CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125294Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	August 29, 2012
From	Albert Deisseroth, MD, PhD
Subject	Cross-Discipline Team Leader (CDTL) Review
NDA/BLA # Supplement#	BLA 125294
Applicant	Sicor Biotech UAB
Date of Submission	
PDUFA Goal Date	August 29, 2012
Non-proprietary name (Trade Name unavailable)	Tbo-filgrastim
Dosage forms / Strength	
Applicant's Proposed Indication(s)	Reduction of the duration of severe neutropenia in patients with non-myeloid malignancies receiving myelosupressive anti-cancer drugs associated with a clinically significant incidence of febrile neutropenia
Recommended:	Approval

Material Reviewed/Consulted	Reviewer/Author
Medical Officer Review	Thomas Herndon, MD
Statistical Review	Kyung Lee, PhD, Mark Rothmann, PhD
Pharmacology Toxicology Review	Robeena Aziz, PhD and Haleh Saber, PhD
ONDQA-CMC Reviews	Jee Chung, PhD, and Janice Brown, PhD
CDRH (consults)	Quynh Nhu Nguyen, PhD
Immunogenicity	Laura Salazar-Fontana, PhD and Susan L Kirshner, PhD
Clinical Pharmacology Review	Bahru Habtemariam, PharmD and Julie Bullock, PharmD
OSI/DGCPC Review	Lauren Iacono-Connors, PhD, and Anthony Orencia, MD

1. Introduction

On November 30, 2009, TEVA Pharmaceuticals USA of Horham, PA. submitted BLA 125294 for tbo-filgrastim (previously known by the code name as XM02). On April 4, 2012, TEV notified the FDA of a change of sponsorship of BLA 125294 from TEVA to Sicor Biotech UAB of Vilnius, Lithuania, an indirect wholly owned subsidiary of Teva Pharmaceuticals USA. TEVA Global Branded Pharmaceutical Products R&D will serve as the US Agent for Sicor. In this report, all actions and issues relating this BLA submission and its review which occurred before April 4, 2012 will reference the Sponsor as TEVA or the Applicant, and those actions or events occurring on or following April 4, 2012 will refer to the Sponsor as the Applicant or as Sicor.

Tbo-filgrastim is a recombinant human N-methionyl granulocyte colony stimulating factor (G-CSF) submitted under section 351(a) of the PHS Act for the indication "reduction of the duration of severe neutropenia in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a clinically significant incidence of febrile neutropenia." A trade name Neutroval originally proposed by the Applicant was rejected by the Division of Medication Error Prevention and Analysis (DMEPA), and the Applicant has stated its intention to submit another proposed trade name after the action on this application. (b) (4)

Tbo-filgrastim was developed in Europe as a similar biological product to filgrastim (Neupogen), a product approved in several European countries. This submission was preceded by a Pre-IND/Pre-BLA meeting which was held with the FDA on November 25, 2008. At the time that the Applicant sought FDA advice through the Pre-BLA meeting, the pivotal trial (XM02-02) already had been completed, so that the FDA did not have an opportunity to provide input into the design of the trial. Many aspects of the clinical trial design and overall development program were not relevant or adequately justified for a product intended for submission under the section 351(a) of the PHS Act . However, with the submission of additional data, adequate data on tbo-filgrastim was provided to establish the safety, purity, and potency of the product for the single indication proposed by Teva.

Tbo-filgrastim was evaluated in a clinical study of 348 adult patients with advanced breast cancer receiving treatment with doxorubicin and docetaxel. Patients were randomly assigned to receive either tbo-filgrastim, a placebo, or a filgrastim product approved in several European countries (a non-US-approved filgrastim product). As discussed further in this memorandum, the data collected for the first primary objective of the pivotal trial XM02-02 (comparison to a non-US-approved filgrastim product) provided only supportive data because TEVA did not provide adequate justification for its study design and statistical analysis. Further, the proposed "equivalence" analysis is not appropriate for demonstrating the safety, purity, and potency of tbo-filgrastim in this BLA. The FDA therefore accepted for the demonstration of effectiveness only the data generated on 212 patients from pivotal trial XM02-02 that were relevant to the second

primary objective of the pivotal trial (XM02-02) which was the testing of a difference in the effect of tbo-filgrastim as compared to placebo on duration of severe neutropenia (DSN). This analysis demonstrated in a statistically significant manner ($p<0.0001$) that tbo-filgrastim was effective in reducing the DSN induced by chemotherapy by 2.7 days as compared to the DSN seen with placebo. From the perspective of an approval of the Applicant's request for marketing approval, this result from the pivotal trial (in addition to safety data from this trial and two other clinical studies) would have been sufficient for approval (due to the robust nature of the result), had it not been for a number of non-clinical but significant deficiencies, which ultimately led to a Complete Response letter being sent to the Applicant (disapproval) on September 29, 2010.

This application (BLA 125294) was supported by multiple clinical studies which are summarized in Table 1.

Table 1: Clinical Program

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

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

History of the Application after Submission of BLA 125294

(b) (4), an inspection of the BioGeneriX AG (b) (4) led to questions about data integrity.

