CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125294Orig1s000

PHARMACOLOGY REVIEW(S)

MEMORANDUM

Tbo-filgrastim (Code name XM02)

Date: August 28, 2012
To: File for BLA 125294
From: John K. Leighton, PhD, DABT
Acting Director, Division of Hematology Oncology Toxicology
Office of Hematology and Oncology Products (OHOP)

I have examined pharmacology/toxicology supporting review of Dr. Masson-Henrichs and reproduction toxicology study review conducted by Drs. Khan and Saber, secondary review memoranda provided by Dr. Pilaro and Dr. Saber, and labeling provided by Dr. Saber. I have also examined the consult review provided by the Maternal Health Team dated August 17, 2010. The major scientific nonclinical issues are: using leukocyte growth factor as the Established Pharmacological Class (EPC), consistent with Neulasta; Pregnancy Category C based on the rabbit study; no carcinogenicity studies are needed for the proposed indication; and lack of genotoxicity studies, which are not needed for protein molecules such as tbo-filgrastim. Nonclinical pharmacology and toxicology are described in the Executive Summary provided by Dr. Masson-Henrichs.

In her review dated November 30, 2009, Dr. Masson-Henrichs provided extensive review of available embryo-fetal reproduction toxicology data that she believed could have been used to support product approval, and concluded that this information was sufficient and that additional studies were not needed. It was subsequently determined that this was not correct, and that the Applicant would need to provide an embryo-fetal development study. This decision is based on the nature of the information submitted to this application. I also note that several of the memoranda provided in support of approval of tbo-filgrastim discuss the possibility of a “class labeling” approach. It should be noted that the use of the term “class labeling” does not appear to be appropriate in this case. The Division of Biological Products also consulted the Maternal Health Team (MHT), which concluded that the ICH Guidance S9: Nonclinical Evaluation for Anticancer Products, did not apply to tbo-filgrastim. Dr. Pilaro, in her supervisory memorandum dated September 20, 2010, refers to a requirement to conduct the complete battery of reproduction toxicology studies (fertility, embryo-fetal toxicology, and pre- and post-natal studies). It should be noted that these conclusions were not consistent with the practice that then existed within the Office of Oncology Drug Products. The Office practice was that for patients with advanced, life-threatening disease, a study examining embryo-fetal toxicity would be sufficient to fulfill reproduction toxicology requirements. This remains current practice. As a supportive care product, tbo-filgrastim does not fall within the Scope of ICH S9. However, OHOP may apply the principles of ICH S9 to these

products if the patient population is as described in the Scope of ICH S9, as appropriate. Thus, the conduct of an embryo-fetal toxicology study in a single species, if positive, would be sufficient to fulfill the requirements for assessment of reproduction toxicology and is consistent with OHOP practice, and FDA relied upon the embryofetal toxicity study conducted and submitted by Teva for its assessment of reproduction toxicology for tbo-filgrastim.

The MHT memorandum referenced above refers to the lack of study data in the application at the time and thus shortcomings in information necessary for review of the Pregnancy and Nursing Mothers subsections of the product label. The study usually submitted for oncology products related to these subsections (*vide supra*) has since been submitted and adequately reviewed and described in the labeling by Drs. Khan and Saber; thus no further consult is necessary.

Dr. Masson-Henrichs' review also discussed certain comparative nonclinical studies with a non-US-approved filgrastim product. It should be noted that these studies already had been conducted prior to the pre-BLA meeting with FDA, and FDA reviewed the data provided, but the comparison to the non-US-approved filgrastim product was not necessary or relied upon to support the safety or pharmacology for tbo-filgrastim.

I agree with Dr. Saber's conclusion that tbo-filgrastim may be approved and that no additional nonclinical studies are needed for the proposed indication.

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/s/

JOHN K LEIGHTON
08/28/2012

MEMORANDUM

XM02 (Proprietary and non-proprietary names are not available)

Date: July 27, 2012
To: File for BLA 125294
From: John K. Leighton, PhD, DABT
Acting Director, Division of Hematology Oncology Toxicology
Office of Hematology and Oncology Products

I have examined pharmacology/toxicology supporting review of Dr. Masson-Henrichs and reproduction toxicology study review conducted by Drs. Khan and Saber, secondary review memoranda provided by Dr. Pilaro and Dr. Saber, and labeling provided by Dr. Saber. The major nonclinical issues are: using leukocyte growth factor as the Established Pharmacological Class, consistent with Neulasta; Pregnancy Category C based on the rabbit study; no carcinogenicity studies are needed for the proposed indication; and lack of genotoxicity studies, which are not needed for protein molecules such as XM02. Nonclinical pharmacology and toxicology are described in the Executive Summary provided by Dr Masson-Henrichs.

I agree with Dr Saber's conclusion that XM02 may be approved and that no additional nonclinical studies are needed for the proposed indication.

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/s/

JOHN K LEIGHTON
07/27/2012

MEMORANDUM

Date: July 26, 2012
From: Haleh Saber, Ph.D.
Pharmacology/Toxicology Supervisor
Division of Hematology Oncology Toxicology (DHOT)
Office of Hematology Oncology Products (OHOP)
Re: Approvability for Pharmacology and Toxicology
BLA: 125294
Product: Trade name and non-proprietary name are not available
XM02 is the code name
Indication: 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
Applicant: Teva Pharmaceuticals USA
Submission: Resubmission; 351(a) BLA
Original submission: 11/30/2009

Teva Pharmaceuticals submitted an original 351(a) BLA in 2009 for their version of recombinant human G-CSF (granulocyte colony-stimulating factor). A trade name Neutroval originally proposed by the Applicant was rejected by the Division of Medication Error Prevention and Analysis (DMEPA). The proposed non-proprietary name of (b) (4) was not accepted either. The code name is XM02.

Nonclinical pharmacology and toxicology studies submitted in 2009 were reviewed by Mary Jane Masson-Hinrichs, Ph.D. Except for the lack of an embryofetal developmental study, the nonclinical package was considered to be adequate. On September 29, 2010, a Complete Response letter was issued for this application.

The current submission contains results of an embryofetal developmental toxicology study in rabbits, conducted with XM02. This study adequately addresses the nonclinical deficiency identified in 2010.

In brief, pregnant rabbits were treated with XM02 during the period of organogenesis. The adverse embryofetal effects are consistent with those reported for approved products (e.g. Neupogen) and those reported in published articles for other G-CSF products. Findings in rabbits include: spontaneous abortion, increased post-implantation loss, reduced fetal weight, reduced litter size, and malformations. Adverse findings are most evident at the high dose of 100 µg/kg/day. This dose resulted in significant increases in white blood cells (WBCs) and differentials.

The adverse embryofetal findings occurred in animals at doses that caused maternal toxicity and significant increases in WBCs above the physiological levels. Patients who will be treated with XM02 will be neutropenic. Dosing in patients will stop when the neutrophil counts reach normal physiological values. The adverse embryofetal findings in animals may not be relevant to patients. In addition, adverse embryofetal effects in

rabbits occurred at exposures that are significantly higher than those reported in patients at the recommended dose of 5 μg/kg/day. Therefore, a pregnancy Category C is proposed for XM02. This is also consistent with labeling for drugs belonging to the same class, such as Neupogen and Neulasta.

All nonclinical sections of the label have been updated in the current review cycle. Revisions to the label are based on nonclinical data reviewed in 2009-2010 and results of the toxicology study reviewed in the current review cycle. The pharmacologic class assigned to XM02 is "leukocyte growth factor". This is based on the established pharmacologic class (EPC) for granulocyte colony-stimulating factors, as listed in the table available on the FDA website: http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/ucm162549.htm

Recommendation: XM02 may be approved for the proposed indication. No additional nonclinical studies are needed to support approval of XM02 for the proposed indication.

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/s/

HALEH SABER
07/26/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY BLA REVIEW AND EVALUATION

Application number:	BLA 125294
Supporting documents:	eCTD SN# 0033 Response to Complete Response Letter
Applicant's letter date:	2/29/2012
CDER stamp date:	2/29/2012
Product:	Trade name is not available Non-proprietary name is not available XM02 (code name)
Indication:	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
Applicant:	Teva Pharmaceuticals USA
Review Division:	Division of Hematology Oncology Toxicology
Reviewers:	Imran Khan, Ph.D. Haleh Saber, Ph.D.
Supervisor/Team Leader:	Haleh Saber, Ph.D.
Division Director:	John Leighton, Ph.D.
Project Manager:	Lara Akinsanya, MS

TABLE OF CONTENTS

1 Executive Summary

1.1 Introduction

Teva Pharmaceuticals USA submitted an original 351 (a) BLA on 11/30/2009 for their version of recombinant, human G-CSF. A trade name Neutroval™ originally proposed by the Applicant was recently rejected by the Division of Medication Error Prevention and Analysis (DMEPA). The proposed non-proprietary name of (b) (4) was not accepted (see the Complete Response letter of 9/29/2010 regarding the established name). The code name is XM02. The name XM02 will be used for this product in the current review.

On September 29, 2010, a Complete Response letter was issued for this application. The Following nonclinical deficiency was included in the letter.

> The literature assessment of the potential reproductive toxicity of granulocyte colony stimulating factor(s) provided in support of BLA 125294 does not fulfill the regulatory requirements for nonclinical developmental and reproductive toxicity studies with Neutroval. Your BLA submitted under section 351(a) of the PHS Act may not rely on published literature describing studies of other biological products, including studies regarding a licensed biological product, to fulfill this requirement for approval.
>
> To complete the application for BLA 125294 under the 351(a) pathway, provide the results of a nonclinical embryo-fetal toxicity study conducted with Neutroval in rabbits as a single, pharmacologically responsive species [refer to ICH S9 Nonclinical Evaluation for Anticancer Pharmaceuticals (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm085389.pdf)]. We recommend that you submit a draft protocol for this study as an amendment to the BLA for review and comment by the nonclinical reviewers prior to initiation of this study.

In her Team Leader Memorandum, Dr. Anne Pilaro elaborated on this deficiency and the rationale for the use of the rabbit as the species for a reproduction toxicology study. The following is from Dr. Pilaro's Memorandum dated Aug 6, 2010.

> There were no reproductive or developmental toxicity (DART) studies conducted with XM02 to support safe use of Neutroval™ in pregnancy. The Sponsor's original justification for the absence of DART studies with XM02 was based on the proposed indication, which limits use of Neutroval™ to patients receiving concomitant treatment with myelosuppressive chemotherapy agents with known developmental and reproductive toxicities. Upon review and discussion with FDA/CDER senior management, FDA determined that it would not be ethical to omit communicating the potential developmental and reproductive risks associated with Neutroval™ in the labeling, since the two currently US-licensed recombinant G-CSF products contain this information in the label. As a result of

this discussion, the Sponsor was requested to provide an assessment of the reproductive toxicities associated with Neutroval™ treatment.

The Sponsor provided several published literature articles demonstrating that both filgrastim (i.e. Neupogen®) and lenograstim, a glycosylated G-CSF that is approved for marketing in Japan, have similar abortifacient effects when pregnant rabbits were dosed during the period of organogenesis. Additionally, Dr. Masson-Hinrichs independently found two other published articles regarding another G-CSF product nartograstim, which demonstrated similar abortifacient effects in rabbits, and an article documenting comparable pharmacodynamic responses in cynomolgus monkeys dosed with filgrastim, lenograstim or nartograstim that serves to "bridge" the *in vivo* responses to G-CSF across all three products in this class.

In brief, the rabbit is a pharmacologically relevant species and sensitive to detect reproductive toxicities associated with G-CSF products.

To address the nonclinical deficiency, the Applicant conducted an embryofetal developmental toxicology study in rabbits.

1.2 Brief Discussion of Nonclinical Findings

Pharmacology, safety pharmacology, pharmacokinetic and general toxicology studies supporting the BLA were submitted in 2009 and reviewed by Dr. Masson-Hinrichs. For nonclinical findings related to XM02, see review of the original BLA by Dr. Masson-Hinrichs and the Team Leader Memorandum of Dr. Pilaro.

Only the results of embryofetal toxicology study are discussed in this section.

Reproductive Toxicology
Pregnant rabbits were treated with 1, 10, or 100 µg/kg/day of XM02 during the period of organogenesis (gestation days 6 through 19) and sacrificed on gestation day 29 (GD29). Pharmacologic effect of the drug was observed in the animals. There was a dose-dependent increase in white blood cells and differentials, with the highest increase in the absolute neutrophil counts. The high dose of 100 µg/kg/day resulted in spontaneous abortion in 12 out of 20 females. This high dose was maternally toxic as demonstrated by body weight (BW) loss during the dosing period (GD6 to GD19) and an overall reduced BW gain compared to control animals. In addition, food consumption was significantly reduced at this dose. A literature search indicates similar abortifacient effects with G-CSF products. The dose of 100 µg/kg/day also resulted in the following uterine and embryofetal findings: increased post-implantation loss (due to increased late resorption), reduced fetal weight, reduced litter size, malformations (including malformed hindlimbs and cleft palate).

The exposure (AUC) values were larger on GD6 compared to GD19. This reduction in the exposure may be due to anti-drug antibody (ADA) formation and increased drug

clearance (ADA formation was not measured in this study). As XM02 is expected to be less immunogenic in humans, the GD6 values may be more relevant for the estimation of animal-to-human AUC ratios. Using the AUC on GD6, the adverse embryofetal findings were observed at exposures that were 50-90 fold the exposures observed in patients at the recommended dose of 5 µg/kg/day.

The adverse embryofetal findings occurred in healthy animals. Patients who will be treated with XM02 will be neutropenic. It is expected that dosing in patients will stop when the neutrophil counts reach normal physiological values. Therefore, the adverse embryofetal findings in animals may not be relevant to humans.

A pregnancy Category C is proposed for XM02. This is also consistent with labeling for drugs belonging to the same class.

1.3 Recommendations

1.3.1 Approvability

Recommending approval.

The Applicant has adequately addressed the nonclinical deficiency described in the Complete Response Letter issued in 2010.

1.3.2 Additional Non Clinical Recommendations

None

1.3.3 Labeling

- Based on the data submitted and reviewed, a pregnancy Category C is recommended.
- A separate labeling review will be provided if deemed necessary.

2 Drug Information

2.1 Drug

CAS Registry Number: 121181-53-1

Generic Name: Not yet assigned

Code Name: XM02

Chemical Name/ Other Names: Recombinant N-methionyl human granulocyte colony-stimulating factor (r-metHuGCSF)

Molecular Formula/Molecular Weight: 175 amino acid single-chain polypeptide/approximately 18.8 KDa

Structure or Biochemical Description: see above for the number of amino acids and the molecular weight.

XM02 is a nonglycosylated recombinant methionyl human granulocyte-colony stimulating growth factor (r-metHuG-CSF) manufactured by recombinant DNA technology using the bacterium strain *E coli* K802.

Pharmacologic Class: leukocyte growth factor

2.2 Relevant INDs, NDAs, BLAs and DMFs

103188 (preIND)

2.3 Drug Formulation

Dosage form and strength:
• 300 µg/0.5 mL in single use prefilled syringe
• 480 µg/0.8 mL in single use prefilled syringe

The proposed routes of administration: subcutaneous (b) (4)

The table below describes the constituents of the drug product (DP):

	300 mcg/0.5 mL Syringe	480 mcg/0.8 mL Syringe
Drug	300 mcg	480 mcg
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

[Tables excerpted from the proposed label Section 11 and slightly modified]

2.4 Comments on Novel Excipients

No novel excipients were identified.

2.5 Comments on Impurities/Degradants of Concern

None at this time.

2.6 Proposed Clinical Population and Dosing Regimen

Indication: 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.

Route of administration: Subcutaneous (b) (4)

Recommended dose based on the label: 5 µg/kg/day administered as a subcutaneous injection (b) (4) The first dose should be administered no earlier than 24 hours following myelosuppressive chemotherapy (CTX) (b) (4) .

2.7 Regulatory Background

- A Complete Response (CR) letter issued on 9/29/2010
- Resubmission (response to CR) received: February 29, 2012

3 Studies Submitted

3.1 Studies Reviewed

Reproductive toxicology:

AA99241: XM02 embryo toxicity study by the subcutaneous route in the rabbit

9 **Reproductive and Developmental Toxicology**

Embryofetal Development

Study title: *XM02 - Embryo toxicity study by the subcutaneous route in the rabbit (Segment II).*

Study no.:	AA99241
Study report location:	NA
Conducting laboratory and location:	(b) (4)
Date of study initiation:	January 5 , 2011
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	XM02, 30 MUI/0.5 mL, Y30025L, 98.9 % (based on RP-HPLC).

Key Study Findings

- The high dose of 100 µg/kg/day resulted in spontaneous abortion in 12 out of 20 females. This dose was maternally toxic as demonstrated by body weight (BW)

loss during the dosing period (GD6 to GD19) and an overall reduced BW gain compared to control animals. Reduced food consumption (FC) of 34% was also noted in this group.

