ng/ml and the ULOQ is 2500 pg/ml.

Pharmacodynamics: A differential automated haematology analyser (Beckman/Coulter AcT) was used at [redacted] (b) (4) for the determination of ANC in blood.

Pharmacokinetic Analysis: PK parameters (AUC, C_{max}, T_{max}, t½) were calculated by non-compartmental methods, using WinNonlin 3.3. AUC was calculated using the linear trapezoidal method. Derived PK parameters are summarized via descriptive statistics (including geometric mean (CV%) per day and treatment group.

Results

Subject Disposition: A total of 260 patients in 47 study sites in 11 countries (Belarus, Slovenia, Portugal, Brazil, Chile, Russia, Hungary, Lithuania, Canada, Romania, and Poland) were enrolled into the study. Of these, 237 patients (XM02 = 158, Filgrastim/XM02 = 79) received chemotherapy (CTX) and study drug in cycle 1.

Of the 237 patients, 188 were male (79.3%) and 49 were female (20.7%). The majority of patients were Caucasian (94.9%); 4.6% were Hispanics and 0.4% were of another race. The treatment groups were similar with regard to the demographic characteristics. There were 4 patients with hepatic impairment, who were exposed to active treatment for a total of 165 days.

Summary of Baseline Patient Demographics.

	XM02 (N=158)	Filgrastim/XM02 (N=79)	Overall (N=237)
Age (yr), mean (SD)	58.8 (8.8)	58.1 (10.1)	58.6 (9.2)
Weight (kg), mean (SD)	69.5 (13.3)	71.3 (13.6)	70.1 (13.4)
BMI (kg/m^2), mean (SD)	23.99 (4.22)	24.41 (4.17)	24.13 ()

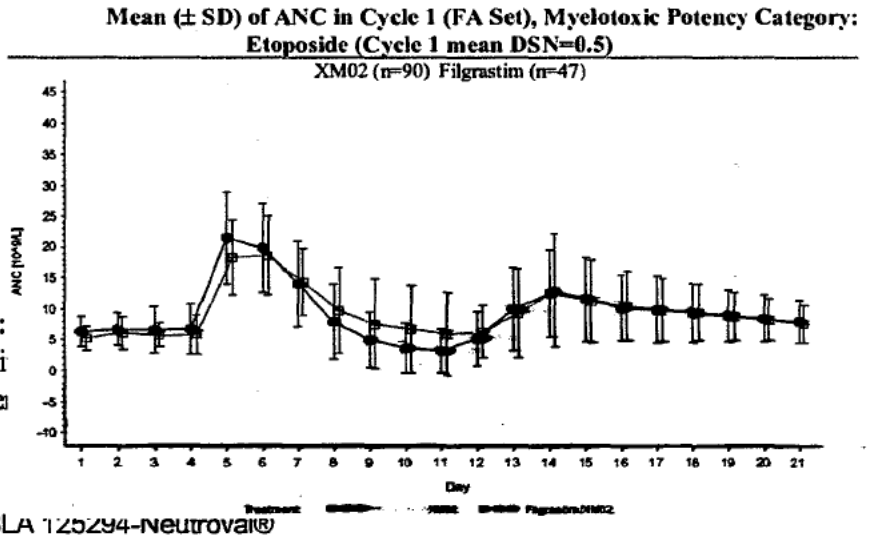
Efficacy Results:

Duration of Severe Neutropenia (DSN) in Cycles 1 and 4: The mean DSN in cycles 1 and 4 was similar between the treatment groups. The majority of patients (82.1% overall for cycle 1 and 85.4% for cycle 4) had a DSN of 0 days. Overall, DSN ranged from 0 to 6 days for cycle 1 and cycle 4. Mean DSN was 0.5 and 0.3 days in cycle 1 for XM02 and filgrastim, respectively, and 0.4 and 0.3 days in cycle 4 after the switch from filgrastim to XM02 in the reference group. In the ANCOVA for DSN in cycle 1, the estimated treatment difference "XM02 minus filgrastim" = 0.157 days, with 95% CI (-0.114, 0.428).

Incidence of Febrile Neutropenia (FN): Across all cycles, there were no incidences of observed FN in either XM02 or filgrastim/XM02 treatment groups. Across all cycles, the incidence of protocol defined FN (corresponding to the intake of systemic antibiotics) was lower in the filgrastim/XM02 group compared to the XM02 group (23.8% and 33.1%, p=0.318).

- FN was defined as a body temperature of >38.5°C for >1h, and ANC <0.5 x 10^9/L, both measured on the same day.

Absolute Neutrophil Count (ANC) Over Time: In cycle 1 in both treatment groups, mean ANC values increased after Day 2, reaching a maximum on Day 5 and then decreased to a nadir on Day 11 (Day 12 filgrastim/XM02 group). Thereafter, mean values in the active treatment groups increased again, reaching a maximum on Day 14. On Day 21, mean values approached those observed on Day 1 in both treatment groups. The ANC profile was similar in subsequent cycles. The etoposide CTX ANC concentration time profile is presented in the figure.