August 27, 2010, TEVA submitted information regarding verification of the clinical data which was brought into question by the FDA's inspection of (b) (4)

September 29, 2010, the FDA issued a complete response letter which described the following 5 deficiencies:

Deficiency #1. Based on the FDA inspection of the BioGeneriX AG facility (b) (4) there was a concern that the integrity of the database for Study XM02-2-INT, the pivotal trial submitted to support the efficacy of the product, may have been compromised. After the initial database lock on January 2, 2006, and subsequent data unblinding, the data base was unlocked and the data were altered on at least two separate dates, i.e. January 17, 2006 and January 23, 2006. The FDA requested information about the quality control and/or quality assurance activities at each stage of data handling, from initial data entry into the data base through the final database lock, that were undertaken to ensure the integrity of safety and efficacy data. In addition, the FDA asked TEVA to provide documentation, including justification and the

audit trail, for all changes made to the database after unblinding. Finally, the FDA requested a detailed analysis of the impact of all changes made to the data base after initial data lock, and unblinding on the evaluation of safety and efficacy data.

(b) (4)

Deficiency #3. TEVA did not provide adequate information concerning the device closure system. Based on FDA assessment, it appears that TEVA is relying solely on the fill weight as the definitive property to decide if the correct amount of therapy is being delivered through the syringe. FDA stated that there are other aspects of syringe and needle performance such as dead space/volume, bond strength between the syringe/needle, and spacing of volumetric graduation markings that can impact the performance of the device. FDA stated that there have been several complaints from the medical community regarding the (b) (4) system that was proposed by TEVA, and the ability for the user to manipulate such prefilled syringes. In communications subsequent to the issuance of the complete response letter of September 29, 2010, FDA specified that TEVA should carry out performance testing on the glass syringes to demonstrate that the pre-filled glass syringes are safe and effective to deliver the drug product (DP) and that this syringe meets the specifications of the following guidance document and FDA Consensus Standards:

a.

b.

c.

d.

(b) (4)

Deficiency #4. FDA stated that the literature assessment of the potential reproductive toxicity of G-CSFs provided in support of BLA 125294 does not fulfill the regulatory requirements for nonclinical developmental and reproductive toxicity studies with tbo-filgrastim. FDA stated that TEVA's 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. FDA stated that TEVA must provide the results of a nonclinical embryo-fetal toxicity study conducted with tbo-filgrastim in rabbits as a single, pharmacologically responsive species, with reference to ICH S9.

Deficiency #5. FDA determined that TEVA's proposed non-proprietary name [redacted] for XM02 was not acceptable for this BLA submitted under section 351(a) of the PHS Act. [redacted]

In addition to these deficiencies, there were a number of non-deficiency comments relating to the manufacturing process, the effect of tbo-filgrastim on cardiac conduction, the development of validated screening assays for the assessment of anti-product antibody response, microbiology, safety and labeling.

Events Subsequent to the Issuance of the Complete Response Letter on September 29, 2010

[redacted], the FDA re-inspected the BioGeneriX AG facility in response to the documents submitted to the FDA by TEVA on August 27, 2010 and thereafter.

December 16, 2011, OSI sent to the OND/OHOP review division a report entitled "Clinical Inspection Summary Addendum" from Lauren Iacono-Connors, PhD of the Good Clinical Practice Assessment Branch of OSI concerning the findings of the [redacted] re-inspection.

This report cited 2 inspectional observations:

Observation 1: there were clear failures to control access to the database via the locking and unlocking processes, and

Observation 2: there was a failure to adequately document significant steps in the control of the data base.

However, the audit trail of the clinical data base, assessed during the [redacted] inspection confirmed that no inappropriate changes were made to the database during time periods when it was in unlocked status. The inspection findings concluded that the primary efficacy data were verifiable and there was no evidence of under reporting of SAEs. The remaining regulatory violations noted during the inspection were considered unlikely to importantly impact data integrity. As a result of these events, a Form FDA

483 was issued to the clinical research organization (CRO) citing 2 inspectional observations (see above).

February 29, 2012, TEVA submitted a response to the Complete Response of September 29, 2010. The PDUFA deadline for the FDA to respond to this response letter to the Complete Response is August 29, 2012. The BLA subsequently was transferred to Sicor Biotech UAB.

June 21, 2012, Sicor submitted a response to an FDA request for additional information that the Agency issued following the receipt of the February 29, 2012 response letter. This submission (Sequence #0036 to BLA 125294) consisted of a report of a performance analysis of the glass syringes that was requested by the FDA in its Complete Response letter of September 29, 2010, but which was not addressed in the February 29, 2012 response letter from TEVA.

Summary of the Response Letter to the September 29, 2010 Complete Response letter from TEVA dated February 29, 2012 and the submission from the Applicant dated June 21, 2012.

TEVA Response to Deficiency #1. TEVA points out that two FDA investigators, Mr. James Kewley, and Mr. Jonathan Helfgott, re-inspected the BiogeneriX site (b) (4) on (b) (4). As pointed out by TEVA, and what is in fact in the December 16, 2011 report of that inspection, the re-inspection did not identify any concerns relating to the integrity of the data base used for Study XM02-02-INT, the pivotal trial of BLA 125294. During this inspection, the quality control and quality assurance safeguards were physically demonstrated to the FDA inspectors which were found by the inspectors to be satisfactory. Inspection of the audit trail at that visit also confirmed that no inappropriate changes were made to the data base. Finally, the OSI report concluded that the FDA inspection revealed that the violations noted during the inspection (see Observations #1 and #2 cited above) were considered unlikely to importantly impact data integrity. Thus, it is the opinion of the CDTL that TEVA has adequately responded to the Deficiency #1 of the Complete Response letter.