- The XM02 dose of 100 µg/kg/day also resulted in the following uterine and embryofetal findings: increased post-implantation loss (due to increased late resorption), reduced fetal weight, reduced litter size, malformations (including malformed hindlimbs/ bone abnormalities, and cleft palate).
- Increases in white blood cells and differentials were observed in all dose groups. Reduced RBCs and associated changes in the RBC indices were seen in mid-dose (MD) and high-dose (HD) animals.
- The NOAEL for maternal toxicity is 1 µg/kg/day based on maternal health (reduced BW gain and FC). The NOAEL for embryo-fetal toxicity is also 1 µg/kg/day based on effects on skeletal malformations.
- Adverse embryofetal effects in animals were mostly evident at HD. This dose results in AUCs that are 50-90 fold the AUCs reported in patients receiving the recommended dose of 5 µg/kg, when using animal AUCs from GD6.

Methods

Doses: 0, 1, 10, and 100 µg/kg/day

Frequency of dosing: Daily from Day 6 to 19 of Gestation inclusive (GD 6-19)
Animals were sacrificed on GD 29

Dose volume: 0.16 mL/kg/day

Route:: Subcutaneous

Formulation/Vehicle: 10 mM sodium acetate pH 4.0, 5 % D-Sorbitol, 0.0025 % polysorbate 80 solution in sterile water for injection.

Species/Strain: New Zealand White rabbit, Crl: KBL (NZW)

Weight: 3-4 kg

Age: 17-19 weeks

Number/Sex/Group: 20 females/group

Satellite groups: 4 females/group

Study design:

Group number	Dose level (µg/kg/day)	Dose volume (mL/kg/day)	Dose concentration (µg/mL)	Number of females	
				Main study	Satellites
1	0	0.16	0	20	4
2	1	0.16	6.2	20	4
3	10	0.16	62	20	4
4	100	0.16	620	20	4

Deviation from protocol: NA

Observations and Results

Mortality

All animals were observed twice daily.

- Compound-related effects on maternal health including abortion (red fluid in the cage prior to aborting) in majority of the pregnant rabbits in the high-dose group (100 µg/kg) resulted in unscheduled sacrifice of 12 out of 20 animals in the main study group and 2 out of 4 in the satellite (TK) group. No other deaths were observed.

Dose	Unscheduled sacrifice	Rationale for euthanizing	Clinical Signs and Observations
0.5	0	-	-
10	0	-	-
100	12/20	Animals aborted (GD 19-27)	BW loss, ↓FC, and red fluid in cage

BW: body weight; FC: food consumption

Clinical Signs

All animals were observed once daily for clinical signs and local reactions to injection. In addition, during the treatment period animals were observed once before and after dosing for abnormal behavior/ reaction to treatment.

- No toxicologically significant finding was observed.

Body Weight

Animals were weighed on days 0, 6, 9, 13, 16, 20, 24 and 29 of gestation.

- While small, body weight loss was seen at high-dose, during the dosing period (GD 6-19): reduction in BW was 20 g or 0.5% of the BW at GD 6.
- Reduced body weight gain was evident at high-dose from GD 0 through GD 29: BW gain was 6% at high-dose and 12% in the control.

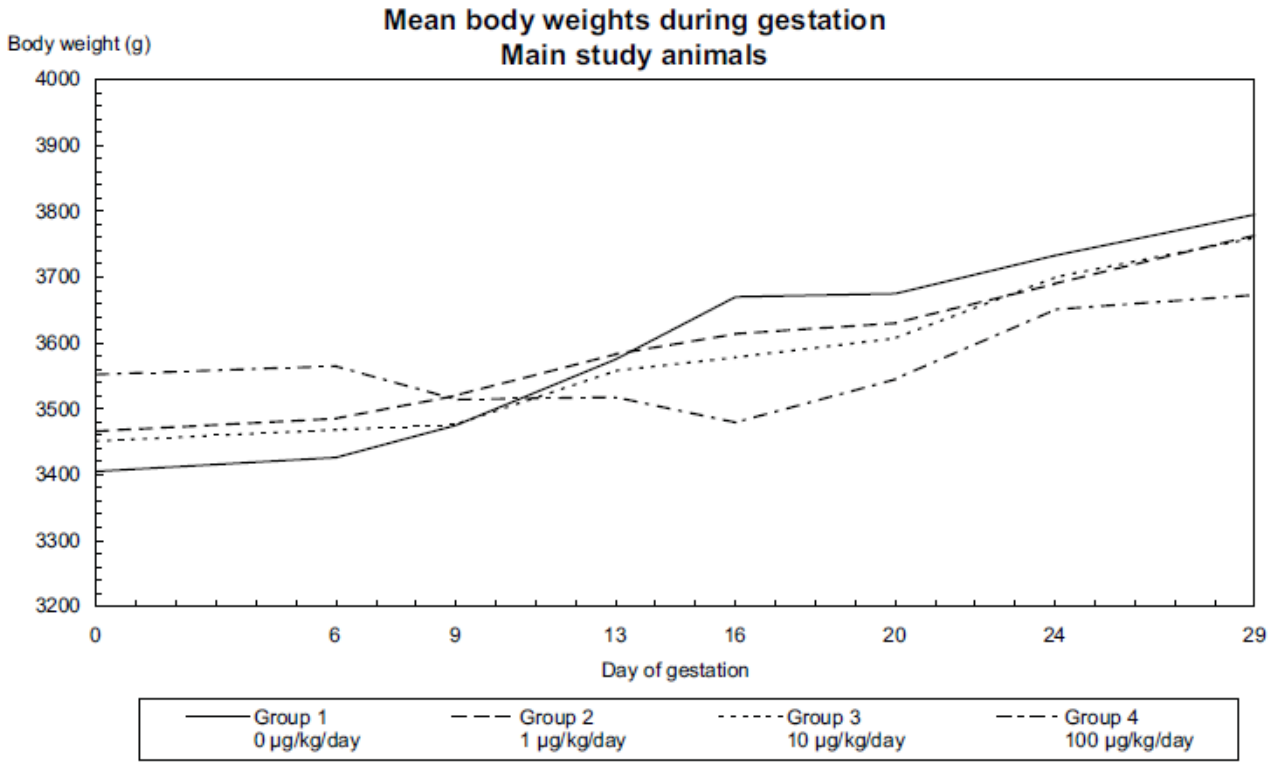


Figure excerpted from the submission.

Food Consumption

Measured daily from the day of arrival of the animals to GD29. Mean values reported for GDs 0-6, 6-9, 9-13, 13-16, 16-20, 20-24 and 24-29.

- Reduced during treatment period (GDs 6-19): ↓18 % at 10 µg/kg/day and ↓34% at 100 µg/kg/day, when compared the control group.
- Effect was reversible when dosing stopped (GD 20-29).

Hematology and additional blood sampling and analysis:

For hematology blood samples (0.5 mL) were collected via the ear artery from all manually restrained unanesthetized main study females on GD 1, 19 and 29 into tubes containing EDTA. Another 1 ml volume of blood was collected similarly from the same animals on the above 3 specific days of treatment into tubes containing no anticoagulants.

- In the 10 and 100 µg/k/day groups a dose-related reduction in RBC counts and related changes in RBC indices were observed on GD19 as compared to control group and pre-test values. Platelets were reduced in all dose groups.

- There was also a dose-related increase in the mean total white blood cells in all dose groups as compared to controls and pre-test values on GD19 ((i.e. approximately 2-fold at 1 µg/kg/day, 4-fold at 10 µg/kg/day, and 6-fold at 100

µg/kg/day compared to the control group). The effect was the result of increase in all white blood cells subsets in the treated groups as compared to controls and pretest values (see Tables below). The highest increase was in the absolute neutrophil counts.

- Findings were reversible during the non-dosing period (GD 20-29).

Group mean hematology parameters
Day: 19 relative to Start Date

Group	RBC	% Δ	Hb	% Δ	PCV	% Δ	MCVfL	% Δ	MCH pg	% Δ	MCHC	% Δ	Reti.(%)	% Δ	Plat.	% Δ
	T/L		g/L		%		fL		pg		g/L		%		Giga/L	
1	6.08		126.70		38.70		63.78		20.87		327.30		5.58		600.30	
2	6.14	1.07	126.10	-0.47	38.59	-0.28	62.99	-1.24	20.58	-1.39	326.80	-0.15	5.26	-5.73	491.7**	-18.09
3	5.61*	-7.77	117.5**	-7.26	35.78**	-7.55	64.05	0.42	21.06	0.91	328.70	0.43	4.87	-12.72	346.3**	-42.31
4	5.35**	-11.90	108.9**	-14.05	32.88**	-15.04	61.64*	-3.36	20.39	-2.30	330.90	1.10	4.33**	-22.40	329.8**	-45.06

% Δ - percent change compared to group 1 (control)

RBC: red blood cell; Hb: hemoglobin; PCV: packed cell volume; MCV: mean corpuscular volume; MCH: mean corpuscular hemoglobin; MCHC: mean corpuscular hemoglobin concentration; Reti: reticulocytes; Plat: platelets.

Group mean hematology parameters
Day: 19 relative to Start Date

	WBC	% Δ	N.Abs.	% Δ	N (%)	% Δ	L.Abs.	% Δ	L (%)	% Δ	M.Abs.	% Δ	M (%)	% Δ
Group	Giga/L		Giga/L		%		Giga/L		%		Giga/L		%	
1	7.59		1.27		16.84		5.60		73.90		0.18		2.28	
2	17.13**	125.70	8.99**	605.65	52.07**	209.20	6.85**	22.33	40.45**	-45.26	0.44**	147.46	2.56	12.28
3	32.91**	333.62	22.98**	1704.00	65.82**	290.86	7.56**	34.97	26.75**	-63.80	1.18**	563.84	3.8**	66.67
4	44.74**	489.47	31.97**	2409.34	68.72**	308.08	8.85**	58.05	22.64**	-69.36	1.61**	809.04	3.62**	58.77

% Δ - percent change compared to group 1 (control)

Group mean hematology parameters
Day: 19 relative to Start Date

	E.Abs.	% Δ	E (%)	% Δ	B.Abs.	% Δ	B (%)	% Δ	LUC.Abs	% Δ	LUC (%)	% Δ
Group	Giga/L		%		Giga/L		%		Giga/L		%	
1	0.16		2.17		0.35		4.54		0.02		0.27	
2	0.31**	90.24	1.79**	-17.51	0.50**	40.96	2.89**	-36.34	0.04	79.17	0.22	-18.52
3	0.38**	134.15	1.17**	-46.08	0.66**	87.29	2.02**	-55.51	0.16**	562.50	0.47**	74.07
4	0.52**	216.46	1.17**	-46.08	1.42**	302.26	3.09**	-31.94	0.37**	1450.00	0.78**	188.89

% Δ - percent change compared to group 1 (control)

WBC: while blood cells; N: neutrophils; L: lymphocytes; M: monocytes.
E: eosinophils; B: basophils; LUC: large unstained cells.
Abs: absolute count.

Although it was indicated in the report (methods and experimental design) that blood samples were collected for anti-drug antibody (ADA) analysis, the result was not reported. In response to an information request for the missing results, the Sponsor indicated that analysis was not performed as they deemed that data from such ADA analysis would have no bearing on the interpretation of the results. Although the ADA analysis would provide useful information and possible explanations for the decrease in $AUC_{0\text{-}24h}$ from GD6 to GD19, the Sponsor's response is acceptable.

Toxicokinetics

Blood (0.5 ml) was collected from each of the 4 animals/group at predose, 0.5 (30 minutes), 1, 2, 4, 8, 12 and 24 hours post-dose on the first and last treatment days (i.e. days 6 and 19 of gestation, respectively).

- The maximum serum concentrations were generally observed between 2 and 4 hours after dosing. The increase in systemic exposure was linear and markedly more than dose-proportional between the low-dose (0.529 µg/kg) and 100 µg/kg on GD6, but non-linear and less than dose-proportional between the low-dose (0.498 µg/kg) and 100 µg/kg on GD19.

- No accumulation of XM02 was observed; on the contrary, $AUC_{0\text{-}24h}$ was 3- to 42-fold lower on GD19 than on GD6.

Mean toxicokinetic parameters of XM02 on day 6 of gestation (G6)

Dose (µg/kg/day)		C_{max} (ng/mL)	T_{max}# (h)	$AUC_{0\text{-}24h}$ (ng.h/mL)	$AUC_{0\text{-}inf}$ (ng.h/mL)	$t_{1/2}$ (h)	Cl/F (L/h)/kg	Vd/F (L/kg)
0.529§	Mean	3.31	4	31.6	30.7	3.18	0.0175	0.0809
	SD	0.575	NA	5.10	4.68	0.626	0.00250	0.0236
	CV%	17.4	NA	16.1	15.2	19.7	14.3	29.2
	n	4	4	3	4	4	4	4
10	Mean	67.7	4	970	1008	4.33	0.0101	0.0629
	SD	12.8	NA	130	NA	NA	NA	NA
	CV%	18.9	NA	13.4	26.8¤	5.13¤	26.8¤	21.8¤
	n	3	3	3	2	2	2	2
100	Mean	1470	2	16345	18000	6.66	0.00558	0.0531
	SD	36.1	NA	564	1328	1.32	0.000397	0.00652
	CV%	2.45	NA	3.45	7.38	19.8	7.11	12.3
	n	3	3	3	3	3	3	3

Print date: 30 March 2011

For T_{max}, median values were calculated instead of the mean
§ actual dose level was taken into account (nominal dose level = 1 µg/kg/day)
¤ As n = 2, delta percent was calculated instead of SD and CV.

Mean toxicokinetic parameters of XM02 on day 19 of gestation (G19)

Dose (µg/kg/day)		C_{max} (ng/mL)	T_{max} # (h)	AUC_{0-24h} (ng.h/mL)
0.498§	Mean	1.04	2	4.03
	SD	0.332	NA	NA
	CV%	31.8	NA	NA
	n	4	4	1
10	Mean	11.9	2	107
	SD	10.8	NA	NA
	CV%	90.6	NA	53.2¤
	n	3	3	2
100	Mean	218	1	406
	SD	NA	NA	NA
	CV%	NA	NA	NA
	n	1	1	1

Print date: 30 March 2011

For T_{max}, median values were calculated instead of the mean
§ actual dose level was taken into account (nominal dose level = 1 µg/kg/day)
¤ As n = 2, delta percent was calculated instead of SD and CV.

Animal-to-human AUC ratios

Geometric Means of AUC Following a Subcutaneous Injection of 5 mcg/kg of XM02 to Healthy Volunteers (01 and 05) or Cancer Patients (02, 03 and 04):

Volunteers and Cancer Patients	AUC* [ng/mL*h]
Phase I study XM02-01-LT	158.45
Phase I study XM02-05-DE	157.58
Phase III study XM02-02-INT	305.3
Phase III study XM02-03-INT	272.48
Phase III study XM02-04-INT	183.49

*AUC0-t in phase I studies, where t = 48 hours; AUC 0-24, in phase III studies
Note: in phase III studies, results are from first injection in first chemotherapy cycle

Data in rabbits			Animal:Human* AUCs	
Dose (µg/kg/day)	**AUC (ng/mL*h) GD6**	**AUC (ng/mL*h) GD19**	**Based on GD6 data**	**Based on GD19 data**
1	31.6	4.0	NA	NA
10	970	107	3-5	0.4-0.5
100	16345	406	50-90	1-2

* AUC data in patients are used as they are deemed more relevant for the labeling.

Dosing Solution Analysis

Samples of 3 mL were taken from each daily preparation at all concentrations, including the control group, and were stored at room temperature until analysis or at approximately -20 °C, if not used, until completion of the study acceptance criteria for analytical results for each group are defined as follows: concentration results were considered acceptable if the difference between the actual mean value and the targeted concentration was 15 %. Results obtained outside of the criteria were considered Out of Specification.

- Although the actual intermediate and high dose groups concentration of XM02 were in agreement with nominal concentrations, the nominal concentration for the 1 μg/kg/day group deviated by approximately 50% (-50.2% to -47.1%) from the actual concentration of 6.2 μg/mL. As a result, in the low-dose group, the actual doses on G6 and G19 were 0.529 μg/kg/day and 0.4988 μg/kg/day, respectively.

Necropsy

Any aborting animals (on the day of abortion) and all surviving animals were sacrificed by sodium pentobarbitone injection and exsanguination. They were dissected and examined for macroscopic pathological changes to determine their pregnancy status, number of corpora lutea, numbers and types of implantations as well as the number and distribution of live fetuses, number and distribution of embryonic / fetal death, individual fetal weights and sex.

- In the 100 μg/kg/day XM02-treated group, two aborting females showed dark areas on the lungs and one of them also had uncollapsed lungs and kidney with mottled appearance.

Cesarean Section Data (Implantation Sites, Pre- and Post-Implantation Loss, etc.)

All fetuses were examined for external defects and sacrificed by sodium pentobarbitone (i.p.). The fetuses were examined viscerally. Heads of approximately half of the fetuses were removed and placed in Harrison's fluid for later examination following sectioning. Ossified fetus skeleton was stained with Alizarin red. The skeletal and fixed visceral exams were performed under low power magnification.