Depth of ANC Nadir in Cycles 1 to 4: x 10^9/L) was lower than in the filgrasti from filgrastim to XM02 in the refere

XM02 group (2.3 x 10^9/L) than in the Filgrastim/XM02 group (3.2 x 10^9//L).

Time to ANC Recovery in Cycles 1 to 4: In cycle 1, the median time to ANC recovery was shorter in the filgrastim/XM02 group (4.5 days) compared to the XM02 group (6.3 days, p=0.038). In cycle 4, after switch from filgrastim to XM02 in the reference group, mean time to ANC recovery was also shorter in the filgrastim/XM02 group (4.5 days) than in the XM02 group (6.4 days).

Body Temperature: For all cycles, mean body temperature values over time were similar in the XM02 and filgrastim/XM02 groups, i.e., they remained fairly constant in the course of the study.

Mortality: In the observation period until Day 127/169, 31 patients died. There were no significant differences between patients treated with XM02 or Filgrastim/XM02 with respect to the mortality rate.

Pharmacokinetic Results: There were 25 patients (XM02 13, filgrastim/XM02 12) in the PK set the majority of which were male (72%) and all were Caucasian. Median age of the patients was 59 years (range: 35 to 78 years). The treatment groups were similar with regard to the demographic characteristics.

Not all patients provided PK samples at each of the profile characterization times. Therefore, results are presented for the PK set including all patient data available with plausible profiles; only 4 profiles were considered implausible (all in cycle 1, 2nd profile): 3 because apparently no study drug was administered, and 1 due to an implausibly high concentration at pre-dose.

Summary of application of study drug at the four pharmacokinetic days - PK set
Excluding implausible profiles

		Application of study drug	XM02 [N= 13]	Filgrastim/XM02 [N= 12]
Cycle 1	first profile	No		
		Yes	13 (100.0%)	12 (100.0%)
	second profile	No		
		Yes	5 (100.0%)	7 (100.0%)
Cycle 4	first profile	No		
		Yes	8 (100.0%)	8 (100.0%)
	second profile	No		
		Yes	6 (100.0%)	4 (100.0%)

Filgrastim/XM02: patients of this group are randomised to Filgrastim in cycle 1 and switch to XM02 afterwards

Geometric mean (CV%) PK parameters are presented in the table for those patients providing plausible PK profiles. In cycle 1 and cycle 4 in both profiles, mean serum concentrations of XM02 and filgrastim increased, reaching a maximum at 4 to 6 hours after dosing, and returned to pre-dose values by 24 hours. Overall, mean filgrastim serum concentrations were lower in cycle 4 than in cycle 1 and this was not related to antibody formation. No accumulation after repeated dosing was observed.

	Cycle 1				Cycle 4			
	First Profile		Second Profile		First Profile		Second Profile	
Parameter	XM02	Neupogen†	XM02	XM02	XM02	XM02	XM02	XM02
AUC_{0-24} (ng/ml*h)	272.5 (61.4)	240.1 (30.9)	200.9 (65.2)	148.2 (120.1)	224.2 (58.6)	225.6 (40.1)	192.7 (92.8)	88.0 (83.4)
C_{max} (ng/ml)	25.22 (59.6)	23.66 (33.3)	14.81 (65.9)	15.64 (157.1)	16.88 (56.4)	21.45 (46.6)	13.52 (95.9)	11.32 (27.5)
	6	6	6	3	12	6	6	4
T_{max} (h)*	(3, 12)	(3, 12)	(4, 12)	(2, 6)	(6, 12)	(3, 12)	(3, 12)	(4, 6)
t½ (h)	3.8 (32.7)	3.8 (30)	4.3 (21.8)	3.6 (46.4)	2.9 (12.6)	3.1 (18.1)	4.7 (33.7)	4.0 (30.7)

Note: First profile was on Day 2 of cycle 1; second profile was on the day the ANC $\geq 2 \times 10^9$/L after nadir in cycle 1.

†Neupogen patients were randomized to filgrastim in cycle 1 and switched to XM02 afterwards

*For Tmax, median (range) is given.

Pharmacodynamic Results: See ANC results above.

Safety (Per Applicant)

Across all cycles and within each cycle, the AE profile was similar between the XM02 and Filgrastim/XM02 groups. The incidence of TEAEs was slightly higher in cycle 1 (76.8%) compared to the other cycles (52.8% to 67.5%).