TEVA Response to Deficiency #2. (b) (4)

Thus, it is the opinion of the CDTL that TEVA has adequately responded to the Deficiency #2 of the Complete Response letter of September 29, 2010.

TEVA Response to Deficiency #3. On June 21, 2012, the Applicant submitted an amendment to BLA125294 (Sequence # 0036) which consisted of a report on the performance of the (b) (4) This report focused on determining the tolerances (both high and low) for each graduation mark on the syringe and whether it achieved a volumetric accuracy of ± 10%. The conclusion of this study is that the (b) (4) met this criterion as the tbo-filgrastim study shows a range of ± 5% range. Thus, it is the opinion of the CDTL that the Applicant has adequately responded to the Deficiency #3 of the Complete Response letter of September 29, 2010.

TEVA Response to Deficiency #4. In response to Deficiency #4, and the request of the FDA that TEVA carry out its own reproductive toxicity study of tbo-filgrastim, TEVA provided the Agency with a completed nonclinical embryo-fetal toxicity study of tbo-filgrastim drug product. Drs. John Leighton and Haleh Saber stated that this reproductive toxicity study was acceptable. Thus, it is the opinion of the CDTL that TEVA has adequately responded to the Deficiency #4 of the Complete Response letter of September 29, 2010 (see Pharmacology-Toxicology review below for details)

TEVA Response to Deficiency #5. TEVA proposed the non-proprietary name tbo-filgrastim in its response to the Complete Response dated September 29, 2010, which the FDA approved. Thus, TEVA has adequately responded to the Deficiency #5 of the Complete Response letter.

TEVA Response to Non-Deficiency Comments: The CDTL has contacted the following review disciplines involved in the review of the BLA 125294. All of these individuals attest to their support of the recommendation of approval of this BLA. The non-deficiency comments from CMC, Immunogenicity, Facilities (BMAP), Microbiology, and Clinical Pharmacology will be completed by the Applicant following approval of tbo-filgrastim by the FDA and these review disciplines are supportive of that. These include:

a. Dr. Thomas Herndon, Clinical Reviewer: The conclusion following the first cycle of review was that the results of a large double blind randomized (3 arm) trial (XM02-02-INT) in which 348 patients with high risk stage II or with stage III or IV breast cancer requiring and receiving myelosuppressive chemotherapy (doxorubicin 60 mg/m^2 and docetaxel 75 mg/m^2 administered up to 4 cycles every 21 days) were randomized 2:2:1 to tbo-filgrastim, a non-US-approved filgrastim product (a filgrastim product (Neupogen) approved in several European countries) and a placebo was that:

i. Tbo-filgrastim was superior to placebo in terms of the primary efficacy endpoint (duration of severe neutropenia in cycle 1 defined as the number of days with grade 4 neutropenia. This was a 2.7 day reduction in DSN with tbo-filgrastim as compared with placebo, $p<0.0001$). Another outcome was that the difference of DSN between tbo-filgrastim and a non-US-approved filgrastim (a filgrastim product approved in several European countries) was 0.03 days, which is within the 95% confidence

interval (-0.26, 0.33), and certainly within the 1 day margin. However, TEVA did not provide adequate justification for the non-inferiority margin of a 1-day difference in mean DSN between the tbo-filgrastim and the non-US-approved filgrastim control arm. In addition, TEVA did not provide adequate justification that a margin based on treatment effects with US-licensed Neupogen could be extrapolated to treatment effects with the European-marketed product. Therefore, claims of non-inferiority to the European-marketed product will not be permitted.

ii. No significant safety signals attributed to tbo-filgrastim were detected during the review of the data on 541 patients exposed to tbo-filgrastim. Bone pain was the most frequent treatment-emergent adverse reaction that occurred in at least 1% or greater in patients treated with tbo-filgrastim at the recommended dose and was numerically two times more frequent than in the placebo group.

iii. None of the 5 deficiencies described in the Complete Response letter are relevant to this interpretation of the issue of efficacy and safety. The clinical reviewer deems the BLA approvable if the 5 deficiencies cited in the Complete Response letter of September 29, 2010 have been resolved.

b. Dr. Jee Chung, the CMC reviewer, had 6 information request comments in the Complete Response Letter (#13-18). Dr. Chung states that the Applicant intends to provide the requested information sometime in the third quarter of 2012 and therefore these comments will become Post Marketing Commitments (PMC). Thus, Dr. Chung states that provided the five deficiencies are resolved, and that the following comments can be imposed as PMCs, that the BLA is approvable. The comments are as follows:

#13: Provide data indicating that SEC provides an accurate measure of aggregate content through the product's shelf life.

#14: Provide a risk assessment of the potential impact that these particulates may have on the quality, safety and efficacy of tbo-filgrastim and propose a strategy that provides an appropriate level of control.

#15: Revise the peptide mapping assay to include quantitative acceptance criteria for peak areas, relative peak heights, and new peaks.

#16: Provide testing for leachates at the end of shelf life for the drug product in the final container closure system in the presence of the drug product (b) (4) and provide a plan for submission of these data.

#17: Provide optimization data for the current assay used to determine plasmid copy number.