- Pregnancy indices and pre-implantation data were comparable among the various groups. There were 18/20, 20/20, 19/20 and 5/8 pregnant females at terminal caesarean section (G29) in groups 1 to 4, respectively. All of these females had viable fetuses. The remaining 12 females in the 100 μg/kg/day group were pregnant, but aborted during the study.

SUMMARY OF CAESAREAN SECTION DATA

		Group 1 Control 0 mcg/kg/day	Group 2 Low dose 1 mcg/kg/day	Group 3 Intermed. dose 10 mcg/kg/day	Group 4 High dose 100 mcg/kg/day
Pregnant	N	18	20	19	5
Dams with no Viable Fetuses	N	0	0	0	0
Dams with Viable Fetuses	N	18	20	19	5
Corpora Lutea	TOTAL	191	220	225	62
No. per animal	MEAN	10.6 d	11.0	11.8	12.4
	S.D.	1.5	1.7	2.2	3.2
Implantation Sites	TOTAL	168	198	203	53
No. per animal	MEAN	9.3 d	9.9	10.7	10.6
	S.D.	2.4	1.9	2.3	3.6
Preimplantation Loss	TOTAL	23	22	22	9
No. per animal	MEAN	1.3 d	1.1	1.2	1.8
	S.D.	1.7	1.3	1.5	0.8
% per animal	MEAN%	12.6 k	9.9	9.5	15.4
	S.D.	19.2	10.7	12.2	7.6
Live Fetuses	TOTAL	160	190	183	27
No. per animal	MEAN	8.9 d	9.5	9.6	5.4**
	S.D.	2.5	2.0	1.8	2.8
Males	TOTAL	78	90	90	11
	MEAN%	48.8 k	47.8	50.3	45.0
	S.D.	13.6	13.8	16.0	37.1
Females	TOTAL	82	100	93	16
	MEAN%	51.2 k	52.2	49.7	55.0
	S.D.	13.6	13.8	16.0	37.1

Statistical key: d=Anova/Dunnett test k=Kruskal-Wallis/Dunn test ** = p<0.01

Note: females in all groups had viable fetuses. However, 12 females in the 100 micg/kg/day group were pregnant but aborted during the study.

- Post-implantation loss was approximately 50% in 100 µg/kg/day group, which also had a markedly lower litter size. The post-implantation loss appears to be due to increased late resorption in the high-dose group. In the 10 µg/kg/day the post-implantation loss was slightly higher (8.9%) than the control (4.9%) but did not reach a statistically significant level. In addition, the post-implantation loss in the historical control group was 9.5%. Hence, the 8.9% post-implantation loss at MD is not considered drug-related.

SUMMARY OF CAESAREAN SECTION DATA

		Group 1 Control 0 mcg/kg/day	Group 2 Low dose 1 mcg/kg/day	Group 3 Intermed. dose 10 mcg/kg/day	Group 4 High dose 100 mcg/kg/day
Postimplantation Loss	TOTAL	8	8	20	26
No. per animal	MEAN	0.4 k	0.4	1.1	5.2**
	S.D.	0.9	0.6	1.1	3.2
% implants per animal	MEAN%	4.6 k	4.0	8.9	48.4**
	S.D.	9.0	5.8	9.1	26.6
Dead Fetuses	TOTAL	0	0	0	0
No. per animal	MEAN	0.0 k	0.0	0.0	0.0
	S.D.	0.0	0.0	0.0	0.0
% of implants per animal	MEAN%	0.0 k	0.0	0.0	0.0
	S.D.	0.0	0.0	0.0	0.0
Resorptions: Early	TOTAL	6	2	6	7
No. per animal	MEAN	0.3 k	0.1	0.3	1.4
	S.D.	0.6	0.3	0.7	2.6
% of implants per animal	MEAN%	3.4 k	1.0	2.9	15.6
	S.D.	5.8	2.9	6.4	29.0
Resorptions: Late	TOTAL	2	6	14	19
No. per animal	MEAN	0.1 k	0.3	0.7	3.8*
	S.D.	0.5	0.6	0.9	3.7
% of implants per animal	MEAN%	1.2 k	3.0	6.0	32.8**
	S.D.	5.2	5.6	7.5	27.8

Statistical key: k=Kruskal-Wallis/Dunn test * = p<0.05 ** = p<0.01

Offspring (Malformations, Variations, etc.)

- There was dose-dependent decrease in fetal body weight in all treatment groups; however, the decrease in the 1 and 10 μg/kg/day groups were not significantly different from the historical control values. The decrease in the 100 μg/kg/day group was about 50% compared to the control group.

SUMMARY OF CAESAREAN SECTION DATA

		Group 1 Control 0 mcg/kg/day	Group 2 Low dose 1 mcg/kg/day	Group 3 Intermed. dose 10 mcg/kg/day	Group 4 High dose 100 mcg/kg/day
Fetal Body Weight (g)	MEAN	38.6 d	35.7	34.0*	21.9**
	S.D.	5.7	4.8	3.2	7.3
	N	18	20	19	5
Male Fetuses	MEAN	39.2 d	35.5	34.5*	26.1**
	S.D.	6.0	4.9	3.2	8.1
Female Fetuses	MEAN	38.2 d	35.8	33.7*	19.2**
	S.D.	6.2	5.4	4.2	5.8

Statistical key: d=Anova/Dunnett test * = p<0.05 ** = p<0.01

- Malformations of the fetuses were evident for both external and visceral observations. The malformations included open eyes, malformed hindlimbs associated with bone abnormalities and cleft palate in the 100 μg/kg/day group. Malformations were not observed in the LD group; however, a fetus in the 10 μg/kg/day group (0.78%) had major abnormalities including open eyes and

malformed hindlimbs consistent with findings in the high dose group; a statistical significance was not reached at MD.

- The higher incidence of embryo-fetal death (average litter size of 5.4 fetuses compared with 8.9 in the control) in the surviving 5 females of the high dose group together with reduced fetal weight (21.9 g compared with 38.6 g in the control) and a high incidence of both major and less severe fetal abnormalities in the majority of fetuses appear to be consistent with the higher abortion rate in the treated animals.

- Consistent with low mean fetal weight and the severe skeletal malformations, a higher percentage of the fetuses in the 100 μg/kg/day group showed reduced ossification of several bones affecting the skull, pelvis, sternum and paws as compared to the concurrent control and historical control data. Slightly reduced ossification was also noted for a few bones in the 10 μg/kg/day group with no similar findings in the 1 μg/kg/day group.

Summary of skeletal anomalies

Finding with % of affected fetuses	Historical control data 2009	Group 1 Control	Group 2 1 µg/kg/day	Group 3 10 µg/kg/day	Group 4 100 µg/kg/day
Number of fetuses	3917	160	190	183	27
Number of fetal heads	2063	84	101	99	13
Incomplete ossification					
Paws					
Tarsal	1.4	1.3	2.1	3.3	**40.7**
Phalanx, forepaw	1.3	1.9	2.1	**7.7**	**66.7**
Phalanx, hindpaw	1.9	4.4	1.6	3.3	**55.6**
Metacarpal, 2^{nd} to 5^{th} digits	0.0	0.0	0.5	1.1	**29.6**
Sternebra					
2^{nd} / 4^{th}	5.3	3.1	4.7	4.9	**51.9**
1^{st} / 3^{rd}	0.7	1.3	2.1	0.5	**25.9**
Skull					
Interparietal	0.8	0.0	0.0	1.0	**15.4**
Frontal	0.0	0.0	0.0	0.0	**23.1**
Squamosal	0.0	0.0	0.0	0.0	**23.1**
Hyoid	16.0	8.3	13.9	**23.2**	**69.2**
Maxilla	0.0	0.0	0.0	0.0	23.1
Pelvis					
Pubis	2.5	2.5	4.7	**8.2**	**25.9**

Summary of skeletal anomalies (cont'd)

Finding with % of affected fetuses	Historical control data 2009	Group 1 Control	Group 2 1 µg/kg/day	Group 3 10 µg/kg/day	Group 4 100 µg/kg/day
Number of fetuses	3917	160	190	183	27
Number of fetal heads	2063	84	101	99	13
Unossified					
Paws					
Metacarpal, 1st digit	8.8	7.5	5.8	9.3	**74.1**
Phalanx, forepaw 1st or 5th digit	8.5	18.1	14.7	**26.2**	**92.6**
Phalanx, forepaw	0.4	0.0	0.0	1.1	**59.3**
Phalanx, hindpaw	1.0	2.5	0.0	2.7	**70.4**
Sternebra					
5th	17.5	4.4	14.2	11.5	**22.2**
6th	4.1	3.1	3.7	4.4	**11.1**
Pelvis					
Pubis	0.2	1.3	1.1	0.5	**18.5**

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

/s/

HALEH SABER
07/26/2012

MEMORANDUM

Neutroval

Date: September 29, 2010
To: File for BLA 125294
From: John K. Leighton, PhD, DABT
Associate Director for Pharmacology/Toxicology
Office of Oncology Drug Products

I have examined pharmacology/toxicology supporting review by Dr. Henrichs and supervisory memorandum provided by Dr. Pilaro for Neutroval, and the subsequent addenda. I concur with their conclusions regarding the adequacy of the pharmacology and toxicology for Neutroval and the recommendations for reproduction toxicology testing. A labeling review has not been conducted.

MEMORANDUM

TO: The file
CC: Patricia Keegan, M.D., Director, Division of Biologic Oncology Products, Office of Oncology Drug Products (OODP), Center for Drug Evaluation and Research (CDER)
FROM: Anne M. Pilaro, Ph.D, Supervisory Toxicologist, Pharmacology/Toxicology Branch, Division of Biologic Oncology Products, OODP, CDER

Sept 29, 2010

STN BLA #: 125294/000
SPONSOR: Teva Pharmaceuticals
PRODUCT: Neutroval™ (tentative, non-proprietary name (b) (4); recombinant, human granulocyte colony stimulating factor [G-CSF])
SUBMISSION TYPE: original BL A application (351(a) pathway); **addendum to initial secondary review document**

DATE: September 29, 2010

SYNOPSIS AND RECOMMENDATION:

The purpose of this addendum to the secondary review of the pharmacology/toxicology data for Teva Pharmaceuticals' biologic licensing application is to document my concurrence with Dr. Masson-Hinrichs' final recommendation that the biologics licensing application for Neutroval™ not be approved for marketing, and be issued a "Complete Response" letter documenting the nonclinical deficiency. Specifically, Teva Pharmaceuticals will be required to conduct an embryo-fetal developmental toxicity study in a single pharmacologically responsive species, to obtain the necessary information to convey the reproductive and developmental risks of Neutroval™ treatment in the product labeling. The rabbit is recommended by Dr. Masson-Hinrichs as the pharmacologically responsive species in which to conduct this testing; the scientific justification for this recommendation is based on literature reports that the rabbit demonstrates abortifacient effects after dosing with other granulocyte colony stimulating factors, while the rat does not. A summary of the findings on which this justification is based is documented in Dr. Masson-Hinrichs' primary review. I also concur with Dr. Masson-Hinrichs' proposed nonclinical language to convey this deficiency to the Sponsor, as documented in the September 20, 2010 addendum to her initial primary review.

A copy of Dr. Masson-Hinrichs' addendum to her primary review, with supervisory sign-off, has been conveyed to the regulatory project manager for inclusion in the final action package. Final language for Section 8.1 (Special Populations: Use in Pregnancy) of the labeling for Neutroval™ has not yet been conveyed to the sponsor, pending their submission and subsequent FDA review of the nonclinical data to address this deficiency.

MEMORANDUM

TO: The file

FROM: Mary Jane Hinrichs, Ph.D, Staff Fellow, Division of Biologic Oncology Products (DBOP), Office of Oncology Drug Products (OODP)

THROUGH: Anne M. Pilaro, Ph.D, Supervisory Toxicologist, DBOP, OODP

BLA #: 125294

SPONSOR: Teva Pharmaceuticals

PRODUCT: Neutroval®; XM02, recombinant granulocyte colony stimulating-factor (GCS-F)

SUBMISSION TYPE: Addendum to nonclinical review following the final decision that product-specific literature cannot be relied upon to support a 351(a) BLA requirement for DART data

DATE: September 29, 2010

SYNOPSIS:

This addendum to the original nonclinical review for BLA #125294 is being written to document that the nonclinical discipline's recommendation for approvability of BLA #125294 is **complete response** following final decision by the Biosimilars Implementation Committee (BIC) that product-specific literature cannot be relied upon to support a 351(a) BLA requirement for DART data. The regulatory history that led to this decision is as follows:

The original BLA submission for Neutroval® did not contain the results of developmental and reproductive toxicity (DART) studies conducted with XM02 to convey the potential developmental and reproductive risks associated with Neutroval® in the drug label. In response to an FDA request to provide an assessment of the potential reproductive toxicity of Neutroval as an amendment to the Biologics Licensing Application, the sponsor submitted a literature-based assessment of the reproductive toxicities associated with other G-CSF receptor agonists to support a 'class-labeling' approach. While it was determined that the reproductive toxicities associated with recombinant G-CSF products, primarily an abortifacient effect, were well-characterized and consistent within the class, final decision regarding the permissibility of using these findings to support a 351(a) BLA requirement for DART data had not been made at the time of the PDUFA goal date for primary BLA reviews. As a result, the finalized primary nonclinical review for Neutroval® did not include a nonclinical recommendation for the

approvability of BLA #125294. On September 7, 2010, the BIC made their final decision that product-specific literature cannot be used in support of a 351(a) BLA requirement for DART data. As a result, the nonclinical recommendation for approval of BLA #125294 is **complete response**.

The OCC-revised nonclinical comment to be relayed to the Sponsor is as follows:

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

To complete the application for BLA 125294 under the 351(a) pathway, provide the results of a nonclinical embryo-fetal toxicity study conducted with Neutroval™ in rabbits as a single, pharmacologically responsive species [refer to ICH S9 Nonclinical Evaluation for Anticancer Pharmaceuticals (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm085389.pdf)]. FDA recommends that Teva submit a draft protocol for this study as an amendment to the BLA for review and comment by the nonclinical reviewers prior to initiation of this study."

This comment was forwarded to the regulatory project manager for inclusion in the CR letter on September 29, 2010.

MEMORANDUM

TO: The file

FROM: Mary Jane Hinrichs, Ph.D., Staff Fellow, Division of Biologic Oncology Products (DBOP), Office of Oncology Drug Products (OODP)

Mary Jane Hinrichs 9/20/2010

THROUGH: Anne M. Pilaro, Ph.D., Supervisory Toxicologist, DBOP, OODP

A M Pilaro 9/20/2010

BLA #: 125294

SPONSOR: Teva Pharmaceuticals

PRODUCT: Neutroval®; XM02, recombinant granulocyte colony stimulating-factor (GCS-F)

SUBMISSION TYPE: Addendum to nonclinical review following the final decision from FDA Office of Chief Counsel and CDER Office of Regulatory Policy that product-specific literature cannot be relied upon to support a 351(a) BLA requirement for DART data

DATE: September 20, 2010

SYNOPSIS:

This addendum to the original nonclinical review for BLA #125294 is being written to document that the nonclinical discipline's recommendation for approvability of BLA #125294 is **complete response** following final decision from FDA regulatory counsel that product-specific literature cannot be relied upon to support a 351(a) BLA requirement for DART data. The regulatory history that led to this decision is as follows:

The original BLA submission for Neutroval® did not contain the results of developmental and reproductive toxicity (DART) studies conducted with XM02 necessary to convey the potential developmental and reproductive risks associated with Neutroval® in the drug label. In response to an FDA request to provide an assessment of the potential reproductive toxicity of Neutroval as an amendment to the Biologics Licensing Application, Teva Pharmaceuticals submitted a literature-based assessment of the reproductive toxicities associated with other G-CSF receptor agonists, to support a 'class-labeling' approach. The nonclinical discipline determined that based on the available literature data the reproductive toxicities associated with recombinant G-CSF products, primarily an abortifacient effect, were well-characterized and consistent within the class. However, final decision regarding the permissibility of using these findings to

support a 351(a) BLA requirement for DART data had not been made by FDA regulatory counsel at the time of the PDUFA goal date for primary BLA reviews. As a result, the finalized primary nonclinical review for Neutroval® did not include a nonclinical recommendation for the approvability of BLA #125294.

On September 7, 2010, FDA regulatory counsel communicated to the Division that product-specific literature cannot be used in support of a 351(a) BLA requirement for DART data. As a result, the nonclinical recommendation for approval of BLA #125294 is now to issue a **complete response** letter, and request that Teva conduct the appropriate nonclinical studies to obtain the necessary data for labeling.

Prior to communicating the need for additional DART studies to the Sponsor in the CR letter, advice was sought from the CDER Office of New Drugs Maternal Health Team (MHT) regarding the types of nonclinical DART studies required to communicate the developmental risks associated with Neutroval® in the label. The MHT responded that since Neutroval® is intended for use as a supportive care agent, it does not fall within the scope of the ICH S9 guidance relating to the Nonclinical Evaluation for Anticancer Pharmaceuticals. Therefore, the MHT stated the appropriate guidances to follow are the ICH S5(R2) (Detection of Toxicity to Reproduction for Medicinal Products) and ICH S6 (Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals) guidances. In accordance with the S5(R2) and ICH S6 guidances, Teva Pharmaceuticals must conduct the full battery of DART studies to evaluate the potential effects of Neutroval® on fertility, as well as embryo-fetal and pre/post-natal development.