- Most commonly reported possibly drug related TEAEs were myalgia (2.1%), back pain (2.1%), anaemia (2.1%), and headache (2.1%). Possibly drug related TEAEs were experienced early in the study, i.e., they were reported within 20 days after study start, or within 6 days after start of a cycle.
- There were no clinically relevant changes of safety laboratory parameters, vital signs, body weight, or physical examination during the study and no clinically relevant differences between the treatment groups. Overall, there were 2 cases of injection site reactions during the study.

Immunogenicity:

Anti-Antibody & Neutralizing Antibodies: Only 4 patients (see tables below) in this trial who received XM-02 only tested positive for binding antibodies. These patients did not have PK data available.

		XM02-03 in Lung Cancer* (N=237)
Binding Antibodies	**Positive for binding antibody at any time in the study**	**4 (1.7%)**
	Positive for binding antibody during study follow-up	**1 (0.4%)**
Neutralizing Antibodies	**Positive for neutralizing antibody at any time in the study**	**4 (1.7%)**
	Positive for neutralizing antibody during study follow-up	**0**

Individual Patient Summary:

ID #	Age, race	Immunogenicity summary
40-407-05	60, Hispanic	ELISA and Luminex positive before cycles 2, 3, and 4, and Luminex positive before cycle 5. Western Blot tests confirmed positive IgG and IgM results before cycles 2 and 3, and positive IgM results before cycles 4 and 5. IgG quantification was below LLOQ before cycles 2, 3, 4, and 5. NAB assays were positive before cycles 2, 3, and 4, with NAB concentrations of 8.0%, 9.7%, and 6.7%, respectively. Before cycle 5, the patient was NAB negative.
50-513-01	48, Caucasian	ELISA negative at all visits and Luminex positive before cycles 2, 3, 4, 5, 6, at end-of-study (EOS), and at the 180 day follow-up visit. Western Blot tests confirmed positive IgG and IgM results before cycles 5, 6, and at antibody follow-up, and positive IgM at EOS. IgG quantification was below LLOQ before cycles 5, 6, at end-of-study, and at the 180 day follow-up visit. NAB assays were positive before cycles 5, 6, at end-of-study, and at the 180 day follow-up visit with NAB concentrations of 4.5%, 3.0%, 7.7%, and 12.6%, respectively.
80-801-02	61, Caucasian	ELISA positive before cycles 4, 5, 6, and at EOS; Luminex was negative at all visits. Western Blot tests confirmed IgG positive results before cycles 4 and 5 and questionable IgG results before cycle 6. IgM was always negative. IgG quantification was below LLOQ before cycles 4 and 5. The NAB assay was positive before cycle 4 only (NAB concentration of 7.0%).
80-807-16	68, Caucasian	ELISA positive and NAB positive at the EOS visit; the NAB concentration was 10%. Western Blot tests confirmed positive IgG and IgM results. IgG quantification was below LLOQ at EOS visit. There was no further testing at the follow-up visit.
None of these 4 patients had PK data. The treatment-emergent AE's in these patients were not considered related to XM02 treatment and did not appear to relate to immunogenicity positivity. Efficacy was not affected in these patients; DSN was between 0 - 5 days and time to ANC recovery was between 0 - 13 days.		

- Patient 40-407-05 (60yo, Hispanic male):
  - This patient had several AE's throughout the study that were considered treatment-emergent AEs, but were not considered related to XM02 treatment (e.g. thrombocytopenia, anemia, vomiting).
  - Clinically, the DSN following Cycles 1 and 4 was 4 and 5 days, respectively. The time to ANC recovery following Cycles 1 and 4 was 12 and 13 days, respectively.
- Patient 50-513-01 (48yo Caucasian male):
  - This patient reported 2 cases of Grade 4 neutropenia and total alopecia. The alopecia was ongoing at end of study. These AEs were not considered related to XM02 treatment.
  - Clinically, the DSN following Cycles 1 and 4 was 3 and 0 days, respectively. The time to ANC recovery following both Cycles 1 and 4 was 11 days.
- Patient 80-801-02 (61yo Caucasian male):
  - This patient did not have AEs reported.
  - Clinically, the DSN following both Cycles 1 and 4 was 0 days. The time to ANC recovery following both Cycles 1 and 4 was 0 days.
- Patient 80-807-16 (68yo Caucasian male):
  - This patient had AE's throughout the study (e.g. nausea, diarrhea, neutropenia, thrombocytopenia, stroke, hyperuricemia). Thrombocytopenia and hyperuricemia were considered possibly related to XM02 treatment and possibly related to chemotherapy. This patient died of disease progression during Cycle 2 (b) (6)

- Clinically, the DSN following both Cycles 1 and 4 was 1 day. The time to ANC recovery following Cycles 1 was 13 days and the data for Cycle 4 are missing.

Conclusions

- XM02 is safe and well tolerated when administered for up to a maximum of 6 CTX cycles in patients with lung cancer.
- XM02 and filgrastim have similar effects with regard to DSN and the incidence of FN in cycle 1 during CTX in patients with lung cancer.
- XM02 and filgrastim have a similar PK profile.