#18: Provide long-term product quality data of tbo-filgrastim formulated with Polysorbate 80 at the upper limit of (b) (4)

c. Dr. Susan Kirschner of Immunogenicity, reported that the Applicant stated that they intend to provide the FDA with information requested in the Complete Response letter (Comments 8-11) relating to methods to be used to assess immunogenicity. Since the primary manifestation of clinically relevant anti-product antibody response manifests as prolonged neutropenia, the clinical safety data obtained in the pivotal study and supportive safety studies were adequate to rule out that an immune response neutralizes the drug product based on the lack of unexpected or unusually prolonged neutropenia observed in clinical studies. Therefore, it was decided that the lack of immunogenicity data would not prevent approval so these comments were not a Complete Response Deficiency. These comments (which are summarized below) would become post marketing requirements (PMRs). The Comments 8-11 are as follows:

> #8: Submit a plan for development of a validated screening assay for anti-product antibody responses to tbo-filgrastim.
> #9: Submit a plan for development of a validated assay for confirmation of anti-product antibodies identified by the screening assay.
> #10: Submit a plan for a validated assay for identification of neutralizing antibodies.
> #11: Provide a plan for assessing the presence, persistence and effects of anti-tbo-filgrastim, anti-G-CSF binding and neutralizing antibodies in at least 500 patients.

d. Dr. Bahru Habtemariam, Clinical Pharmacology, stated that the FDA IRT group requested that the QT_c protocol be done (b) (4) . Dr. Habtemariam reported that as of June 28, 2012, the FDA received notification from the Applicant that (b) (4) . As noted below, submission and evaluation of data from the completed thorough QT trial typically is not required prior to licensure for supportive care products in the oncology setting, such as tbo-filgrastim. Thus, at this time, there are not issues from Clinical Pharmacology and the application is approvable provided that the 5 deficiencies of the Complete Response letter of September 29, 2010 have been resolved. The completion of the QT_c trial will be a post marketing requirement (PMR).

e. Dr. Patricia Hughes (BMAP) has provided a non-deficiency comment relating to the drug substance manufacturing process to improve microbial control. BMAP requested the following from the Applicant which will become PMCs:

> 6.a. In–process and final tbo-filgrastim bioburden and endotoxin data for the (b) (4) following the proposed changes;
> 6.b. Microbial control data for the storage (b) (4)

6.c. Identify any additional changes that could affect microbial process control.

f. BMAP provided another non-deficiency comment (Comment #12) in the Complete Response letter of September 29, 2010. Comment 12 requested that the Applicant submit the results of the re-evaluation of the bioburden limit after 30 commercial batches of the drug substance and to propose new (b) (4) (b) (4) bioburden action limit that more accurately reflects process capability. This will become a PMC.

Efficacy as Measured by the Primary Endpoint (The following statement was excerpted from the reviews of Dr. Patricia Keegan and Dr. Kun He). Tbo-filgrastim was superior to placebo in terms of the primary efficacy endpoint (duration of severe neutropenia in cycle 1 defined as the number of days with grade 4 neutropenia-2.7 days reduction in DSN with tbo-filgrastim, $p<0.0001$).

Although the clinical trial included a second primary endpoint based on comparison to a filgrastim product approved in several European countries, this comparison provides only supportive data due to flaws in the study design. The proposed "equivalence" analysis is not appropriate for demonstrating the safety, purity, and potency of tbo-filgrastim in this BLA. TEVA did not provide adequate justification for the non-inferiority margin of a 1-day difference in mean DSN between the tbo-filgrastim and the filgrastim product which was approved in several European countries in the control arm. In addition, TEVA did not provide adequate justification that a margin based on treatment effects with US-licensed Neupogen could be extrapolated to treatment effects with the European-marketed product. Thus, although the data demonstrated that the 95% confidence interval (-0.26, 0.33) for mean difference between tbo-filgrastim and the filgrastim product approved in several European countries in DSN lay within the 1 day margin proposed by TEVA, claims of non-inferiority to the European-marketed filgrastim product or any other filgrastim product will not be permitted.

Safety: No significant safety signals attributed to tbo-filgrastim were detected during the review of the data on 541 patients exposed to tbo-filgrastim. Bone pain was the most frequent treatment emergent adverse reaction that occurred in at least 1% or greater in patients treated with tbo-filgrastim at the recommended dose and was numerically two times more frequent than in the placebo group.

Benefit Risk Assessment: The benefit risk profile for tbo-filgrastim for the proposed indication is favorable.

CDTL Recommendation: Grant approval of tbo-filgrastim for the reduction of the duration of severe neutropenia in patients with non-myeloid malignancies receiving myelosupressive anti-cancer drugs associated with a clinically significant incidence of febrile neutropenia

2. Background (This section excepted from the Clinical Review of Dr. Thomas Herndon).

Intensive cytotoxic chemotherapy for the treatment of cancer often causes profound neutropenia, which may result in hospitalization for treatment of fever or cause potentially fatal infections. The definition of neutropenia varies from institution to institution but is usually defined as an absolute neutrophil count (ANC) ≤ 500 cells/mcL or <1,000 cells/mcL with a predicted nadir of < 500 cells/mcL. There is an increased risk of an occult infection in patients with an ANC < 1,000 cells/μL, and the risk of infection increases as the ANC decreases. Fever in a neutropenic patient is usually defined as a single temperature of > 38.3^{o}C, or a sustained temperature > 38.0^{o}C for more than one hour. Occasionally, a neutropenic patient may not present with fever despite the presence of infection. This occurs more often in elderly patients or patients receiving corticosteroids or other anti-pyretics or immunosuppressive therapy.