The revised nonclinical comment to be relayed to the Sponsor is as follows:

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

To complete the application for BLA 125294 under the 351(a) pathway, provide the results from the complete battery of fertility, embryo-fetal and pre/post-natal nonclinical developmental toxicity studies conducted with Neutroval™ in pharmacologically responsive species [refer to ICH S5(R2): *Detection of Toxicity to Reproduction for Medicinal Products* (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm074950.pdf) and ICH S6 (R1): *Preclinical Evaluation of Biotechnology-Derived Pharmaceuticals* (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM194490.pdf)]. FDA recommends that Teva submit draft

protocols for these studies as an amendment to the BLA for review and comment by the nonclinical reviewers prior to initiation of these studies."

This comment was forwarded to the regulatory project manager for inclusion in the CR letter on September 20, 2010.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY BLA REVIEW AND EVALUATION

Application number:	125294
Supporting document/s:	0000
Applicant's letter date:	November 30, 2009
CDER stamp date:	November 30, 2009
Product:	Non proprietary name not yet assigned
Indication:	(b) (4) by febrile neutropenia, in cancer patients receiving myelosuppressive anti-cancer drugs associated with a clinically significant incidence of severe neutropenia (b) (4)
Applicant:	Teva Pharmaceuticals
Review Division:	Division of Biologic Oncology Products
Reviewer:	Mary Jane Masson Hinrichs, Ph.D. 8/9/10
Supervisor/Team Leader:	Anne M. Pilaro, Ph.D. 8/9/10
Division Director:	Patricia Keegan, M.D.
Project Managers:	Danyal Chaudhry
	Erik Laughner

Template Version: December 7, 2009

Disclaimer

Except as specifically identified, all data and information discussed below and necessary for approval of STN BLA #125294 are owned by Teva Pharmaceuticals or are data for which Teva Pharmaceuticals has obtained a written right of reference. Any information or data necessary for approval of STN BLA #125294 that Teva Pharmaceuticals does not own or have a written right to reference constitutes one of the following: (1) published literature, or (2) a prior FDA finding of safety or effectiveness for a listed drug, as described in the drug's approved labeling. Any data or information described or referenced below from a previously approved application that Teva Pharmaceuticals does not own (or from FDA reviews or summaries of a previously approved application) is for descriptive purposes only and is not relied upon for approval of STN BLA #125294.

TABLE OF CONTENTS

Table of Tables

Table of Figures

1 Executive Summary

1.1 Recommendations

1.1.1 Approvability

At the time this review is completed, the nonclinical discipline's recommendation for approval of BLA 125294 is pending decision by the Office of Chief Counsel (OCC) and the Center Director regarding use of information in the literature to assess the potential developmental and reproductive risks associated with recombinant granulocyte colony stimulating factor use.

In the event that it is deemed inappropriate to use this information to support approval of Neutroval™, the nonclinical recommendation for BLA 125294 will be **complete response**.

1.1.2 Additional Non Clinical Recommendations

In the event that it is deemed inappropriate to use literature information to communicate the potential developmental and reproductive risks of granulocyte colony stimulating factor (Refer to Section 1.1.1) in the label, the Sponsor will be requested to perform an embryo-fetal toxicity study in a single species to assess the developmental and reproductive toxicities of Neutroval™.

DRAFT Comment to be relayed to Sponsor in the CR letter

"The literature assessment of the potential reproductive toxicity of Neutroval™ provided by Teva in support of BLA 125294 is not sufficient to fulfill the regulatory requirements for nonclinical developmental and reproductive toxicity studies with Neutroval™. A BLA submitted under the 351(a) pathway cannot rely on published literature, including publications regarding a licensed biologic product without written authorization from the license holder of that BLA, to fulfill a requirement for approval.

To complete the application for BLA 125294 under the 351(a) pathway, provide the results of a nonclinical embryo-fetal toxicity study conducted with Neutroval™ in a single, pharmacologically responsive species, as outlined in ICH S9 Nonclinical Evaluation for Anticancer Pharmaceuticals (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm085389.pdf). FDA recommends that Teva submit a draft protocol for this study as an amendment to the BLA for review and comment by the nonclinical reviewers prior to initiation of this study."

1.1.3 Labeling

The nonclinical section of the label cannot be completed until a decision by OCC has been made regarding use of literature to communicate the potential developmental and reproductive risks of Neutroval™ (Refer to Section 1.1.1).

1.2 Brief Discussion of Nonclinical Findings

Neutroval™ (tentative nonproprietary name (b) (4) code name XM02) is a recombinant methionyl human granulocyte colony stimulating factor (G-CSF) intended for use in patients undergoing myelosuppressive chemotherapy to decrease the incidence of febrile neutropenia, a serious hematologic toxicity characterized by fevers and low neutrophil counts (i.e. neutropenia). It is identical to the non-glycosylated form of naturally-occurring G-CSF, with the exception of the addition of an N-terminal methionine necessary for expression in *Escherichia coli*. As proof of concept, primary pharmacology studies demonstrated that XM02 binds to the G-CSF receptor with high affinity and mimics the effects of endogenous G-CSF by stimulating the in vivo proliferation of neutrophils.

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

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

There were no developmental and reproductive toxicology studies conducted with XM02. The Sponsor's proposed justification for the absence of these studies was based on the clinical indication, which limits use of Neutroval™ to cancer patients receiving concomitant therapy with anti-cancer agents with known reproductive and developmental risks. Upon review of this justification, it was determined that it would be unethical not to communicate the potential reproductive and developmental risks associated with Neutroval™, since there are currently two US-licensed, recombinant G-CSF products that contain information in the label regarding potential abortifactient effects. The Sponsor was therefore requested to "...provide an assessment of the potential reproductive toxicity of Neutroval as an amendment to the Biologics Licensing Application." In response to this request, the Sponsor submitted a literature-based assessment of the reproductive toxicities associated with other G-CSF receptor agonists to support a 'class-labeling' approach. Upon review of the submitted literature, it was determined that the developmental and reproductive toxicities associated with recombinant G-CSF products, primarily an abortifacient effect, were well-characterized and consistent within the class. Therefore, in the event that it is deemed permissible to use this information to support a BLA, a class labeling approach to communicate the developmental and reproductive risks of Neutroval™ is acceptable from the nonclinical perspective.

2 Drug Information

2.1 Drug

2.1.1 CAS Registry Number (Optional)

121181-53-1

2.1.2 Generic Name

Not yet assigned

Comment: This issue will be addressed in an addendum once the non-proprietary name has been finalized.

2.1.3 Code Name

XM02

2.1.4 Chemical Name

Recombinant N-methionyl human granulocyte colony-stimulating factor (r-metHuG-CSF)

2.1.5 Molecular Formula/Molecular Weight

175 amino acid single-chain polypeptide/approximately 18.8 KDa

2.1.6 Structure

Figure 1 Amino acid sequence of XM02

(Extracted from eCTD 3.2.S.1.2, page 3)

2.1.7 Pharmacologic class

Leukocyte growth factor

2.2 Relevant IND/s, NDA/s, and DMF/s

pIND 103188

2.3 Clinical Formulation

2.3.1 Drug Formulation

Neutroval™ for injection will be supplied in pre-filled syringes in strengths of 0.3 and 0.48 mg [redacted] It is formulated as an [redacted] (pH 4.2), sterile, [redacted] solution containing sorbitol [redacted] and polysorbate 80 ([redacted]

2.3.2 Comments on Novel Excipients

None

2.3.3 Comments on Impurities/Degradants of Concern

None

2.4 Proposed Clinical Population and Dosing Regimen

The proposed indication for Neutroval™ is to [redacted] y febrile neutropenia, in patients with cancer receiving myelosuppressive anti-cancer drugs associated with a clinically significant incidence of severe neutropenia [redacted].

The recommended dose is 5 μg/kg/day Neutroval™ [redacted] following treatment with myelosuppressive chemotherapy for cancer. Neutroval™ is intended for the subcutaneous (SC) route of administration.

2.5 Regulatory Background

BLA 125294 was submitted to the Agency in the absence of a pre-existing IND, as all clinical trials were conducted outside of the USA.

The first communication between the Agency and the Sponsor regarding Neutroval™ occurred during a preIND/preBLA meeting held on November 28, 2009. At this meeting, the Sponsor requested the Agency's advice on the adequacy of the filgrastim development program to support a BLA in the United States. The Agency informed the Sponsor that although the nonclinical development program appeared to be acceptable, the adequacy of the data to support approval would be a review issue. The Sponsor was also provided with the following advice regarding nonclinical developmental and reproductive toxicity testing of XM02:

"...the BLA (and any future BLA) should address the potential developmental and reproductive toxicity of XM02. If nonclinical developmental and reproductive toxicity data are not provided as part of the initial registration package, their absence should be

scientifically justified. Please be aware that Teva cannot rely up on proprietary nonclinical data submitted to another BLA to support the safety of XM02 without written authorization from the license holder of that BLA. FDA advises that if a BLA is submitted for an indication that would include treatment of patients at risk for reproductive or developmental toxicity, and if the BLA lacks sufficient information regarding developmental and reproductive toxicity following exposure to XM02, then full nonclinical reproductive and developmental toxicity testing in pharmacologically responsive species will be required."

3 Studies Submitted

3.1 Studies Reviewed

Study Title	Study #	GLP	EDR Location
Pharmacology			
Comparative study of the binding of XM02 and Neupogen® to the G-CSF receptor	CIR060314	No	4.2.1.1.1.
Receptor binding assay evaluated using a cell-based bioassay	RDR006	No	4.2.1.1.1.
Neupogen® receptor binding assay evaluated using a cell-based bioassay	RDR007	No	4.2.1.1.1.
An efficacy assessment of XM02 and Neupogen® in a cyclophosphamide (CPA)-induced neutropenic mouse model	590162	No	4.2.1.1.1.
An efficacy assessment of XM02 and Neupogen® in a CPA-induced neutropenic mouse model	590207	No	4.2.1.1.1.
Safety Pharmacology			
An acute SC injection toxicity study with modified Irwin Screen and a 14-day observation of XM02 in rats	500077	Yes	4.2.1.3.1.
A pharmacological assessment of the effect of XM02 on the respiratory system of rats	690032	Yes	4.2.1.3.1.
A cardiovascular profile study following a single SC injection of XM02 in the unrestrained conscious Beagle dog	690033	Yes	4.2.1.3.1.
Pharmacokinetics (PK)			
PK study of XM02 in the Sprague Dawley rat following daily SC injections for 4 weeks	460021	Yes	4.2.2.2.1.
PK study of XM02 after single intravenous (IV) or SC administration in Cynomolgus monkeys	16207-02	Yes	4.2.2.2.1.
28-day immunological comparison of XM02 vs. Neupogen® by daily SC administration to rats interrupted by a 2-week treatment-free period	19332-05	Yes	4.2.2.2.1.

Study Title	Study #	GLP	EDR Location
Toxicology			
26-week SC injection study toxicity study (with a 4-week interim study) in rats	500108	Yes	4.2.3.2.1.
26-week SC injection toxicity study (with a 4-week interim study) in Cynomolgus monkeys	500109	Yes	4.2.3.2.1.
Other Toxicology			
Vein and tissue irritancy study of XM02 in male New Zealand White rabbits	500536	Yes	4.2.3.6.1.
Vein and tissue irritancy study of XM02 and Neupogen® in the rabbit	501717	Yes	4.2.3.6.1.
Investigation of the effect of XM02 on human malignant cell lines	Spd-0-01	No	4.2.1.2.1.

3.2 Studies Not Reviewed

None

3.3 Previous Reviews Referenced

None

4 Pharmacology

4.1 Primary Pharmacology

Neutroval™ (XM02) is a recombinant methionyl human G-CSF intended to reduce the risk of febrile neutropenia in cancer patients receiving myelosuppressive chemotherapy. Clinical trials with Neutroval™ demonstrated a significant decrease in the duration of severe neutropenia (i.e. abnormally low neutrophil counts), a well-established surrogate endpoint for febrile neutropenia (Meza et al., 2002) in this patient population.

Neutrophils are derived from myeloid progenitor cells in the bone marrow, which proliferate and differentiate into granulocytes upon activation of cell surface receptors for G-CSF (Metcalf and Nicola 1983). They are the most abundant cells of the innate immune response, forming the first line of defense against bacteria and other foreign invaders in an antigen non-specific manner. Severe neutropenia, a serious hematologic toxicity commonly associated with myelosuppressive chemotherapy in cancer patients (Cappozzo, 2004), results in highly increased susceptibility to infections.

As evidence of XM02's biologic activity, the Sponsor submitted data demonstrating that XM02 binds to the G-CSF receptor with high affinity (Study# CIR060314), stimulates the in vitro proliferation of murine granulocyte progenitor cells (Study# RDR006 and

RDR007), and increases absolute neutrophil counts in an in vivo neutropenic mouse model (Study# 590162 and 590207).

Binding Affinity to G-CSF Receptor (Study# CIR060314)
EDR 4.2.1.1.1.
The binding affinity of XM02 (Lot# P05-002; a clinical lot) to the human G-CSF receptor was assessed in vitro using BIACORE technology. Recombinant G-CSF (Neupogen®, European Union [EU]-sourced) was used as a positive control. Testing was conducted under nonGLP conditions by (b) (4) Briefly, recombinant human G-CSF receptor was convalently linked to the matrix of the BIACORE biosensor chip and the relative binding affinities (K_D) of XM02 and Neupogen® were evaluated in real time by injecting 0, 8, 31, 125, and 500 nM XM02 or Neupogen® over the immobilized G-CSF receptor. The K_D of XM02 and Neupogen® were 27 nM and 34 nM (CV 16%), respectively.

In Vitro Proliferation Bioassay (Study# RDR006 and RDR007)
EDR 4.2.1.1.1.
The in vitro biological activity of XM02 was assessed in two independent nonGLP studies (conducted by Sicor Biotech UAB, Lithuania) using a cell-based proliferation assay. Recombinant G-CSF (Neupogen®, EU-sourced) was included as a positive control. Briefly, murine (b) (4) cells expressing cell surface G-CSF receptors were incubated with serial dilutions of XM02 or Neupogen® for 48 hours. Proliferation was quantified using the Cell Titer Aqueous Proliferation Assay (Promega, Madison WI). In the first experiment, the average EC_{50} for XM02 (Lot# P-05-005) and Neupogen® were 14.9 and 14.4 pM, respectively, and the concentrations of XM02 and Neupogen® required to induce maximal cell proliferation were 23.2 and 23.8 pM, respectively. In the second experiment, the average EC_{50} were calculated using multiple lots of XM02 [Lot# 010301, 020301, 030301, P3-010302E, P3-020302E, P3-040402, P3-030401, P3-020401; none were the clinical lot]. In this experiment, the average EC_{50} of XM02 and Neupogen® were 5.71 and 5.73 pM, respectively, and the concentrations of XM02 and Neupogen® required to induce maximal cell proliferation response were 10.89 and 10.37 pM, respectively.

In Vivo Efficacy Assessment of XM02 and Neupogen® in a Cyclophosphamide (CPA)-Induced Neutropenic Mouse Model (Study# 590162 and 590207)
EDR 4.2.1.1.1.
The in vivo biologic activity of XM02 (Lot#P04-025; similar to clinical lot as per communication with the CMC reviewer) was assessed in a neutropenic Balb/c mouse model in two independent nonGLP studies performed by (b) (4) (b) (4) Recombinant G-CSF (Neupogen®, EU-sourced) was included as an active control in both studies. Briefly, male mice were rendered neutropenic by intraperitoneal (IP) injections of 100 mg/kg CPA twenty four hours prior to study initiation. On days 1 to 5, mice (n=6) received daily SC injections of 0, 0.1, 0.2, 0.5, 1, 2, or 5 μg/kg/day XM02 or Neupogen®. In vivo proliferation of neutrophils was assessed by determining absolute neutrophil counts on days 3 and 5. Animals were

also monitored for mortality, signs of ill health, and body weights throughout the experiment.

A large percentage of the day 3 blood samples from Study# 590162 were unusable due to excessive clotting during blood collection. The experiment was repeated in Study# 590207; however, the difficulties in blood collection were not overcome and a large percentage of the day 3 blood samples were also unusable. As a result, absolute neutrophil counts could only be determined on day 5. On this day, dose-dependent increases in neutrophil counts were observed in mice treated with XM02 or Neupogen® without any significant differences in potency between the two agents. The lowest pharmacologically active dose of either agent was 2 μg/kg and the maximal pharmacodynamic (PD) effect was observed at 5 μg/kg. No unscheduled deaths or abnormal clinical signs occurred in either experiment.

4.2 Secondary Pharmacology

No secondary pharmacology studies were submitted in the BLA.

4.3 Safety Pharmacology

GLP safety pharmacology studies were conducted to assess the potential toxicological effects of a single SC injection of 3500 μg/kg XM02 on the nervous, cardiovascular, and respiratory systems of rats and Beagle dogs. There were no significant toxicological findings in any of the studies. Study details are outlined below.