4.2.5 Study# XM02-04-INT: Phase 3 trial – Non-Hodgkin Lymphoma

Study #	XM02-04-INT
Investigator	Multi-center
Study Sites	Faculdade de Medicina, Departamento de Oncologia, Brazil
Study Period	December 24, 2004 – March 27, 2006

Title: Safety and Efficacy of XM02 in patients with Non-Hodgkin-Lymphoma receiving chemotherapy, A multinational, multicenter, randomized, controlled study.

Objectives

Primary: Demonstration of safety of XM02 when administered for up to a maximum of 6 cycles in patients with Non-Hodgkin-Lymphoma (NHL) receiving chemotherapy (CTX) according to the cyclophosphamide-hydroxydaunomycin-oncovin-prednisolon (CHOP) regimen.

Secondary:

- Demonstration of efficacy of XM02 (in the first cycle compared to Filgrastim) in patients with NHL.
- Evaluation of PK properties of XM02 in comparison to Filgrastim.

Study Rationale (Per Applicant): This study was performed in NHL patients in order to assess safety in haematological malignancies.

Test Drug

XM02 Batch numbers and expiry dates:

- P-04-024 Apr 2006 (initially Jul 2005)
- P-04-025 May 2006 (initially Aug 2005)
- P-05-002 Nov 2006

Filgrastim (Neupogen®) Batch numbers and expiry dates:

- N0856AA Jan 2006
- N0875AA Mar 2006
- N0911AA Apr 2006
- N1005AA Apr 2007

Study Design

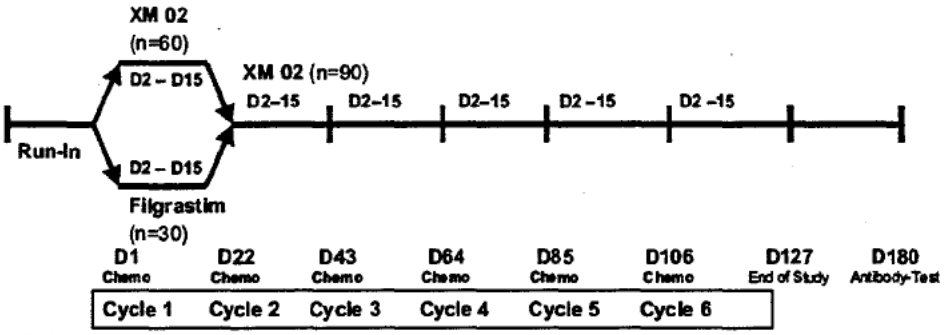
This was a multinational, multicenter, randomized (2:1), controlled phase 3 trial in patients with chemotherapy (CTX) naïve aggressive Non-Hodgkin-Lymphoma (NHL) (allowed subtypes: diffuse large B cell lymphoma, mediastinal large B cell lymphoma, follicular lymphoma grade 3, anaplastic large cell lymphoma) needing CTX were enrolled (N=92).

- Patients were randomized to treatment with either XM02 (n=63) or Filgrastim (n=29) in the CTX cycle 1. In the subsequent cycles, all patients received XM-02. Filgrastim or XM-02 was administered daily starting 1 day after CTX as SC 5 µg/kg injection for 5 – 14 days in each cycle.
    - The CTX regimen in this study was according to the CHOP protocol: Cyclophosphamide IV 750 mg/m^2, doxorubicin IV 50 mg/m^2, vincristine IV 1.4

mg/m^2 (maximum 2 mg) on Day 1 of each cycle, and prednisolone 100 mg/day orally from Days 1 – 5. Patients on CHOP could receive rituximab (stratification criterion). Up to 6 CTX cycles could be used.

- PK properties of XM02 and Neupogen® were examined in up to 12 patients per treatment group (XM02 and Neupogen®/XM02) in a parallel-group design.

Figure 1: Study Design and Plan



breviations: D = day, Chemo = chemotherapy

Sampling times

Pharmacokinetic blood samples for the determination of serum concentrations of XM02, filgrastim, or endogenous G-CSF were taken in CTX cycle 1 and cycle 4 on Day 2 of a cycle (first profile), and on the day the ANC had reached ≥2 x 10^9/L after nadir (second profile). On the 4 PK days, samples were collected at pre-dose and 1, 2, 3, 4, 6, 12, and 24 h post-dose.

Pharmacodynamic blood samples were drawn pre-dose for the determination of ANC:

- In cycle 1: within 24 hours before CTX and then daily until Day 15, or longer until the patient's ANC reached ≥2.0 x 10^9/L.
- In cycle 4, within 24 hours before CTX, and then daily starting on Day 5 until Day 15, or longer until the patient's ANC reached ≥2.0 x 10^9/L.