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

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

Table 2: FDA Approved Agents for the proposed indication

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

3. CMC

Dr. Jee Chung, the CMC reviewer had 6 information request comments in the Complete Response Letter (#13-18). Dr. Chung states that the Applicant intends to provide the requested information sometime in the third quarter of 2012 and therefore these comments will become Post Marketing Commitments (PMC). The comments are as follows:

#13: Provide data indicating that SEC provides an accurate measure of aggregate content through the product's shelf life.

#14: Provide a risk assessment of the potential impact these particulates may have on the quality, safety and efficacy of tbo-filgrastim and propose a strategy that provides an appropriate level of control.

#15: Revise the peptide mapping assay to include quantitative acceptance criteria for peak areas, relative peak heights, and new peaks.

#16: Provide testing for leachates at the end of shelf life for the drug product in the final container closure system in the presence of the drug product (b) (4) and provide a plan for submission of these data.

#17: Provide optimization data for the current assay used to determine plasmid copy number.

#18: Provide long-term product quality data of tbo-filgrastim formulated with Polysorbate 80 at the upper limit of (b) (4)

This section was excerpted from the review of Dr. Jee Chung.

Recommendation of ONDQA:

Dr. Chung states that provided the five deficiencies outlined in the Complete Response letter of September 29, 2010 are resolved, that the BLA is approvable, providing that the provisions of the above comments can be imposed as post marketing commitments.

Dr. Jee Chung, the CMC reviewer had 6 information request comments in the Complete Response Letter (#13-18). Dr. Chung states that the Applicant intends to provide the requested information sometime in the third quarter of 2012 and therefore these comments will become Post Marketing Commitments (PMC). The comments are as follows:

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#15: Revise the peptide mapping assay to include quantitative acceptance criteria for peak areas, relative peak heights, and new peaks.

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#18: Provide long-term product quality data of tbo-filgrastim formulated with Polysorbate 80 at the upper limit of (b) (4)

This section was excerpted from the review of Dr. Jee Chung.

4. Nonclinical Pharmacology/Toxicology

Nonclinical pharmacology and toxicology studies submitted in 2009 were reviewed by Mary Jane Masson-Hinrichs, Ph.D.

On September 29, 2010, a Complete Response letter was issued for this application. Except for the lack of an embryofetal developmental study, the nonclinical package was considered to be adequate. For patients with advanced, life-threatening disease, a study examining embryo-fetal toxicity would be sufficient to fulfill reproduction toxicology requirements; the complete battery of reproduction toxicology studies would usually not be required. As a supportive care product, tbo-filgrastim does not fall within the Scope of ICH guidance S9: Nonclinical Evaluation for Anticancer Products. 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.

The current submission contains results of an embryo-fetal developmental toxicology study in rabbits, conducted with tbo-filgrastim. This study adequately addresses the nonclinical deficiency identified in 2010. In brief, pregnant rabbits were treated with tbo-filgrastim during the period of organogenesis. 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 embryo-fetal 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 tbo-filgrastim will have chemotherapy induced neutropenia. 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 embryo-fetal effects in Reference ID: 3165240 2 rabbits occurred at exposures that are significantly higher than those reported in patients at the recommended dose of 5 μ g/kg/day. Therefore, a pregnancy Category C is proposed for tbo-filgrastim. 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 tbo-filgrastim 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.

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.

The conclusion of Dr. Saber's and Dr. Leighton's review is that tbo-filgrastim may be approved and that no additional nonclinical studies are needed for the proposed indication.

(This section was excerpted from the memoranda of Dr. Haleh Saber and Dr. John Leighton).

Recommendation of Nonclinical Pharmacology/Toxicology: Tbo-filgrastim may be approved for the proposed indication. No additional nonclinical studies in the Pharmacology/Toxicology area are needed to support approval of tbo-filgrastim for the proposed indication.

5. Clinical Pharmacology

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

The selection of dose and dose regimen for the phase 3 trials were based on the data obtained in the phase 1 trials and historical clinical use with an FDA-approved product, Neupogen. To support approval for this indication, the sponsor conducted two phase 1

PK/PD trials in healthy subjects (N=176) and three phase 3 trials in patients with breast cancer (N=348), lung cancer (N=240), or non-Hodgkin lymphoma (NHL, N=92). Pharmacokinetics Findings: The pharmacokinetics (PK) of tbo-filgrastim was studied in both healthy subjects and in cancer patients. Reference ID: 3167976 3

Healthy Subjects: Subjects in the phase 1 trials were assigned to receive single 5 or 10 μg/kg IV or SC doses of tbo-filgrastim or a non-US-approved filgrastim product approved in several European countries. The absolute bioavailability of 5 and 10 μg/kg SC tbo-filgrastim was 33% and 45%, respectively. After single dose SC administration of 5 μg/kg tbo-filgrastim (N=33), the geometric mean (CV%) of serum Cmax was 18 ng/mL (41%) and of AUC0-48h was 158 ng*h/mL (37%). The median T max was 6 hours and the median half-life (t½) was 8.9 hours. Increasing the dose of tbo-filgrastim from 5 to 10 μg/kg resulted in an approximately 3-fold increase in both Cmax and AUC0-48h.