Neurological Effects

An Acute Subcutaneous Injection Toxicity Study Using a Modified Irwin Screen with XM02 in the Albino Rat (Study# 500077)

EDR 4.2.1.3.1.

The objective of this study was to evaluate the potential toxicological effects of XM02 on the central nervous systems of Sprague Dawley (SD) CD® rats using a modified Irwin Screen test. In this GLP study (performed by (b) (4) (b) (4) 8 to 10 week-old male and female SD CD® rats (8/sex/group main study animals with an additional 9/sex/group satellite toxicokinetic [TK] animals) were treated with a single SC injection of 0 (vehicle control) or 3500 μg/kg XM02 (Lot # 020301; similar to clinical lot as per communication with the CMC reviewer) followed by a 14-day observation period. A blinded modified Irwin Screen test was performed pretreatment and at 1, 2, 4, 24, and 48 hours post XM02 treatment to assess the following endpoints:

- Body temperature
- Body position
- Restlessness
- Writhing
- Stereotypic behavior
- Convulsions and tremors
- Grooming
- Pupil size
- Respiratory rate/pattern
- Locomotor activity level
- Defecation/urination
- Escape response
- Lacrimation
- Salivation
- Righting reflex
- Cutaneous blood flow
- Corneal reflex
- Pinna reflex
- Tail pinch
- Auricular startle
- Positional passivity

- Ease of Removal
- Gait
- Palpebral closure
- Diarrhea
- Body tone
- Straub tail
- Vocalization
- Geotropism
- Piloerection

Rats were also evaluated for mortality, clinical signs, body weights, hematology, clinical chemistry, urinalysis, and TK throughout the study. At necropsy, macroscopic observations were recorded, as well as microscopic observations of a limited number of tissues, including heart, liver, kidneys, lungs, spleen, bone and marrow and any gross lesions.

There were no findings of neurotoxicity as assessed by the modified Irwin Screen test. XM02 treatment had no effects on mortality, clinical signs, or body weight, nor did it result in any macroscopic or microscopic changes. The only XM02-related effects were an approximate 2.5- and 3.5-fold increase in monocyte and neutrophil counts, respectively. TK analysis demonstrated adequate exposure to XM02 during the study, with a mean C_{max} and $AUC_{0\text{-}inf}$ of approximately 25,000 ng/mL and 175,000 ng*h/mL, respectively.

Pulmonary Effects

A Pharmacological Assessment of the Effect of XM02 on the Respiratory System of the Albino Rat (Study# 690032)

EDR 4.2.1.3.1.

The objective of this study was to evaluate the potential toxicological effects of XM02 on the respiratory systems of albino rats using 'head out' volume displacement plethysmography. In this GLP study (performed by (b) (4) (b) (4) 7 week-old male albino rats (6/group) were treated with a single SC injection of 0 (vehicle control) or 3500 μg/kg XM02 (Lot # 020301; similar to clinical lot as per communication with the CMC reviewer) followed by a 24-hour observation period. Pulmonary effects were determined using 'head out' volume displacement plethysmographs to measure tidal volume, respiratory rate, and derived respiratory minute volume [RMV] continuously starting 15 minutes prior to dosing and ending 4 hours post dose. Additional 15-minute measurements were taken at 6 and 24 hours. Rats were also evaluated for mortality, clinical signs, and body weights throughout the study.

No respiratory effects were observed during the 24-hour observation period. There were also no effects on mortality, clinical signs, or body weights.

Cardiovascular Effects

A Cardiovascular Profile Study Following a Single Subcutaneous Injection of XM02 in the Unrestrained Conscious Beagle Dog (Study# 690033)

EDR 4.2.1.3.1.

The objective of this GLP study (performed by (b) (4) was to evaluate the potential cardiovascular effects of XM02 in male beagle dogs using telemetry. Briefly, 7 to 8 month-old male dogs were subjected to a surgical procedure to insert telemetry monitoring catheters into the left ventricle, pulmonary

artery, and abdominal aorta, which were held in place with a specialized jacket for the duration of the experiment. Following an overnight recovery period of at least 16 hours, conscious, unrestrained dogs (3/group) were treated with a single SC injection of 0 (vehicle control) or 3500 μg/kg XM02 (Lot # 020301) followed by a 48-hour observation period. Cardiovascular effects were determined by taking six-lead electrocardiogram (ECG) recordings at 4 time points in the 90-minute pre-dosing period, and then again at 5, 15, 30, 60 minutes and 2, 3, 4, 6, 8, 12, 14, 16, 24, and 48 hours post dosing. ECG recordings were read by a board-certified cardiologist to determine the effects of XM02 on the RR, PR, QRS, QT, ST, and QTc intervals. Other cardiovascular endpoints included systemic blood pressure, left ventricular pressure, contractility, pulmonary artery pressure, heart rate, cardiac output, stroke volume, and body temperature. Dogs were also evaluated for mortality and clinical signs throughout the study.

No cardiovascular effects were observed during the 48 hour observation period. There were also no effects on mortality or clinical signs.

5 Pharmacokinetics/ADME/Toxicokinetics

5.1 PK/ADME

Pharmacokinetics of XM02 in the Male SD Rat Following Daily Subcutaneous Injections for 4 Weeks (Study# 460021)

EDR 4.2.2.2.1.

The objective of this GLP study (performed by (b) (4) was to determine the pharmacokinetic (PK) profile of XM02 (Lot# 020301) in male SD rats after 28-days of repeat dosing. Briefly, rats (4/timepoint) received daily SC injections of 0.5 mg/kg XM02 for a total of 28 days. On days 1 and 28, serial blood samples were collected pre-dose and at 0.5, 1, 2, 3, 4, 5, 6, 8, 10, 12, and 24 hours post-dose to evaluate XM02 plasma concentration by ELISA. PK parameters (C_{max}, t_{max}, AUC, and $t_{1/2}$) were calculated using the standard software program WinNonlin (v 3.2). Rats were also evaluated for mortality, clinical signs, and body weights throughout the study.

Results:

Day	T_{max} (h)	C_{max} (ng/mL)	$AUC_{0\text{-}inf}$ (ng*h/mL)	$T_{1/2}$ (h)
1	1	5213	18779	2.1
28	1	5261	18462	3.1

Similar C_{max} and AUC values on days 1 and 28 demonstrate little to no accumulation of XM02 after repeat dosing. XM02 also had no effects on mortality, clinical signs, or body weights.

Pharmacokinetic Study of XM02 after Single Intravenous or Subcutaneous Administration to Cynomolgus Monkeys (Study# 16207/02)

EDR 4.2.2.2.1.

The objective of this GLP study (performed by (b) (4)) was to determine the PK and pharmacodynamic (PD) profile of XM02 after a single SC or IV injection of 800 μg/kg XM02 in cynomolgus monkeys (3/group). Serial blood samples were collected at 0, 5, 15, and 30 minutes and then at 1, 2, 4, 8, 24, 30, and 48 hours post-dose, with the exception that no 5 minute sample was collected from SC-treated animals. The plasma concentration of XM02 was determined by ELISA. PK parameters (C_{max}, t_{max}, AUC, and $t_{1/2}$) were calculated using TopFit 2.0 software. Monkeys were also evaluated for mortality, clinical signs, body weights, and hematology throughout the study.

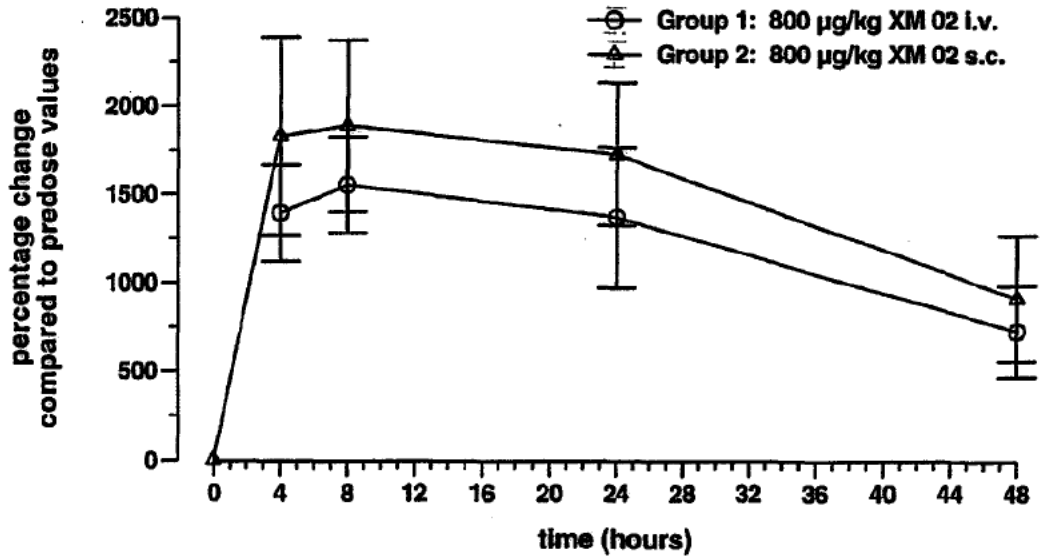
Results:

Route of Admin	T_{max} (h)	C_{max} (ng/mL)	$AUC_{0\text{-}inf}$ (ng*h/mL)	$T_{1/2}$ (h)
IV	0.1	19133	44815	2.6
SC	4	3083	35611	3.4

As expected, peak plasma values (C_{max}) and total exposure ($AUC_{0\text{-}inf}$) were approximately 6- and 1.25-fold lower following SC administration than after the IV route of administration, respectively. Despite the differences in exposure, there were no statistically significant differences in neutrophil counts between the two routes of administration (Figure 2). No mortalities, clinical signs, or body weight effects were observed during the study.

Figure 2: Increase in absolute neutrophil counts following a single IV or SC injection of XM02 in Cynomolgus monkeys

(Extracted from Study Report# 16207/02, page 21)



A 28-Day Immunological Comparison of XM02 vs. Neupogen® by Daily Subcutaneous Administration to Rats Interrupted by a Two-Week Treatment-Free Period (Study# 19332-05)

EDR 4.2.2.2.1.

The objective of this GLP study (performed by (b) (4) was to compare the PK and PD profile of XM02 (Lot# P05-002; clinical lot) vs. a comparator recombinant G-CSF product (Neupogen®; EU-sourced) in male and female SD rats. An assessment of the relative immunogenicity of the two recombinant G-CSF products was included as a secondary objective.

Comment: Discussion of the relative immunogenicity of XM02 and Neupogen® in rats will be limited to the effects of anti-drug antibodies on exposure (AUC) and PD endpoints, as it is not possible to extrapolate findings of immunogenicity in animals to the clinical setting.

The dosing schedule of 4-weeks daily treatment interrupted by a 2-week drug free period was chosen to mimic the intended clinical schedule. Briefly, rats (20/sex/group for PD analysis; 7/sex/group for PK analysis) were treated with daily SC injections of 0, 5, 25, or 125 μg/kg XM02 or Neupogen® at a dose volume of 1 mL/kg for 2 weeks followed by a 2-week drug free period. After the rest period, daily SC injections were resumed for another 2 weeks, followed by a 2-week recovery period prior to euthanization. Serial blood samples were collected at 0, 0.3, 1, 2, 4, 8, 12, and 24 hours post-dose to determine XM02 plasma concentration by ELISA. PK parameters (C_{max}, AUC, and $t_{1/2}$) were calculated using TopFit 2.1 software. Anti-drug antibodies (ADA) were assessed on days 28 and 56 by ELISA. Rats were also evaluated for mortality, clinical signs, body weights, food consumption, ophthalmology, clinical chemistry, urinalysis, and hematology during the study.

The PK profiles of XM02 and Neupogen® were highly similar (

Figure 3), with comparable C_{max}, AUC, and $t_{1/2}$ values at all dose levels (Tables 1 and 2). In addition, both drugs exhibited a dose-proportional increase in exposure, and there were no significant differences between the PK profiles of male and female rats.

Table 1: PK parameters of XM02 in rats after daily SC dosing

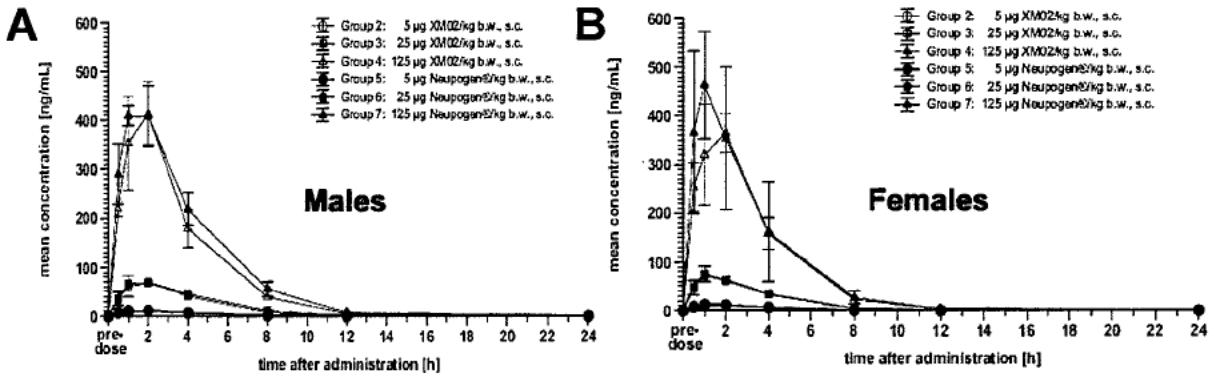
Dose (μg/kg)	Day	Sex	C_{max} (ng/mL)	$t_{1/2}$ (h)	AUC (0-tlast) (ng*h/mL)	AUC/dose
5	1	M	10.9	2.45	52.6	10.5
		F	13.3	2.29	39.8	8.0
25	1	M	68.0	2.26	326.1	13.0
		F	72.8	1.66	287.6	11.5
125	1	M	413.4	2.65	1743.6	13.9
		F	365.4	1.49	1488.8	11.9
5	42	M	11.0	1.06	43.5	8.7
		F	12.9	1.47	34.6	6.9
25	42	M	73.1	1.16	312.2	12.5
		F	69.2	1.29	277.0	11.1
125	42	M	452.6	1.28	2107.2	16.9
		F	584.7	1.26	2327.2	18.6

Table 2: PK parameters of Neupogen® in rats after daily SC dosing

Dose (μg/kg)	Day	Sex	C_{max} (ng/mL)	$t_{1/2}$ (h)	AUC (0-tlast) (ng*h/mL)	AUC/dose
5	1	M	11.8	1.89	52.9	10.6
		F	11.6	1.15	48.7	9.7
25	1	M	69.6	1.86	328.8	13.2
		F	75.5	1.63	284.4	11.4
125	1	M	409.7	1.89	1961.1	15.7
		F	463.7	1.43	1659.0	13.3
5	42	M	12.4	1.89	44.1	8.8
		F	6.9	1.34	30.8	6.2
25	42	M	77.0	1.68	264.3	10.6
		F	77.2	1.06	304.8	12.2
125	42	M	390.6	1.53	1565.1	12.5
		F	546.8	1.08	2199.0	17.6

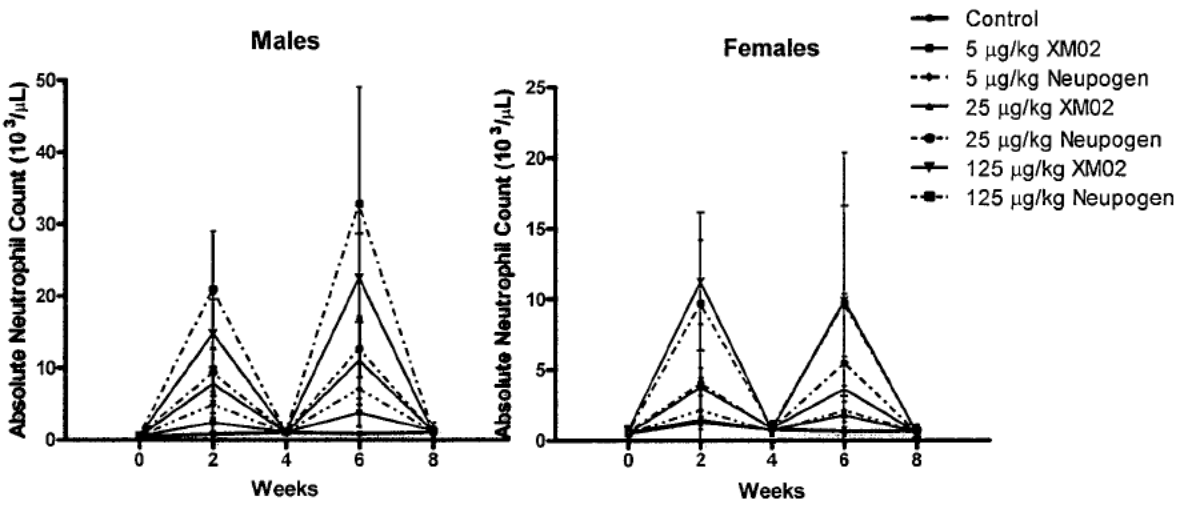
Figure 3: Plasma concentrations of XM02 and Neupogen® in rats after a single SC injection

(Extracted from Study Report# 19332-05, page 77)



In general, the PD effects of XM02 and Neupogen® were highly similar (Figure 4) as there were no significant differences in absolute neutrophil counts within dose levels. In addition, dose-dependent increases in absolute neutrophil counts were observed with both drugs. There was also an approximately 2-fold greater increase in absolute neutrophil counts in male rats than in female rats after treatment with either drug; however, these sex-related differences were not due to differences in exposure (Tables 1 and 2).