Immunogenicity samples were collected for both XM02 and filgrastim at:

- Screening
- 24h before each cycle
- End of study visit (Day 85)
- Follow-up visit (Day 180)

ECG samples were not collected.

Assay Method

Pharmacokinetics: Analysis of r-MetHuG-CSF concentrations in blood serum was performed using a GLP validated method based on the enzyme-linked immunosorbent assay (ELISA) kit (Quantikine®, R&D Systems, USA) at [redacted] (b) (4). The assay LLOQ is 39 ng/ml and the ULOQ is 2500 pg/ml.

Pharmacodynamics: A differential automated haematology analyser (Beckman/Coulter AcT) was used at [redacted] (b) (4) for the determination of ANC in blood.

Pharmacokinetic Analysis: PK parameters (AUC, C_{max}, T_{max}, $t_{1/2}$) were calculated by non-compartmental methods, using WinNonlin 3.3. AUC was calculated using the linear trapezoidal method. Derived PK parameters are summarized via descriptive statistics (including geometric mean (CV%) per day and treatment group.

Results

Subject Disposition: Overall 92 patients were enrolled in the trial, 48 (52.2%) were male and 44 (47.8%) were female. The majority of patients were Caucasian (88.0%); 8.7% were Hispanics, 1.1% Blacks, and 2.2% were of another race. The treatment groups were similar with regard to the demographic characteristics.

Summary of Baseline Patient Demographics.

	XM02 (N=63)	Filgrastim (N=29)	Overall (N=92)
Age (yr), mean (SD)	50.2 (16.1)	56.7 (15.4)	52.3 (16.1)
Weight (kg), mean (SD)	69.7 (13.2)	72.6 (14.9)	70.6 (13.7)
BMI (kg/m^2), mean (SD)	25.16 (4.07)	26.13 (5.91)	25.47 (4.71)

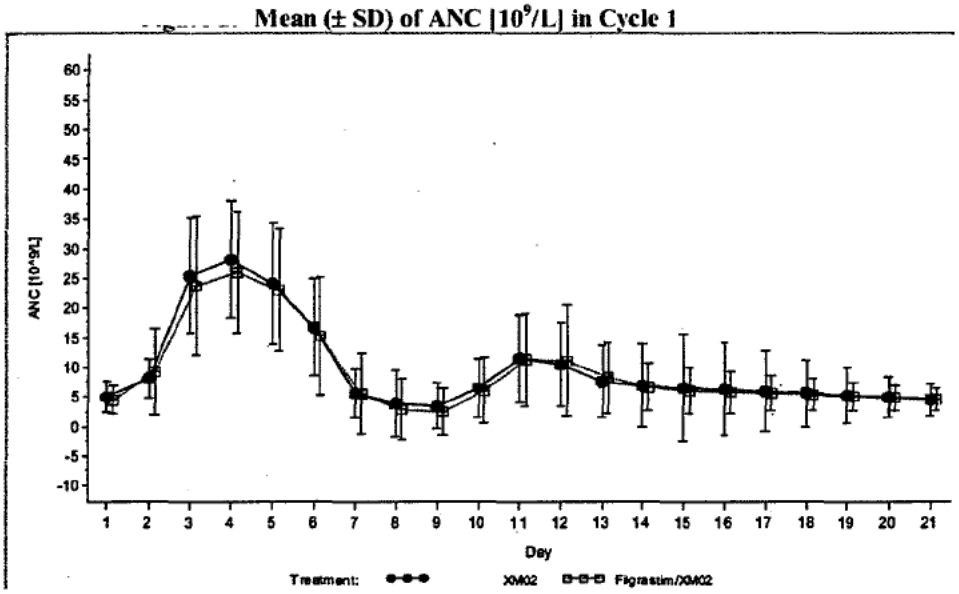
Efficacy Results:

Duration of Severe Neutropenia (DSN) in Cycles 1 and 4: The mean DSN in cycles 1 and 4 was similar in both treatment groups. The majority of patients had a DSN of 0 days. Overall, DSN ranged from 0 – 5 days. Mean DSN was 0.5 and 0.9 days in cycle 1, and 0.2 and 0.7 days in cycle 4 in the XM02 and filgrastim/XM02 group, respectively. ANCOVA for XM02 vs. filgrastim/XM02 for DSN in cycle 1 showed no statistical differences between XM02 and Filgrastim (estimated difference "XM02 minus Filgrastim" = -0.378 days, with 95% CI [-0.837, 0.081], p=0.1055).

Incidence of Febrile Neutropenia (FN): Across all cycles, there were no incidences of observed FN in either XM02 or filgrastim/XM02 treatment groups. The incidence of protocol defined FN was lower in the XM02 group compared to the filgrastim/XM-02 group (31.7% and 41.4%, respectively, p=0.2094).