Cancer Patients: PK data were obtained from patients with breast cancer, lung cancer and NHL (N=12 per group) who received SC tbo-filgrastim 5 μg/kg/day. Following the 1st tbo-filgrastim dose in cycle 1, the geometric mean (CV%) of serum Cmax and AUC0-48h were 36 ng/mL (41 %) and 305 ng*h/mL (35%) in breast cancer, 25 ng/mL (60%) and 273 ng*h/mL in lung cancer (61 %), and 20 ng/mL (24%) and 184 ng*h/mL (23%) in NHL, respectively. For the 3 groups combined, the median Tmax was between 4 to 6 hours and the median t½ was between 3.2 to 3.8 hours. The terminal half-life was calculated from serum levels measured up to 24 hours as compared to up to 48 hours in the healthy subjects. Accumulation after repeated dosing was not observed. No dose adjustment based on cancer type is warranted.

No gender-related differences were observed in the pharmacokinetics of tbo-filgrastim following a SC administration. Mild renal impairment (creatinine clearance 60-89 mL/min; N=l1) had no clinical meaningful effect on tbo-filgrastim pharmacokinetics. No dose adjustment is recommended for mild renal impairment. The pharmacokinetic profile in patients with moderate and severe renal impairment has not been assessed. However, based on the safety margin of tbo-filgrastim and the lack of relationship between the incidence of the major adverse event (bone pain) and degree of renal impairment, a tbo-filgrastim dosage adjustment would not be clinically warranted. The pharmacokinetic profile in patients with hepatic impairment has not been studied.

Immunogenicity: The incidence of anti-tbo-filgrastim antibody formation obtained in clinical studies is not considered reliable since it was not assessed using validated assay methods. The unvalidated immunogenicity assays yielded the following results: Less than 1 % (5 out of 541) of patients treated with tbo-filgrastim tested positive for binding antibodies during study treatment; 4 of the 5 tested positive for neutralizing antibodies. No evidence of toxicity profile or clinical response was associated with binding antibody or neutralizing antibody development. The impact of immunogenicity on tbo-filgrastim PK could not be assessed since tbo-filgrastim PK data were not collected in patients who tested positive for binding or neutralizing antibodies.

QT/QTc Evaluation: The potential effects of tbo-filgrastim on the QTc interval were not adequately evaluated in clinical trials included in the BLA since ECGs were monitored at

times when tbo-filgrastim was totally cleared from systemic circulation. A post-marketing requirement to perform a QTc study in either healthy subjects or patients at the highest dose tested is recommended. Protocol XM02-TQT-103 was provided by the applicant in this submission to address this issue. Clinical pharmacology and the FDA Interdisciplinary Review Team (IRT) provided comments regarding the proposed protocol to the applicant on 5/25/2012.

There was insufficient information submitted in the BLA to characterize the effects of tbo-filgrastim on the QT_c interval since ECGs were obtained at times when tbo-filgrastim was cleared from the systemic circulation. FDA is requesting that the Applicant carry out a study to evaluate the effects of tbo-filgrastim on the QT_c in the post marketing period. (b) (4) The completion of this trial will be a Post Marketing Requirement (PMR). Submission and evaluation of data from the completed thorough QT trial typically is not required prior to licensure given that tbo-filgrastim is a supportive care product in the oncology setting. This section was excerpted from the review of Dr. Bahru Habtemariam and Dr. Joseph Grillo and Dr. Nam Atiqur Rahman.

Recommendation of Clinical Pharmacology: (b) (4) Thus, at this time, there are no issues from Clinical Pharmacology and the application is approvable provided that the 5 deficiencies in the Complete Response letter of September 29, 2010 have been resolved. The recommendation of Clinical Pharmacology is for approval of the BLA with a post marketing requirement to carry out a QT_c study.

6. Clinical Microbiology

BMAP (Dr. Patricia Hughes) has provided a non-deficiency comment relating to the drug substance manufacturing process to improve microbial control. Dr. Hughes requested that the Applicant provide the following as PMCs:

a. In–process and final bioburden and endotoxin data for the (b) (4) following the proposed changes;

b. Microbial control data for the storage (b) (4);

c. Identify any additional changes that could affect microbial process control.

BMAP also provided another non-deficiency comment in the September 29, 2010 Complete Response Letter (Comment #12). Comment 12 requested that the Applicant submit the results of the re-evaluation of the bioburden limit after 30 commercial batches

of the drug substance and to propose new (b) (4) bioburden action limit that more accurately reflects process capability. This will become a PMC. (This section was based on the review of Dr. Patricia Hughes).

Recommendations of Microbiology: Providing that the above comments are carried out by the Applicant as post marketing commitments, the recommendation is for approval of the BLA.

7. Clinical/Statistical-Efficacy (The following is based on the reviews from Dr. Laura Lu and Dr. Kun He of the Biostatistics Review Division).

The conclusion following the first cycle of review was that the results of a large double blind randomized (3 arm) trial (XM02-02-INT) in which 348 patients with high risk stage II or with stage III or IV breast cancer requiring and receiving myelosuppressive chemotherapy (doxorubicin 60 mg/m and docetaxel 75 mg/m administered up to 4 cycles every 21 days) were randomized 2:2:1 to tbo-filgrastim, a non-US-approved filgrastim, (a filgrastim product approved in several European countries) and a placebo was that:

a. Tbo-filgrastim was superior to placebo in terms of the primary efficacy endpoint (duration of severe neutropenia in cycle 1 defined as the number of days with grade 4 neutropenia-2.7 days reduction in DSN with tbo-filgrastim, $p<0.0001$).
b. Although the data demonstrated that the 95% confidence interval (-0.26, 0.33) for mean difference between tbo-filgrastim and the European-approved filgrastim product in DSN lay within the 1 day equivalence margin (b) (4) (b) (4) the data submitted by the applicant do not support an "equivalence" claim between tbo-filgrastim and US-licensed Neupogen.