Figure 4: Increase in absolute neutrophil counts following daily treatment with XM02 or Neupogen® in rats



There were no treatment-related mortalities or clinical signs during the study. There were also no effects on body weights, food consumption, ophthalmology, or urinalysis.

All toxicological findings were similar in XM02- and Neupogen®-treated rats. Hematological findings consisted of reversible, dose-dependent increases in neutrophil (Figure 4) and monocyte counts (~ 2-fold), as well as a slight decrease in platelets (up to ~15%) in the absence of corresponding effects on platelet function (i.e. thromboplastin time [TPT] or activated partial thromboplastin time [aPTT]). Other toxicological findings were reversible increases in alkaline phosphatase (ALP) levels (~ 2-fold) and increased spleen weights (~ 50%) in high dose animals.

While ADA were detected in XM02- and Neupogen®-treated rats at all dose levels (Table 3), these antibodies did not appear to affect exposure to either drug as indicated by consistent AUC values (Tables 1 and 2) and absolute neutrophil counts (Figure 4).

Table 3: Incidence of ADA in XM02- and Neupogen®-treated rats

(Extracted from Study Report# 19332-05, page 79)

	5 µg/kg/day XM02	25 µg/kg/day XM02	125 µg/kg/day XM02	5 µg/kg/day Neupogen ®	25 µg/kg/day Neupogen ®	125 µg/kg/day Neupogen ®	Vehicle
Pre-dose	0/40 (0%)	0/40 (0%)	0/40 (0%)	0/40 (0%)	0/40 (0%)	0/40 (0%)	0/40 (0%)
TD 28	3/40 (7.5%)	8/40 (20.0%)	6/40 (15.0%)	4/40 (10.0%)	7/40 (17.5%)	13/39 (33.3%)	0/40 (0%)
TD 56	7/39 (17.9%)	9/40 (22.5%)	7/40 (17.5%)	4/40 (10.0%)	9/39 (23.1%)	15/38 (38.5%)	0/40 (0%)

TD test day

6 General Toxicology

6.1 Single-Dose Toxicity

No single-dose toxicity studies were conducted with XM02.

6.2 Repeat-Dose Toxicity

Study title: A 26-Week Subcutaneous Injection Toxicity Study (with a 4-Week Interim Study) in the Albino Rat

Study no.:	500108
Study report location:	EDR 4.2.3.2.1.
Conducting laboratory and location:	(b) (4)
Date of study initiation:	12-May-2003
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	XM02, Lot# 020301 and P3-010303, 99.8

and 100.9% pure, respectively. Both lots were deemed similar to the clinical lot by the CMC reviewer, Dr. Jee Chung.

Key Study Findings

Findings of severe joint pain and limited use of hind limbs and/or paws secondary to enlarged joints, with histological findings of granulocytic infiltrates and hyperostosis resulted in a significant number of mortalities (12/60) in the high dose group. The other major toxicities associated with XM02 treatment were moderate-to-severe bone marrow hypercellularity, marked splenic extramedullary hematopoiesis, decreased body weight and food consumption, as well as increased spleen weights, ALP, neutrophils, and monocytes. These toxicities were dose-dependent, reversible, and related to the exaggerated pharmacology of G-CSF receptor agonists.

The MTD in this study was 50 μg/kg.

Methods

Doses:	0 (vehicle control), 5, 50, and 500 μg/kg/day
Frequency of dosing:	Daily
Route of administration:	SC
Dose volume:	0.48 mL/kg/day
Formulation/Vehicle:	Sterile buffered solution containing 0.6 mg/mL acetic acid, 50 mg/mL sorbitol, and 0.025 mg/mL polysorbate 80
Species/Strain:	Rat/Sprague-Dawley CD®
Number/Sex/Group:	20
Age:	8-10 weeks
Weight:	265-327 g (males); 196-244 g (females)
Satellite groups:	*Recovery animals*: 10/sex/group (control and high dose only) *4-week interim animals*: 10/sex/group (control and high dose only)
Unique study design:	An interim assessment of toxicity was performed at 4-weeks
Deviation from study protocol:	No significant deviations from protocol

Observations and Results

Mortality

The following animals were euthanized in moribund condition, with the exception of #4029(*) who was found dead during week 4 of the recovery period:

Dose Group	Animal # *(Week of Euthanization)*	
	Male	**Female**
Mid dose	3011 *(21)*	
High dose	4017 *(7)*, 4026 *(11)*, 4014 *(12)*, 4009 *(16)*, 4020 *(17)*, 4005 *(21)*, 4006 *(21)*, 4008 *(21)*, 4022 *(22)*, 4016 *(25)*, 4029* *(30)*	4623 *(19)*

All 13 animals listed above exhibited clinical signs of severe pain related to swollen, red hind limbs and paws. Histological findings of marked granulocytic infiltrations in articular surfaces and surrounding soft tissue of the bone suggest that these findings are related to exaggerated pharmacological effects of G-CSF treatment.

There was also the premature euthanization of a single low dose female rat (#2519) during week 17 due to low neutrophil counts (0.4 x $10^3/\mu L$). Corresponding high ADA titers suggested that the low neutrophil counts were likely related to the formation of neutralizing anti-G-CSF antibodies. There were no adverse clinical signs, loss of body weight, or histological findings at the time of death.

The following 5 animals died due to complications associated with blood collection:

Control: 1 female rat (#1521)
Low dose: 2 female rats (#2508 and 2514)
Mid dose: 1 female rat (#3506)
High dose: 1 female rat (#4502)

Clinical Signs

Clinical signs	Weeks 0 to 4			Weeks 5 to 26			Recovery Period		
	5 µg/kg	50 µg/kg	500 µg/kg	5 µg/kg	50 µg/kg	500 µg/kg	5 µg/kg	50 µg/kg	500 µg/kg
Limited use of hind paws or limbs		2/40 (5%)	11/60 (18%)	1/40 (3%)	10/40 (25%)	29/60 (48%)	n/a	n/a	7/20 (35%)
Swollen hind paws or limbs		5/40 (13%)	5/60 (8%)	3/40 (8%)	11/40 (28%)	37/60 (62%)	n/a	n/a	9/20 (45%)
Skin lesions on hind paws					3/40 (8%)	6/60 (10%)	n/a	n/a	

Clinical signs of painful, swollen joints resulting in limited use of hind limbs and/or paws were observed in XM02-treated animals. These effects were dose-dependent and trending towards reversible in recovery animals.

Body Weights

Reversible, dose-dependent decreases in mean body weights were observed in mid- and high-dose male rats (~9 and 15%, respectively). There were no treatment-related effects on body weights in female rats.

Feed Consumption

Reversible, dose-dependent decreases in food consumption were observed in mid- and high-dose male rats (~8 and 15%, respectively). There were no treatment-related effects on food consumption in female rats.

Ophthalmoscopy

No treatment-related effects.

ECG

Not assessed.

Hematology

	Main Study			Recovery
	5 µg/kg	**50 µg/kg**	**500 µg/kg**	**500 µg/kg**
White blood cells (wbc)	0.25 fold	2-fold	7-fold	Baseline
Neutrophils	3-fold	20-fold	50-fold	Baseline
Monocytes	1-fold	3-fold	9-fold	Baseline
Platelets			-0.25-fold (males only)	10% lower than control values (males only)

*Fold changes vs. control values.

All hematological effects were dose-dependent, related to the exaggerated pharmacology of G-CSF receptor agonists, and with the exception of slightly decreased platelet counts, fully reversible.

Comment: The slight decrease in platelet counts is unlikely to represent a significant clinical concern, as there were no corresponding changes in APTT or PT.

Clinical Chemistry

A reversible, dose-dependent increase in ALP was observed in mid- and high-dose rats (2- and 7-fold, respectively).

Comment: Elevated ALP is likely related to increased neutrophil counts as neutrophils contain ALP (Stewart, 1974), which can be released into the bloodstream by damaged or dead neutrophils (Izumi et al., 2005).

Urinalysis

No treatment-related effects.

Gross Pathology

	Main Study			Recovery
Observation	**5 μg/kg**	**50 μg/kg**	**500 μg/kg**	**500 μg/kg**
Enlarged lymph nodes	1/40 (3%)	5/40 (13%)	3/40 (8%)	2/20 (10%)
Enlarged spleens	2/40 (5%)	6/40 (15%)	37/40 (93%)	4/20 (20%)
Joint enlargement	2/40 (5%)	11/40 (28%)	15/20 (75%)	9/20 (45%)

All macroscopic findings were dose-dependent and trending towards reversible in recovery animals.

Organ Weights

A dose-dependent increase in spleen weights (1.25-fold low-dose; 1.5-fold mid-dose; 3-fold high-dose) was observed in XM02-treated rats. This finding was trending towards reversible in recovery animals.

Histopathology

Adequate Battery

Yes

Peer Review

No

Histological Findings

Tissue/Observation	Males				Females			
	0 µg/kg	5 µg/kg	50 µg/kg	500 µg/kg	0 µg/kg	5 µg/kg	50 µg/kg	500 µg/kg
Bone marrow								
Myeloid hypercellularity	0	20[(3)]	20[(5)]	19[(5)]	0	17[(3)]	20[(5)]	20[(5)]
Joint								
Hyperostosis	0	1	10	13	0	1	1	3
Fibrosis	0	1	10	13	0	1	1	3
Inflammation	0	1	10	13	0	1	1	3
Joint femoro-tibial								
Physeal dystrophy	0	0	0	1	0	0	0	0
Hyperostosis: femur	0	0	1	3	0	0	0	0
Hyperostosis: tibia	0	0	0	1	0	0	0	0
Liver								
Extramedullary hematopoiesis	0	0	0	9	3	0	0	1
Mononuclear cell infiltrates	0	1	0	1	0	0	1	0
Lymph node								
Hemorrhage	0	0	2	8	1	1	3	3
Spleen								
Extramedullary hematopoiesis	1	19[(2)]	19[(3)]	20[(5)]	5	16[(2)]	19[(3)]	19[(4)]
Inflammation: serosa	0	1	2	3	0	0	0	1

*Bracketed numbers represent the following grades: grade 1 = minimal, grade 2 = slight, grade 3 = moderate, grade 4 = marked, and grade 5 = severe
*20/sex/group

The major histological findings of bone marrow hypercellularity and splenic extramedullary hematopoiesis are related to proliferative effects of XM02 on myeloid progenitor cells. These effects were dose-dependent and trending towards reversible in recovery rats.

Additional findings of joint fibrosis, hyperostosis, and inflammation are also likely related to the proliferation of myeloid progenitor cells in the bone marrow. These findings were dose-dependent and trending towards reversible in recovery animals.

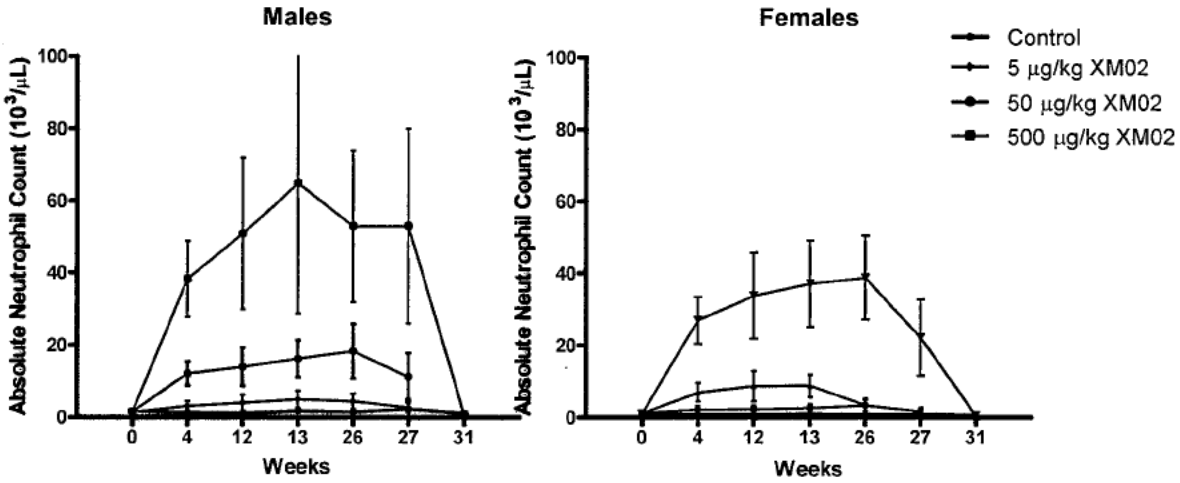
Special Evaluation

None

Toxicokinetics

A toxicokinetic (TK) assessment of XM02 was not performed; however, weekly determination of absolute neutrophil counts was conducted as a surrogate estimate of XM02 exposure (Figure 5). As demonstrated by the consistent, dose-dependent increase in absolute neutrophil counts over the 26-week treatment period, rats were exposed to XM02 during the study.

Figure 5: Timecourse of absolute neutrophil counts in the rat GLP repeat dose toxicity study



Immunogenicity

ADA were detected in 2 low dose, 2 mid dose, and 1 high dose animal between weeks 12 and 26.

Comment: Although ADA were generally associated with lower neutrophil counts in affected animals, the consistent, dose-dependent increase in mean neutrophil counts (Figure 5) over the 26-week treatment period suggests that ADA did not significantly interfere with the interpretation of the toxicity findings in this study.

Stability and Homogeneity

- All formulations were prepared on a daily basis from weeks 1 to 9, and then on a weekly basis from week 10 onward.
- XM02 was stable under the conditions of use.
- All formulations met the specifications for homogeneous mixtures.

- With the exception of the low dose group on days 1 (73.3%), 8 (64.2%), and 41 (80.6%), all samples were within the acceptance limit of deviation (±10 %). This deviation did not significantly impact the interpretation of this study as the low dose was lower than the MTD.

Study title: A 26-week subcutaneous injection toxicity study (with a 4-week interim study) in the Cynomolgus monkey

Study no.:	500109
Study report location:	EDR 4.2.3.2.1.
Conducting laboratory and location:	(b) (4)
Date of study initiation:	16-June-2003
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	XM02, Lot # 020301 and P3-010303, 99.8 and 100% purity, respectively. Both lots were deemed similar to the clinical lot by the CMC reviewer, Dr. Jee Chung.

Key Study Findings

Daily treatment with up to 125 μg/kg XM02 was well-tolerated in monkeys. The major toxicities were related to the proliferative effects of XM02 on myeloid progenitor cells. Specifically, moderate-to-severe bone marrow hypercellularity, marked blood vessel leukocytosis, as well as mild-to-marked granulocytic infiltrations in the spleen, liver, kidneys, and testes were observed in treated animals. These toxicities were dose-dependent and reversible in recovery animals.

The MTD in this study was 125 μg/kg.

Methods

Doses:	0, 5, 25, and 125 μg/kg/day
Frequency of dosing:	Daily
Route of administration:	SC
Dose volume:	0.12 mL/kg/day
Formulation/Vehicle:	Sterile buffered solution containing 0.6 mg/mL acetic acid, 50 mg/mL sorbitol, and 0.025 mg/mL polysorbate 80
Species/Strain:	Monkey/Cynomolgus
Number/Sex/Group:	4
Age:	1.5 to 2.5 years
Weight:	1.8 – 2.4 kg (males); 1.6 – 2.1 kg (females)
Satellite groups:	*Recovery animals*: 3/sex/group (control and high

dose only)
4-week interim animals: 3/sex/group (control and high dose only)

Unique study design: An interim assessment of toxicity was performed at 4-weeks

Deviation from study protocol: No significant deviations from protocol

Observations and Results

Mortality

No treatment-related mortalities.

Clinical Signs

No treatment-related effects.

Body Weights

No treatment-related effects.

Feed Consumption

No treatment-related effects.

Ophthalmoscopy

No treatment-related effects.

ECG

No treatment-related effects.

Hematology

	Main Study			Recovery
	5 µg/kg	**25 µg/kg**	**125 µg/kg**	**125 µg/kg**
Wbc	2.5-fold	3-fold	6-fold	Baseline
Neutrophils	3-fold	7-fold	12-fold	Baseline
Monocytes	1-fold	1.5-fold	2-fold	Baseline
Red blood cell (rbc)		-5%	-10%	Baseline
Hemoglobin			-15%	Baseline
Platelets		-15%	-25%	-20%

*Compared to control values.

The major hematological findings were dose-dependent, related to the proliferative effects of XM02 on myeloid progenitor cells, and reversible, or trending towards reversible, in recovery animals.