- FN was defined as a body temperature of >38.5°C for >1h, and ANC <0.5 x 10^9/L, both measured on the same day.

Absolute Neutrophil Count (ANC) Over Time: In cycle 1 in both treatment groups, mean ANC values increased after Day 2, reaching a maximum on Day 4 and then decreased to a nadir on Day 9. Thereafter, mean values increased again, reaching a maximum on Day 11. On Day 21, mean values approached those observed on Day 1 in both treatment groups (see figure). The ANC profile was similar in subsequent cycles.



Depth of ANC Nadir in Cycles 1 to 4: In cycle 1, the mean ANC nadir in the XM02 and filgrastim group were 1.7 x 10^9/L and 1.1 x 10^9/L, respectively; p=0.1531. Similar data were observed in cycle 4.

Time to ANC Recovery in Cycles 1 to 4: In cycle 1, the mean time to ANC recovery was similar in the XM02 group (6.0 days) and the filgrastim/XM02 group (6.7 days, p=0.4939). Similar data were observed in cycle 4.

Body Temperature: For all cycles, mean body temperature values over time were similar in the XM02 and filgrastim/XM02 groups, and remained fairly constant during the course of the study.

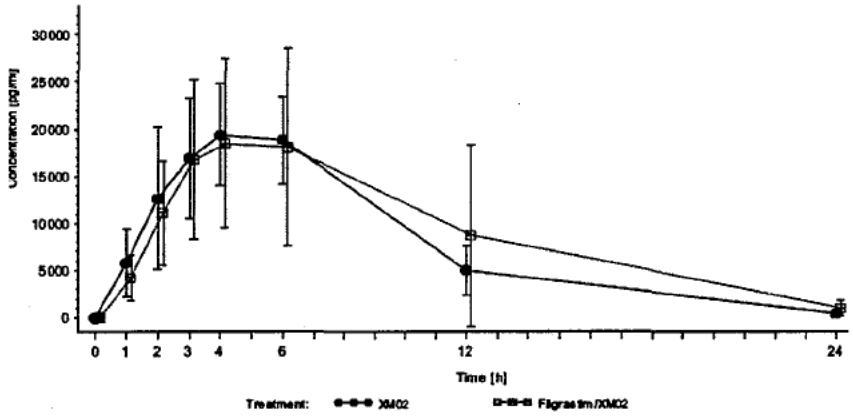
Mortality: In the period until Day 127, 1 patient (filgrastim/XM02 group) died due to disease progression (not reported as AE) 1 month after last study drug in cycle 2.

Pharmacokinetic Results: There were 15 patients in the PK set (11 XM02, 4 filgrastim), the majority of which were male (60%) and all patients were Caucasian. Median age of the patients was 53 years (range: 22 to 76 years). The treatment groups were similar with regard to the demographic characteristics.

In cycle 1 and 4 in both profiles, mean serum concentrations of XM02 and filgrastim (filgrastim administered in cycle 1 only) increased, reaching a maximum at 4 to 6 hours after dosing, and returned to pre-dose values by 24 hours (see figure). Having 4 patients in the Neupogen®/XM02 group resulted in a large variability of PK results in this group. Only patients providing profiles for each of the 4 PK profiles is summarized in the Table (XM02 N=10 of 11, Filgrastim N=2 of 4). Geometric mean (CV%) PK parameters are presented in the table for those patients providing all 4 PK profiles. No accumulation after repeated dosing was observed. Mean serum concentrations for Neupogen were generally lower in cycle 4 than in cycle 1, and this was not related to antibody

formation.

4: Mean (± SD) Serum Concentrations of XM02 and Filgrastim in Cycle 1, First Profile – PK Set



	Cycle 1				Cycle 4			
	First Profile		Second Profile		First Profile		Second Profile	
Parameter	XM02	Neupogen	XM02	Neupogen	XM02	Neupogen	XM02	Neupogen
AUC_{0-24}	187.7	156.9	139.5	216.4	186.5		143.1	102.2
(ng/ml*h)	(23.2)	(6.1)	(44.8)	(24)	(37.9)	82.5 (28.1)	(59.8)	(72.2)
	20.73	19.79	19.57	28.03	20.49		18.01	
C_{max} (ng/ml)	(23.1)	(25.8)	(37.7)	(8)	(40)	8.43 (41.8)	(50.3)	14.57 (81.1)
	5	3.5	4	5	5	4.5	5	3.5
T_{max} (h)*	(2, 6)	(3, 4)	(4, 6)	(4, 6)	(4, 6)	(3, 6)	(4, 6)	(3, 4)
	3.3	3.2		3.0		3.1	3.2	3.3
t½ (h)	(16.7)	(15.4)	3.2 (11.5)	(5.6)	3.0 (10.5)	(6.7)	(8.5)	(4.1)

Note: First profile was on Day 2 of cycle 1; second profile was on the day the ANC $\geq 2 \times 10^9$/L after nadir in cycle 1.
*For Tmax, median (range) is given.