Recommendation of the Biostatistics Review Division and the Clinical Review Division: None of the 5 deficiencies are relevant to the interpretation of the issue of efficacy. The clinical reviewer deems the BLA approvable if the 5 deficiencies cited in the Complete Response letter have been resolved.

8. Safety (The following is excerpted from the Safety Review of Dr. Thomas Herndon, Medical Reviewer).

The review of safety was focused on the analyses of 541 patients with cancer who received the tbo-filbrastim dosing regimen proposed for labeling, 5 mcg subcutaneously once daily. Analyses of the safety databases were performed to analyze the individual tbo-filgrastim trials, and pooled safety data for the three key tbo-filgrastim trials in patients with cancer. Among the patients entered on Studies XM02-02, XM02-03 and

XM02-04, there were no deaths attributable to tbo-filgrastim. Less than 1% of the SAEs in the tbo-filgrastim therapy groups were considered study drug related by the investigator and the Applicant. The review of these cases showed that in study XM02-02, one patient had an allergic reaction associated with bronchospasm in cycle 1 following the 10th dose of study drug, and one patient had an episode of syncope. The patient with bronchospasm tolerated tbo-filgrastim upon rechallenge. In XM02-03, 3 patients had 4 SAEs that were thought to be possibly related to the study drug and or the chemotherapy by the investigator. One patient had a myocardial infarction. Another patient experienced thrombocytopenia which was more likely thought to be due to the chemotherapy.

The major significant adverse event thought to be associated with the study drug was bone pain. The incidence of bone pain in the XM02-02 clinical trial in patients with cancer was 23.5% for tbo-filgrastim, 20.6% for the non-US-approved filgrastim (a filgrastim product approved in several European countries), and 9.7% for placebo. No patient discontinued tbo-filgrastim due to bone pain.

Notably, there were no cases of splenic rupture. The medical reviewer examined 37 patients who received tbo-filgrastim with an AE of abdominal pain for splenic rupture and none were found. In study XM02-03, there was one case of acute respiratory distress syndrome but this was not considered to be due to tbo-filgrastim.

The conclusion of the safety review was that no significant safety signals attributed to tbo-filgrastim were detected during the review of the data on 541 patients exposed to tbo-filgrastim. Bone pain was the most frequent treatment-emergent adverse reaction that occurred in at least 1% or greater in patients treated with tbo-filgrastim at the recommended dose and was numerically two times more frequent than in the placebo group..

Recommendation of the Medical Reviewer: Approval of the BLA provided that the 5 deficiencies in the September 29, 2010 Complete Response letter are resolved.

9. Advisory Committee Meeting

Not applicable.

10. Pediatrics

The application contained a pediatric deferral request and a pediatric plan to be reviewed by the PeRC (August 11, 2010). The PeRC recommended that the Applicant proceed with PK/PD and safety studies followed by an efficacy study in an open label study (N=50) in children with solid tumors having no bone marrow involvement. The PeRC recommended not doing the efficacy study if the PK/PD study showed that the data was consistent with data already available from adults. (This is excerpted from the CDTL review of Dr. Suzanne Demko.)

I have considered the discussion in the Pediatric Section of Dr. Patricia Keegan's earlier review; however, consistent with the PeRC recommendation, we are not requiring an efficacy study at this time.

11. Other Relevant Regulatory Issues

- **Application Integrity Policy (AIP):** Issues resolved as described above.
- **Exclusivity or Patent Issues of Concern:** None
- **Financial Disclosures**: Adequate and complete.
- **Other GCP Issues**: None
- **Office of Scientific Investigation (OSI) Audits:** Based on the FDA inspection of the BioGeneriX AG facility (b) (4) there was a concern that the integrity of the database for Study XM02-2-INT, the single trial submitted to support the efficacy of the product, may have been compromised. After the initial database lock on January 2, 2006, and subsequent data unblinding, the data base was unlocked and the data were altered on at least two separate dates, i.e. January 17, 2006 and January 23, 2006. The FDA requested information about the quality control and/or quality assurance activities at each stage of data handling, from initial data entry into the data base through the final database lock, that were undertaken to ensure the integrity of safety and efficacy data. In addition, the FDA asked the Applicant to provide documentation, including justification and the audit trail, for all changes made to the database after unblinding. Finally, the FDA requested a detailed analysis of

the impact of all changes made to the data base after initial lock, and unblinding on the evaluation of safety and efficacy data.

The Applicant points out that two FDA investigators, Mr. James Kewley, and Mr. Jonathan Helfgott re-inspected the BiogeneriX site (b) (4) on (b) (4) (b) (4). As pointed out by the Applicant, and what is in fact in the December 16, 2011 report of that inspection, the re-inspection did not identify any concerns relating to the integrity of the data base used for Study XM02-02-INT, the pivotal trial of BLA 125294. During this inspection, the quality control and quality assurance safeguards were physically demonstrated to the FDA inspections which were found by the inspectors to be satisfactory. Inspection of the audit trail at that visit also confirmed that no inappropriate changes were made to the data base. Finally, the OSI report concluded that the FDA inspection revealed that the violations noted during the inspection (see Observations #1 and #2 cited above) were considered unlikely to importantly impact data integrity. Thus, it is the opinion of the CDTL that the Applicant has adequately responded to the Deficiency #1 of the Complete Response letter.