Comment: The slight decreases in rbc, hemoglobin, and platelets are likely related to 'crowding' of the bone marrow caused by increased granulocyte production. As noted in the rat GLP repeat dose toxicity study, the platelet effects are not likely a significant clinical concern as there were no corresponding changes in APTT or PT.

Clinical Chemistry

A reversible, dose-dependent increase in ALP was observed in mid- and high-dose monkeys (1.5- and 2-fold, respectively). There was also a reversible 40% increase in cholesterol levels in high dose monkeys.

Urinalysis

No treatment-related effects.

Gross Pathology

	Main Study			Recovery
Observation	**5 μg/kg**	**25 μg/kg**	**125 μg/kg**	**125 μg/kg**
Enlarged lymph nodes			1/14 (7%)	
Enlarged spleens			14/14 (100%)	1/6 (16%)
Bone thickening			2/14 (14%)	1/6 (16%)

The macroscopic findings were dose-dependent and trending towards reversible in recovery animals.

Organ Weights

A dose-dependent increase in spleen weights (1.5-fold low dose; 2.5-fold mid dose; 4-fold high dose) was observed in XM02-treated monkeys. This finding was trending towards reversible in recovery animals. There was also a slight increase in liver weights in mid- and high-dose monkeys (up to 20%) that was fully reversible in recovery animals.

Histopathology

Adequate Battery

Yes

Peer Review

No

Histological Findings

Tissue/Observation	Males				Females			
	0 µg/kg	5 µg/kg	50 µg/kg	500 µg/kg	0 µg/kg	5 µg/kg	50 µg/kg	500 µg/kg
Blood vessel								
Leucocytosis	0	0	1	4	0	3	4	4
Bone marrow								
Myeloid hypercellularity	0	3 (3)	3 (3)	4 (4)	0	4 (3)	4 (3)	4 (4)
Histiocytosis	0	3 (2)	3 (2)	2 (1)	0	3 (1)	3 (2)	1 (1)
Bone								
Hyperostosis	0	0	0	1 (4)	0	0	0	1 (4)
Fracture	0	0	0	0	0	0	1	0
Injection sites (scapular)								
Inflammation	0	2 (1)	3 (1)	2 (1)	0	0	1 (1)	1 (1)
Kidney								
Granulocytic infiltrates	0	0	0	3	0	0	0	1
Liver								
Granulocytic infiltrates	0	0	0	4 (1)	0	0	2 (1)	3 (1)
Lymph node								
Granulocytic infiltrates	0	0	0	2	0	0	0	0
Spleen								
Granulocytic infiltrates	0	4 (2)	3 (3)	4 (4)	0	4 (2)	4 (3)	4 (4)
Histiocytosis	0	3 (2)	3 (2)	4 (4)	0	4 (2)	4 (2)	4 (4)
Testis								
Granulocytic infiltrates	0	0	1	2	-	-	-	-

*Bracketed numbers represent the following grades: grade 1 = minimal, grade 2 = slight, grade 3 = moderate, grade 4 = marked, and grade 5 = severe
*4/sex/group

The predominant histological findings of hypercellularity and histiocytosis in the bone marrow, leukocytosis in blood vessels, and granulocytic infiltrates in the kidney, liver, lymph nodes, spleen, and testis are all related to the proliferative effects of G-CSF on myeloid progenitor cells. These findings were dose-dependent and trending towards reversible in recovery animals.

There were also findings of proliferative hyperostosis affecting the periosteum and/or endosteum of the femur, tibia, radius, humerus, ulna, and/or fibia of 2/8 high dose animals. While these bone findings were less marked in the monkey than in the rat, the histological similarities suggest that the bone changes are mediated by similar mechanism of actions in the two species.
Comment: These effects are likely related to the exaggerated pharmacology of G-CSF, as G-CSF is known to increase bone resorption through osteoclast activation (Takamatsu et al., 1998).

There were also signs of dose-independent, treatment-related local irritant effects that were fully reversible in recovery animals.

Special Evaluation

None

Toxicokinetics

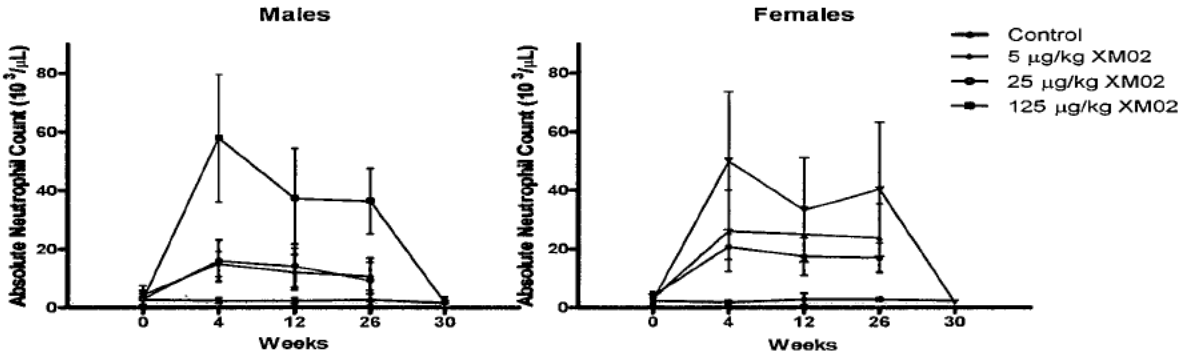
The TK profile of XM02 was determined on days 1 and 28 in high dose animals only. No determination of XM02 exposure was performed at week 26.

Dose (µg/kg)	Day	Sex	C_{max} (ng/mL)	$t_{1/2}$ (h)	Vz (mL/kg)	CL (mL/h/kg)	AUC (0-tlast) (ng*h/mL)
125	1	M	1024	3.9	218	39.2	3169
		F	908	3.5	239	48.0	2597
	28	M	905	10.5	500	33.1	3724
		F	812	7.8	398	35.4	3510

There were no sex-related differences in exposure or accumulation of XM02 during the 28-day interval.

In addition, weekly absolute neutrophil counts were determined to assess whether PD effects were maintained throughout the study. The results in Figure 6 demonstrate that exposure to XM02 was maintained throughout the 26 weeks of treatment.

Figure 6: Timecourse of absolute neutrophil counts in the Cynomolgus monkey GLP repeat dose toxicity study



Immunogenicity

Low titers of ADA were detected in 3/8 low-dose, 6/8 mid-dose, and 9/14 high-dose animals between weeks 12 and 26; however, exposure to XM02 was not significantly affected as absolute neutrophil counts remained elevated throughout the study (Figure 6).

Stability and Homogeneity

- All formulations were made fresh on a daily basis from weeks 1 to 9, and then on a weekly basis from week 10 onward.
- XM02 was stable under the conditions of use.
- All formulations met the specifications for homogeneous mixtures.
- With the exception of the low dose group, who only received 48.3 and 85.4% of the intended dose on weeks 3 and 5, respectively, all samples were within the acceptance limit of deviation (±10 %). This deviation did not significantly impact the interpretation of this study as these animals were only affected for 2 out of 26 weeks and the low dose was significantly lower than the MTD.

7 Genetic Toxicology

An assessment of the genotoxic potential of XM02 was not required, as large molecular weight proteins are not expected to cross the nuclear membrane to interact with DNA or other chromosomal material (refer to ICH S6 Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM194490.pdf).

8 Carcinogenicity

An assessment of carcinogenicity was not required for XM02 due to its intended use in cancer patients undergoing treatment with myelosuppressive chemotherapies (refer to ICH S9 Nonclinical Evaluation for Anticancer Pharmaceuticals http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm085389.pdf).

9 Reproductive and Developmental Toxicology

There were no developmental and reproductive toxicology studies conducted with XM02.

The Sponsor's original justification for the absence of these studies (refer to Toxicology Written Summary; EDR 2.6.6.6, page 13) was based on the proposed clinical indication, which limits use of Neutroval to patients with cancer receiving concomitant treatment with myelosuppressive chemotherapy agents with demonstrated reproductive and/or developmental toxicity. Upon review, it was decided that although the concomitant chemotherapy drugs represent a significantly greater developmental and reproductive toxicity risk than Neutroval™, it would be unethical to simply state in the label that the developmental and reproductive risks of Neutroval™ are unknown, as there are currently two US-licensed recombinant G-CSF products (i.e. Neupogen® and Neulasta®) that do contain information regarding risks of use during pregnancy in the label. As a result, the Sponsor was asked to "provide an assessment of the potential reproductive toxicity of Neutroval as an amendment to the Biologics Licensing Application." The Sponsor's assessment, submitted on June 15, 2010, included a biochemical/pharmacokinetic comparison of XM02 to Neupogen®, as well as information from the open literature regarding the developmental and reproductive toxicities associated with two other marketed G-CSF receptor agonists, filgrastim and lenograstim. These data were submitted in support of a request to use a class labeling approach, with a category 'C' warning, for the Neutroval™ label.

Comment: Upon review, the biochemical/pharmacokinetic comparison to Neupogen® was deemed irrelevant. The submission was not filed as a 351(k) (i.e. biosimilar) application, and the Sponsor did not obtain right of reference to Neupogen®. Instead, the decision to review the developmental and reproductive toxicity findings from other marketed G-CSF products in consideration of a class labeling approach was based solely upon pharmacology studies demonstrating that XM02 binds the G-CSF receptor with high affinity, and behaves as a G-CSF receptor agonist in vivo and in vitro (refer to section 4.1).

As mentioned above, the literature assessment included summary results of embryo-fetal toxicity studies in rats and rabbits conducted with filgrastim (Keller and Smalling 1993) and lenograstim (Hara et al., 1990; Sugiyama et al., 1990). Both lenograstim and filgrastim are recombinant G-CSF products with identical amino acid sequences to Neutroval™. While filgrastim is a nonglycosylated protein made in E. coli, and therefore

highly similar to Neutroval™, lenograstim is a glycosylated protein made in Chinese Hamster Ovary cells. The toxicity findings in these studies are summarized in Table 4:

Table 4: Summary results of embryo-fetal toxicity studies conducted with filgrastim and lenograstim in rats and rabbits

	Maternal effects	Fetal effects
Rat Studies		
Filgrastim	• No effects	• No lethal, teratogenic, or behavioral effects
Lenograstim	• No effects	• No abortions/death • No effects on fetal viability or fetal development • No teratogenicity
Rabbits		
Filgrastim	• Decreased maternal body weight gain and food consumption	• Increased embryolethality and fetal resorption • No teratogenicity
Lenograstim	• Decreased maternal body weights and food consumption	• High incidence of abortion and spontaneous resorption • Decreased fetal weights • No teratogenicity or abnormalities

* Animals were dosed daily during the period of organogenesis

The developmental and reproductive toxicities were consistent within species. Neither drug had any developmental or reproductive toxicity effects in rats. In rabbits, both drugs had findings of decreased maternal body weight gain and food consumption, as well as increased embryolethality and resorption. There were no teratogenic effects with either drug. These findings suggest that the major developmental and reproductive toxicity associated with G-CSF receptor agonists is increased risk of spontaneous abortion.

Comment: In addition to the embryo-fetal studies performed with lenograstim and filgrastim, this reviewer has identified summary results of embryofetal studies conducted with a third recombinant G-CSF product, nartograstim (Cavallaro et al., 2000; Kato et al., 2001). Like Neutroval™ and filgrastim, nartograstim is a non-glycosylated recombinant G-CSF; however, it is a mutein with a five amino acid substitution at the N-terminal region. In these studies, rats and rabbits were treated daily during the period of organogenesis. The results of these studies were similar to those observed with lenograstim and filgrastim (Table 4). Specifically, there were no reported toxicities in rats, and in rabbits, the major toxicities were limited to decreased maternal body weight gain and food consumption, as well as an increased incidence of abortions/resorptions and decreased fetal body weights. No developmental abnormalities or teratogenic effects were observed in either species. These findings support the class labeling approach, as they provide additional evidence that the developmental and reproductive

toxicities of G-CSF receptor agonists are well-characterized and consistent within the class.

*Comment: This reviewer also found information in the open literature to bridge the developmental and reproductive effects of the 3 recombinant G-CSF products (i.e. filgrastim, lenograstim, and nartograstim). Specifically, a paper was found in which monkeys were treated with nartograstim, filgrastim, or lenograstim to determine the differences in the PK/PD profiles after SC dosing (Tanaka et al., 1997). Despite the slight differences in structure, all 3 G-CSF products had highly similar PK profiles (*Table 5*) and identical PD effects (i.e. increased neutrophil counts) in vivo (*Figure 7*). These findings further support the class labeling approach for Neutroval™.*

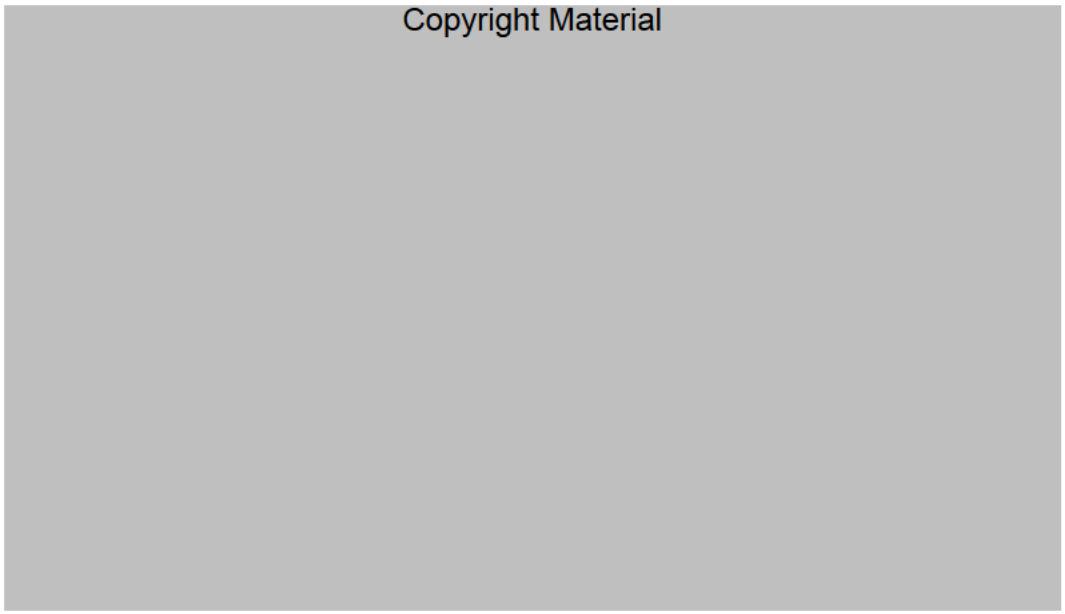
Comment: It is the opinion of this reviewer that there is sufficient information in the literature to support class labeling for the reproductive risks of Neutroval™ treatment; however, final decision regarding this matter is pending consult to OCC, who will decide the permissibility of using literature to support the requirements of a BLA.

Table 5: PK parameters in Cynomolgus monkeys following a single SC injection with 5 μg/kg with filgrastim, lenograstim, and nartograstim

(Table extracted from (Tanaka et al., 1997))

Figure 7: Absolute neutrophil counts in Cynomolgus monkeys in response to daily SC injections with 1.5 μg/kg of lenograstim, filgrastim, or nartograstim for 5 consecutive days

(Figure extracted from [Tanaka et al., 1997])



10 Special Toxicology Studies

Local Irritancy Studies in Male New Zealand White Rabbits (Study# 500536 and 501717)
(EDR 4.2.3.6.1.)

Two GLP studies (performed by (b) (4) were conducted to investigate the local irritancy potential of XM02 in male New Zealand White rabbits by the IV, intramuscular (IM), SC, perivenous (PV), and intra-arterial (IA) routes of administration. A similar study design was employed in both studies. Briefly, each rabbit received injections of XM02 by all 5 routes of administration, for a total of 5 injections. Draize evaluations were performed at 0, 1, 2, 4, and 6 hours post dose, as well as twice daily for the next 5 days to determine the local irritancy potential of XM02. Rabbits were also monitored for mortality and clinical signs, as well as macro- and microscopic changes at the injection sites.

The first study (Study# 500536) compared the local irritancy effects of XM02 (Lot# FT-01 04 04; deemed similar to the clinical lot by the CMC reviewer) to control solutions. Specifically, rabbits (4/group) were treated with injections of saline (negative control), XM02 diluent containing 0.6 mg/mL acetic acid, 50 mg/mL sorbitol, and 0.025 mg/mL polysorbate 80 (vehicle control), 1.26 mg XM02, or 2.46 mg XM02 by the 5 different routes of administration. The second study (Study# 501717) employed the use of a positive control group (Neupogen®; EU-sourced) against which to compare the local irritancy effects of XM02 (Lot# P04-025; deemed similar to the clinical lot by the CMC

reviewer). In this study, groups of rabbits (4/group) received injections of saline (negative control), XM02 diluent (vehicle control), 240 μg XM02 or Neupogen®, or 480 μg of XM02 or Neupogen® by the 5 routes of administration.