ANOVA of XM02 versus filgrastim showed no significant differences with regard to the relative bioavailability (F) of the 2 drugs in the 1st and 2nd profile of cycle 1 (i.e., geomeans of AUC_{0-12}, AUC_{0-24}, and C_{max} were very similar in the XM02 and filgrastim groups.

Relative bioavailability: ANOVA of XM02 vs. Filgrastim - PK set
Only patients providing all 4 profiles with active drug application

		Geometric Means		Relative bioavailability (XM02/Filgrastim)		
Cycle	Profile	XM02	Filgrastim	Ratio	90% CI	
Derived PK parameter: AUC(0-12) [h*pg/ml]						
Cycle 1	first profile	156055.87	132758.14	1.175	[0.812,	1.702]
	second profile	126764.63	192203.72	0.660	[0.339,	1.285]
Derived PK parameter: AUC(0-24) [h*pg/ml]						
Cycle 1	first profile	187717.62	156859.41	1.197	[0.822,	1.743]
	second profile	139615.80	216405.49	0.645	[0.316,	1.314]
Derived PK parameter: Cmax [pg/ml]						
Cycle 1	first profile	20728.39	19786.08	1.048	[0.703,	1.561]
	second profile	19671.35	28031.51	0.698	[0.384,	1.270]

Based on 1-way ANOVA for log-transformed PK parameter values

Pharmacodynamic Results: See ANC results above.

Safety (Per Applicant)

Across all cycles and within each cycle, there were no statistically significant differences between the treatment groups with regard to the AE profile. The incidence of TEAEs was slightly higher in cycle 1 (66.3%) compared to the other cycles (25.0% to 51.2%).

- Most frequently reported possibly drug related TEAEs were bone pain (9.8%) and arthralgia (4.3%). Possibly drug related TEAEs were experienced early in the study, i.e., they were reported within 20 days after study start, or within 4 days after start of a cycle.
- There were no clinically relevant changes of safety laboratory parameters, vital signs, body weight, or physical examination during the study and no clinically relevant differences between the treatment groups. Overall, there were 2 cases of injection site reactions during the study.

Immunogenicity: No samples could be quantified for IgG after study drug administration, no patients were positive in the BIAcore. No patient was positive for NAB.

Anti-Antibody & Neutralising Antibodies: Only 1 patient (#50-525-02) in the trial who received only XM-02 tested positive in the Western Blot IgG and IgM test at the follow-up visit on day 180. However, this sample could neither be quantified for IgG nor was it tested positive in the BIAcore or NAB, respectively. This patient did not have PK data available. No patient was tested NAB positive during the course of the trial.

		XM02-04 in NHL* (N=92)
Binding Antibodies	Positive for binding antibody at any time in the study	0
	Positive for binding antibody during study follow-up	1 (1.1%)
Neutralizing Antibodies	Positive for neutralizing antibody at any time in the study	0
	Positive for neutralizing antibody during study follow-up	1 (1.1%)

- Patient 50-525-02 (56yo, Caucasian female) Summary: ELISA negative at all visits and Luminex positive at all visits (except before cycle 1 and cycle 3). Western Blot tests confirmed positive IgG and IgM at the antibody follow-up visit with a quantification below LLOQ. The antibody assay at the follow-up visit was positive with an inhibition of 2.8%. The Luminex results were considered implausible because the test was already positive at screening. However, as NAB was positive at the follow-up visit, the results were considered as plausible.
  - This patient had AE's throughout the study (e.g. iron-deficient anema, and, angiospasm of retina, and increased uric acid). These AEs were not considered related to XM02 treatment.

- Clinically, the DSN following Cycles 1 and 4 was 8 and 0 days, respectively. The time to ANC recovery following Cycles 1 and 4 was 8 and 0 days, respectively.

Conclusions

- XM-02 is safe and well tolerated when administered for up to a maximum of 6 cycles of CTX in patients with NHL.
- XM-02 and filgrastim have similar effects with regard to DSN, the incidence of FN, ANC nadir, and the time to ANC recovery in cycle 1 during CTX in patients with NHL.
- XM-02 and filgrastim have a similar PK profile.