12. Labeling

The labeling has been agreed upon by the Applicant and by the FDA.

13. Recommendations/Risk Benefit Assessment

- **Recommended Regulatory Action**: Approval
- **Risk Benefit Assessment:** (The following statement is based on the review of Dr. Thomas Herndon, Medical Reviewer). **Efficacy:** Tbo-filgrastim was superior to placebo in terms of the primary efficacy endpoint (duration of severe neutropenia in cycle 1 defined as the number of days with grade 4 neutropenia-2.7 days reduction in DSN with tbo-filgrastim, $p<0.0001$). A comparative claim between tbo-filgrastim and US-licensed Neupogen was not established. **Safety** There are no unanticipated or significant safety signals with the use of tbo-filgrastim. **Benefit Risk Assessment:** The benefit risk profile for tbo-filgrastim for the proposed indication is favorable.

CDTL Recommendation: The recommendation of the CDTL reviewer is approval.

- Recommendation for Postmarketing Risk Evaluation and Management Strategies

None

- Recommendation for Other Postmarketing Commitments

PMC#1: To submit data on [redacted] accumulated after manufacture of 30 commercial batches and any changes to currently proposed [redacted] action limits of [redacted] prior to [redacted] in a CBE-30 supplement.

Final Protocol Submission:	N/A
Study Completion:	12/2016
Final Report Submission:	03/2017

PMC#2: To submit winter shipment data form the shipping qualification study in a CBE-0 supplement.

Final Protocol Submission:	04/2012
Study Completion:	01/2013
Final Report Submission:	05/2013

PMC#3: To submit the following data obtained after implementation of changes made to improve microbial control in the drug substance manufacturing process: a. In-process and final filgrastim bioburden and endotoxin data for the [redacted] following the proposed changes; b. Microbial control data for storage [redacted] c. Any other changes and data that could affect microbial process control (for example, changes in hold times). The information should be submitted as a CBE-30 supplement by September 30, 2012.

Final Protocol Submission:	06/2010
Study Completion:	03/2011
Final Report Submission	09/2012

PMC#4: To verify that the SE-HPLC method can accurately detect aggregates by using an orthogonal method conducted with stressed drug substance and drug product samples.

Final Protocol Submission:	04/2011
Study Completion:	03/2013
Final Report Submission:	03/2013
Assay Development Findings:	03/2013

PMC#5: To characterize using orthogonal methods, and monitor, throughout the dating period, sub-visible particulates (SVPs) in the range between [redacted] and to propose an appropriate control strategy based on the risk to product quality, safety and efficacy.

Final protocol Submission:	04/2011
Study Completion:	03/2013
Final Report Submission:	03/2013
Assay Development Findings:	03/2013

PMC#6: To conduct a validation study for a quantitative peptide map method for release and stability testing and set appropriate release and stability specifications for the quantitative peptide map based on the analytical capabilities, clinical trial experience, and manufacturing history.

Final Protocol Submission:	04/2011
Study Completion:	05/2012
Final Report Submission:	03/2013

PMC#7: To conduct a quantitative (ppb and ppm) leachables study and risk assessment of leachates into the drug product and/or (b) (4) in the final container closure system using methods that are suitably validated for its intended purpose.

Final Protocol Submission:	10/2012
Study Completion:	02/2013
Final Report Submission:	06/2013

PMC#8: To formulate during product, at laboratory scale, using polysorbate 80 (b) (4) and evaluate the effects of the polysorbate 80 on product quality over time.

Final Protocol Submission:	12/2012
Study Completion:	03/2016
Final Report Submission:	05/2016
Assay Development Findings:	05/2016

- Recommendation for Other Postmarketing Requirements

PMR#1: Conduct a clinical trial per ICH E14 to assess the potential for tbo-filgrastim to prolong the QT interval.

Final Protocol Submission:	02/29/2012
Trial Completion:	11/30/2013
Final Report Submission:	06/30/2014

PMR#2: To develop validated screening and confirmatory assays to assess for the presence of anti-tbo-filgrastim antibodies. The validation of the assay should include the sensitivity and specificity for detection of anti-tbo-filgrastim antibodies that are also cross-reactive with native human granulocyte colony stimulating factor (G-CSF).

Final Protocol Submission:	09/2012
Study Completion:	02/2013
Final Report Submission:	04/2013

PMR#3: To develop a validated assay for identification of anti-product antibodies that neutralize the bioactivity of tbo-filgrastim. The validation of the assay should include the sensitivity and specificity for detection of anti-

tbo-filgrastim antibodies that area also cross-reactive with and neutralize the bioactivity of anti- human granulocyte colony stimulating factor (G-CSF).

Final Protocol Submission:	09/2012
Study Completion:	03/2012
Final Report Submission:	05/2013

PMR#4: To conduct an assessment for the presence of anti-tbo-filgrastim and anti-native human G-CSF binding antibodies using a validated assay in at least 500 patients enrolled/to be enrolled in one or more clinical trials. To conduct an assessment for neutralizing antibodies using a validated assay in all patients with binding antibodies to tbo-filgrastim or native G-CSF and in all patients with evidence of unexplained, persistent neutropenia. Sicor should provide a listing of the clinical trials in which this assessment will be conducted.

Final Protocol Submission:	08/2013
Study Completion:	08/2014
Final Report Submission:	10/2014

- Recommended Comments to Applicant

None

Appears this way on original

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

/s/

ALBERT B DEISSEROTH
08/29/2012