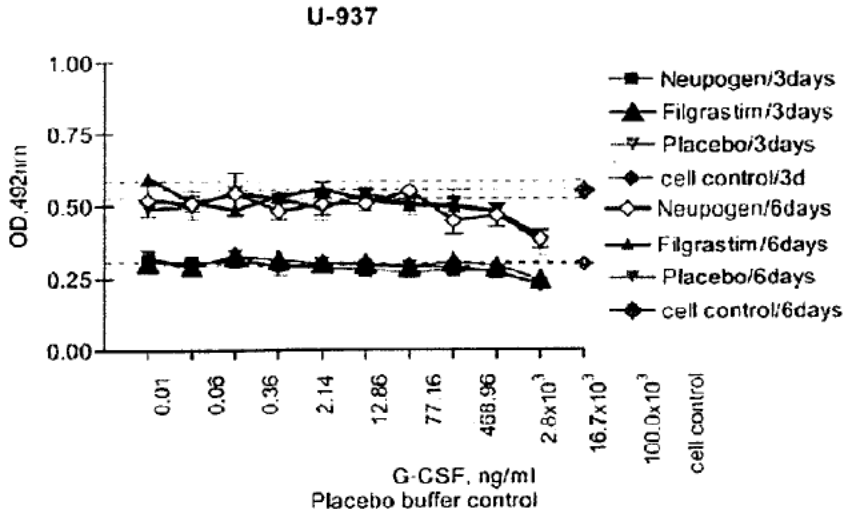
There were no XM02-related local irritancy effects in either study. There were also no effects on mortalities or clinical signs.

Investigation of the Effect of XM02 on Malignant Cells (Study# SPD-0-01)
(EDR 4.2.1.2.1.)

The objective of this nonGLP study (performed by SICOR Biotech UAS, Lithuania) was to evaluate the proliferative potential of XM02 on human malignant cell lines expressing the G-CSF receptor. Five human cell lines, U-937 (histiocytic lymphoma), K-562 (chronic myelogenous leukemia), SK-OV-3 (adenocarcinoma), T-24 (bladder cancer), and NIH:OVCAR-3 (ovarian epithelial adenocarcinoma) were incubated with 10 pg/mL to 100 μg/mL XM02 (Lot# P03-040402) or Neupogen® (EU-sourced) for 72 or 144 hours. Proliferation was assessed using the Cell Titer Aqueous Proliferation Assay (Promega). Neither XM02 nor Neupogen® induced proliferation in any of the cell lines. A representative graph of the results in U-937 cells is shown in Figure 8 below.

Figure 8: Treatment with XM02 or Neupogen® does not induce proliferation of U-937 cells

(Extracted from Study# SPD-0-01, page 4)



Comment: The tumorigenic potential of XM02 is unknown, as these studies did not evaluate the long-term proliferative effects of XM02 on G-CSF receptor-expressing malignancies in vivo.

11 Integrated Summary and Safety Evaluation

Table 6: Summary of Toxicity Studies

Study	Species	NOAEL (mg/kg)	Maximum tolerated dose
CNS Safety Pharmacology 0 or 3500 μg/kg	Rats	3500 μg/kg	N/A
Respiratory Safety Pharmacology 0 or 3500 μg/kg	Rats	3500 μg/kg	N/A
Cardiac Safety Pharmacology 0 or 3500 μg/kg	Dogs	3500 μg/kg	N/A
28-day repeat dose PK study 0 or 500 μg/kg	Rats	N/A	500 μg/kg
Single dose IV and SC PK study 0 or 800 μg/kg	Monkeys	N/A	800 μg/kg
28-day repeat dose with 2-week treatment-free period PK study 0, 5, 25, or 125 μg/kg	Rats	N/A	125 μg/kg
GLP 26-week repeat dose toxicity study 0, 5, 25, or 125 μg/kg	Monkeys	5 μg/kg	125 μg/kg
GLP 26-week repeat dose toxicity study 0, 5, 50, and 500 μg/kg	Rats	None	50 μg/kg

Pharmacology

As evidence of XM02's biologic activity, primary pharmacology studies were conducted and demonstrated that XM02:

- Binds to the G-CSF receptor with high affinity
- Stimulates the in vitro proliferation of murine granulocyte progenitor cells
- Increases in the number of circulating neutrophils in an in vivo neutropenic mouse model

PK/PD

PK/PD studies in monkeys (single injection/dose level) and rats (repeat injections/multiple dose levels) demonstrated:

- Dose-dependent increases in absolute neutrophil counts in both species
- A $t_{1/2}$ of ~2 to 3 hours in both species
- A dose-proportional increase in exposure (AUC) in rats, with no significant differences between male and female animals
- ADA did not significantly affect exposure to XM02 in rats, as AUC values and neutrophil counts remained elevated on day 42

Safety Pharmacology

There were no treatment-related effects on the respiratory or central nervous systems in rats or the cardiovascular systems in dogs after a single dose of 3500 μg/kg XM02.

Repeat Dose Toxicity Studies

The nonclinical safety of XM02 was assessed in two GLP 26-week repeat dose toxicity studies with a 4-week recovery period in rats (5, 50, and 500 μg/kg XM02) and monkeys (5, 25, and 125 μg/kg XM02). These studies demonstrated:

- The major toxicities of marked-to-severe bone marrow hypercellularity, marked splenic extramedullary hematopoiesis (rat)/granulocytic infiltrations (monkey), mild-to-severe bone thickening, increased ALP, and increased spleen weights were dose-dependent, related to the exaggerated pharmacology of G-CSF receptor agonists, and largely reversible in recovery animals
- The major toxicities were similar in both species
- The bone findings were more severe in rats than in monkeys. In rats, clinical signs of painful, swollen, red hind limbs and/or paws were observed at all dose levels, while in monkeys, findings were limited to macroscopic observations of bone thickening in high dose animals only. Histological findings of hyperostosis and granulocytic infiltrates in articular surfaces suggested that the mechanism is related to the exaggerated pharmacology of G-CSF receptor agonists. These toxicities were also dose-dependent and fully (monkeys) or partially (rats) reversible in recovery animals.
- The rat was the most sensitive species, as there were a significant number of mortalities (12/60) in the high dose group due the severe bone/joint pain, resulting in the determination of 50 μg/kg XM02 as the MTD in the rat. In contrast, doses up to 125 μg/kg XM02 were well-tolerated in the monkey.

Special Toxicity Studies

- XM02 did not demonstrate any local irritancy potential in rabbits by the SC, IV, IM, PV, or IA routes of administration.
- XM02 did not demonstrate proliferative effects on 5 G-CSF receptor-expressing tumor cell lines in vitro; however, these short-term, in vitro studies do not adequately evaluate the potential tumorigenicity of XM02.

Genotoxicity/Carcinogenicity

- Genotoxicity studies were not appropriate, as large molecular weight proteins are not expected to cross the nuclear membrane to interact with DNA.
- An assessment of carcinogenicity was not needed for the proposed patient population.

Developmental and Reproductive Toxicity

- No DART studies were conducted with XM02. The Sponsor's original justification for the absence of these studies was based on the proposed indication, which limits use of Neutroval™ to patients receiving concomitant treatment with myelosuppressive chemotherapy agents with known developmental and reproductive toxicities.

- Upon review, it was determined that it would be unethical to not communicate the potential developmental and reproductive risks associated with Neutroval™ as there are currently 2 US-licensed recombinant G-CSF products that do contain this information in the label. As a result of this discussion, the Sponsor was requested to provide an assessment of the reproductive toxicities associated with Neutroval™ treatment.
- The Sponsor's response to this request was to provide information from the open literature regarding the known developmental and reproductive toxicities associated with other recombinant G-CSF products to support a 'class label' approach. This information included summary results of embryo-fetal toxicity studies conducted with filgrastim and lenograstim in rats and rabbits.
- Upon review of this information, it was determined that the major reproductive and developmental toxicity associated with other marketed G-CSF receptor agonists is increased risk of spontaneous abortion, without any signs of teratogenicity. As this effect was well-characterized and consistent within the class, it was determined that there is sufficient information in the open literature to support a class label approach for Neutroval™; however, final decision regarding this matter is pending consult to OCC.

12 Appendix/Attachments

APPENDIX I

Published References Regarding the Developmental and Reproductive Toxicities of G-CSF Receptor Agonists

The following references from the open literature were provided by the Sponsor (amendment to BLA; STN# 125294/016) in response to a request to provide an assessment of the potential developmental and reproductive risks of Neutroval™, but unless noted in the sections above, these references were not included in this review.

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PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA/BLA or Supplement

NDA/BLA Number: 125294 **Applicant: Teva** **Stamp Date: Nov 30,2009**

Drug Name: Neutroval **NDA/BLA Type:**

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

	Content Parameter	Yes	No	Comment
1	Is the pharmacology/toxicology section organized in accord with current regulations and guidelines for format and content in a manner to allow substantive review to begin?	x		
2	Is the pharmacology/toxicology section indexed and paginated in a manner allowing substantive review to begin?	x		
3	Is the pharmacology/toxicology section legible so that substantive review can begin?	x		
4	Are all required (*) and requested IND studies (in accord with 505 b1 and b2 including referenced literature) completed and submitted (carcinogenicity, mutagenicity, teratogenicity, effects on fertility, juvenile studies, acute and repeat dose adult animal studies, animal ADME studies, safety pharmacology, etc)?	x		
5	If the formulation to be marketed is different from the formulation used in the toxicology studies, have studies by the appropriate route been conducted with appropriate formulations? (For other than the oral route, some studies may be by routes different from the clinical route intentionally and by desire of the FDA).	N/A		
6	Does the route of administration used in the animal studies appear to be the same as the intended human exposure route? If not, has the applicant submitted a rationale to justify the alternative route?	x		
7	Has the applicant submitted a statement(s) that all of the pivotal pharm/tox studies have been performed in accordance with the GLP regulations (21 CFR 58) or an explanation for any significant deviations?	x		
8	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	x		

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	Comment
9	Are the proposed labeling sections relative to pharmacology/toxicology appropriate (including human dose multiples expressed in either mg/m2 or comparative serum/plasma levels) and in accordance with 201.57?			TBD requires review of supporting data.
10	Have any impurity – etc. issues been addressed? (New toxicity studies may not be needed.)	N/A		
11	Has the applicant addressed any abuse potential issues in the submission?	N/A		
12	If this NDA/BLA is to support a Rx to OTC switch, have all relevant studies been submitted?	N/A		

IS THE PHARMACOLOGY/TOXICOLOGY SECTION OF THE APPLICATION FILEABLE? Yes

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

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

Reviewing Pharmacologist — Date: Jan 6, 10

Team Leader/Supervisor — Date: Jan 6, 2010

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

MEMORANDUM

TO: The file
CC: Patricia Keegan, M.D., Director, Division of Biologic Oncology Products, Office of Oncology Drug Products (OODP), Center for Drug Evaluation and Research (CDER)
FROM: Anne M. Pilaro, Ph.D, Supervisory Toxicologist, Pharmacology/Toxicology Branch, Division of Biologic Oncology Products, OODP, CDER 8/9/2010

STN BLA #: 125294/000
SPONSOR: Teva Pharmaceuticals
PRODUCT: Neutroval™ (tentative, non-proprietary name [(b) (4)] recombinant, human granulocyte colony stimulating factor [G-CSF])
SUBMISSION TYPE: original BL A application (351(a) pathway)
DATE: August 6, 2010

SYNOPSIS:
Teva Pharmaceuticals has submitted an original BLA application for their version of recombinant, human G-CSF, trade name Neutroval™. The tentative, non-proprietary name for this product is [(b) (4)]; however, assignment of the non-proprietary name is pending further discussion by the Center Director for the FDA/CDER, and the FDA Office of Chief Counsel.

Neutroval™ (G-CSF; code name XM02) is indicated "… [(b) (4)] febrile neutropenia, in cancer patients receiving myelosuppressive anti-cancer drugs associated with a clinically significant incidence of severe neutropenia [(b) (4)]." Nonclinical studies investigating the pharmacology, pharmacokinetics and toxicology of XM02 were submitted with the biologics licensing application (BLA) in support of the safety of Neutroval™. In the Highlights section of the label, Neutroval™ is defined as a "leukocyte growth factor" for the pharmacologic class. Consistent with other granulocyte colony stimulating factors, Neutroval™ acts through a specific receptor present on the surface of hematopoietic cells of the late myeloid lineage, to promote the growth and differentiation of mature neutrophils. When patients with cancer are treated with myelosuppressive chemotherapy and concomitant Neutroval™, neutrophil proliferation, differentiation and maturation are stimulated, febrile neutropenia is decreased and severe and/or life-threatening infections are prevented.

The nonclinical data in support of Neutroval™ for the proposed indication were reviewed by the primary reviewer, Mary Jane Masson-Hinrichs, Ph.D., and are briefly summarized in the "Executive Summary" and "Integrated Summary and Safety Evaluation" sections of her review. Pharmacology, safety pharmacology, pharmacokinetic evaluations and toxicology studies supporting the BLA for Neutroval™ were conducted *in vitro* using assays with human and mouse cells or immobilized recombinant human G-CSF receptor, and *in vivo* in 6-month repeat-dose toxicity studies in cynomolgus monkeys and Sprague-Dawley rats. The *in vitro* and *in vivo* pharmacodynamic effects of XM02 were consistent with stimulation of hematopoietic cells through the G-CSF receptor, and the binding affinity of Neutroval™ for the human

G-CSF receptor was comparable to that reported for another G-CSF, i.e. Neupogen®. Toxicities associated with XM02 treatment of rats and monkeys were consistent between the two species and included dose-dependent, marked to severe bone marrow hyperplasia, enlarged spleens (rats) or splenic neutrophilic infiltrates, increased serum alkaline phosphatase levels, and bone thickening. All findings were considered related to an exaggerated pharmacologic response to XM02, and are consistent with the toxicity profiles of other approved G-CSFs.

There were no nonclinical genotoxicity or carcinogenicity studies performed withXM02, as per the guidance provided in ICH S6 *"Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals"* and ICH S9 *"Nonclinical Safety Evaluation for Anticancer Pharmaceuticals."* There were no reproductive or developmental toxicity (DART) studies conducted with XM02 to support safe use of Neutroval™ in pregnancy. The Sponsor's original justification for the absence of DART studies with XM02 was based on the proposed indication, which limits use of Neutroval™ to patients receiving concomitant treatment with myelosuppressive chemotherapy agents with known developmental and reproductive toxicities. Upon review and discussion with FDA/CDER senior management, FDA determined that it would not be ethical to omit communicating the potential developmental and reproductive risks associated with Neutroval™ in the labeling, since the two currently US-licensed recombinant G-CSF products contain this information in the label. As a result of this discussion, the Sponsor was requested to provide an assessment of the reproductive toxicities associated with Neutroval™ treatment.

The Sponsor provided several published literature articles demonstrating that both filgrastim (i.e. Neupogen®) and lenograstim, a glycosylated G-CSF that is approved for marketing in Japan, have similar abortifacient effects when pregnant rabbits were dosed during the period of organogenesis. Additionally, Dr. Masson-Hinrichs independently found two other published articles regarding another G-CSF product nartograstim, which demonstrated similar abortifacient effects in rabbits, and an article documenting comparable pharmacodynamic responses in cynomolgus monkeys dosed with filgrastim, lenograstim or nartograstim that serves to "bridge" the *in vivo* responses to G-CSF across all three products in this class.

I concur with Dr. Masson-Hinrichs' opinion expressed in her review, i.e. that the major reproductive and developmental toxicity risk of all marketed G-CSF products is increased risk of spontaneous abortion, and that this effect is well characterized and consistent within the class and is supported by the information in the published literature. However, final decision regarding the acceptability of published literature information to support product labeling for communication of risk is pending further discussion by the Center Director for the FDA/CDER, and the FDA Office of Chief Counsel. If FDA senior management concur that the published information is sufficient and appropriate to support a "class label" for the reproductive risks of Neutroval™ and all other human recombinant G-CSF products, then this decision will be communicated to the Sponsor and final labeling negotiations will commence. If it is decided that the Sponsor may not rely on the available information in the literature to support their labeling, additional nonclinical DART testing will be required. Once this decision has

been reached, Dr. Masson-Hinrichs will amend her review to provide an addendum discussing the outcome of the decision; for now, the recommendation is not to approve this BLA application and issue a Complete Response letter documenting this deficiency. A draft comment for communication to Teva Pharmaceuticals conveying the requirement for additional information regarding the reproductive and developmental risks associated with Neutroval™ treatment is included in Dr. Masson-Hinrichs' primary review.

Recommendation: I concur with Dr. Masson-Hinrichs' conclusions regarding the nonclinical findings for Neutroval™, the current recommendation that the licensing application not be approved for marketing and be issued a "Complete Response" letter documenting the nonclinical deficiency, and the proposed nonclinical language to convey this deficiency to the Sponsor as documented in Dr. Masson-Hinrichs' review. A copy of Dr. Masson-Hinrichs' review, with supervisory sign-off, has been conveyed to the regulatory project manager for inclusion in the final action package. Further nonclinical action by the review team is pending decision from the FDA/CDER Center Director and Office of Chief Counsel on the suitability of relying on published literature to support the labeling of Neutroval™ for Section 8.1 (Special Populations: Use in Pregnancy). Final labeling has not yet been conveyed to the sponsor, pending this decision.