4.3 CLINICAL PHARMCOLOGY AND BIOPHARMACEUTICS FILING FORM

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

Office of Clinical Pharmacology and Biopharmaceutics
New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
BLA Number	125294/0	**Brand Name**	Neutroval
OCP Division (I, II, III, IV, V)	OCP DCP5	**Generic Name**	(b) (4)
Medical Division	DBOP	**Drug Class**	G-CSF
OCP Reviewer	Sarah J. Schrieber	**Indication(s)**	Neutropenia
OCP Team Leader	Hong Zhao	**Dosage Form**	300 µg/0.5 ml PFS; 480 µg/0.8 ml PFS
Pharmacometrics Reviewer	n/a	**Dosing Regimen**	5 µg/kg/d
Date of Submission	11/30/09	**Route of Administration**	SC
Estimated Due Date of OCP Review	7/30/10	**Sponsor**	Teva Pharmaceuticals
Medical Division Due Date	8/12/10	**Priority Classification**	Standard
PDUFA Due Date	9/30/10		

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	x			
Tabular Listing of All Human Studies	x			
HPK Summary	x			
Labeling	x			
Reference Bioanalytical and Analytical Methods	x			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	x			
multiple dose:	x	2	2	
Patients-				
single dose:	x			
multiple dose:	x	3	3	
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD -				
Phase 2:				

File name: 5_Clinical Pharmacology and Biopharmaceutics Filing Form/Checklist for NDA_BLA or Supplement 090808

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

Phase 3:	x	3	3	
PK/PD -				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies				
Bio-waiver request based on BCS				
BCS class				
Dissolution study to evaluate alcohol induced dose-dumping				
III. Other CPB Studies				
Genotype/phenotype studies				
Chronopharmacokinetics				
Pediatric development plan	x			
Literature References	x			
Total Number of Studies		5	5	

Filability and QBR comments		
	"X" if yes	Comments
Application filable?	x	Reasons if the application is not filable (or an attachment if applicable) For example, is clinical formulation the same as the to-be-marketed one?
Comments sent to firm?	x	Comments have been sent to firm (or attachment included). FDA letter date if applicable.
QBR questions (key issues to be considered)	What are the PK parameter values in the proposed indicated population? What is the PD profile in the proposed indicated population? What is the immunogenicity rate and does it impact the PK and PD? Is there an exposure-response relationship? Do intrinsic or extrinsic factors impact the PK and PD in the indicated patient population?	
Other comments or information not included above	Email PM request form: Pharmacometrics@fda.hhs.gov	
Primary reviewer Signature and Date		
Secondary reviewer Signature and Date		

On **initial** review of the NDA/BLA application for filing:

	Content Parameter	Yes	No	N/A	Comment
Criteria for Refusal to File (RTF)					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?	x			
2	Has the applicant provided metabolism and drug-drug interaction information?		x		
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?	x			

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4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?	x			
5	Has a rationale for dose selection been submitted?	x			
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?	x			
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	x			
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?	x			
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
	Data				
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	x			
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			x	
	Studies and Analyses				
11	Is the appropriate pharmacokinetic information submitted?	x			
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?	x			
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?	x			
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?			x	
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			x	Deferral requested
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			x	Deferral requested
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?		x		Only healthy PK and PD data included
	General				
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	x			
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?			x	

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE?

Yes

If the NDA/BLA is not fileable from the clinical pharmacology perspective, state the reasons and provide comments to be sent to the Applicant.

File name: 5_Clinical Pharmacology and Biopharmaceutics Filing Form/Checklist for NDA_BLA or Supplement 090808

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/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.

Clinical Pharmacology Information Requests:

1. Conduct the following analyses described in 1a-d below and propose labeling language describing the clinically relevant findings, as appropriate, to replace the currently proposed language summarizing healthy volunteer results (i.e. Label Sections 12.2 and 12.3).
    a. Directly compare the Neutroval pharmacodynamic (PD) results (e.g. ANC, CD34+) from each of the three phase 3 trials and provide a description of similarities and/or differences observed between the three patient populations. Additionally, compare these data to the two phase 1 healthy volunteer trial PD results.
    b. Combine the Neutroval PD data from the three phase 3 trials and provide a summary of PD results for the oncology patient population as a whole. Present the data as geometric mean with standard deviation and median with range as appropriate for individual PD parameters. Include the data file(s) used to generate the results.
    c. Combine the Neutroval pharmacokinetic (PK) data from the three phase 3 trials and provide a summary of PK results for the oncology patient population as a whole. Present the data as geometric mean with coefficient of variation and median with range as appropriate for individual PK parameters. Include the data file(s) used to generate the results.
    d. Evaluate the effect of neutrophil count, and other potential contributing factors, on Neutroval PK (e.g. relationship between neutrophil count and plasma clearance) in each of the 3 oncology patient populations separately, as well as combined, and provide a summary of the findings.
2. Provide a table listing of patients with renal or hepatic impairment included in the BLA submission, organized by trial number. Include available renal and hepatic function parameters such as SCr, CLCr calculated by the Cockcroft Gault equation, LFT, T.Bili, platelet count, etc for each patient in the listing. Also, provide summaries of the following information for each patient: PK and PD data, safety, and clinical efficacy.

Reviewing Clinical Pharmacologist — Date

Team Leader/Supervisor — Date

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