RECORD OF TELEPHONE CONVERSATION

BLA: 125164

Product: PegEpo

Sponsor: Roche

Today's date: June 11, 2007

Speakers: Karen Weiss and Dwaine Rieves for FDA and Cindy Dinella for Roche

FDA: Karen Weiss, Dwaine Rieves, Ruyi He, John Lee and Florence Moore

Roche: Cindy Dinella, Lisa Luther, Philippe Van der Auwera, Bruno Osterwalder, Chris Dougherty Krishnan Viswanadhan

FDA called Roche in order to obtain Roche's perspective regarding any need for Roche to present their data at a September advisory committee that had been planned to focus upon class issues with the ESAs. FDA noted that if Roche wanted to present at the committee, then the agenda could be modified to include a discussion of Roche safety and efficacy data and to include questions to the committee regarding the data. FDA indicated that FDA did not have a preference if Roche participated or not but wanted to give Roche the option of deciding to present or not to present at the AC if needed.

FDA indicated that the AC will focus on PMC studies that have demonstrated safety signals focusing on these safety and efficacy signals of these other ESAs. FDA reiterated that the purpose of the AC meeting is to discuss the class of ESAs and not for a specific approval. Mircera falls under this class and the labeling for all ESAs will apply to Mircera. FDA stated that Roche's participation in the AC will not determine the approvability of Mircera. FDA commented that that it is unlikely that the AC would recommend the withdrawal of any of the ESA products but if that were to happen it will apply to all ESA products.

Roche indicated they might have misunderstood FDA regarding the purpose of the AC meeting and acknowledged FDA's comment. Roche stated that they will discuss FDA's comments internally and give FDA feedback by Thursday, June 14, 2007 on their decision to present or not to present at the September AC.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

From: **Florence O. Moore, M.S.** FM

To: **File: STN 125164/0**

Subject: **Filing Meeting Summary**

Sponsor: **Hoffman La-Roche.**

Product: **Pegserepoetin alfa**

Date, Location, & Time of Meeting: **June 1, 2006**
WO, Conference Room 2376
1:00 p.m. – 2:00 p.m.

Purpose:

To discuss the filablity of STN: 125164/0 for Pegserepoetin alfa and discuss CMC, Clinical Pharmacology, Clinical Studies, deficiencies identified.

Relevant Milestones:

- BLS Filed: June 1, 2006
- Deficiencies identified: TBD
- First Action Due Date: February 17, 2007

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration

CENTER FOR DRUG EVALUATION AND RESEARCH

TEL: 301-827-1790 FAX: 301-480-3256

6/1/06

TO: Florence Moore

FROM: Dan H. Pluznik

FAX#: 301 796-9849

Number of pages: 7

COMMENTS:

STN 125164/0 Product Pegsecrepoetin [Mircera] Part B Page 1

Part B – Product/CMC/Facility Reviewer(s)

CTD Module 2 Contents	Present?		If not, justification, action & status
Overall CTD Table of Contents [2.1]	(Y)	N	
Introduction to the summary documents (1 page) [2.2]	(Y)	N	
Quality overall summary [2.3]	(Y)	N	
◻ Drug Substance	(Y)	N	
◻ Drug Product	(Y)	N	
◻ Facilities and Equipment	(Y)	N	
◻ Adventitious Agents Safety Evaluation	(Y)	N	
◻ Novel Excipients	(Y)	N	
◻ Executed Batch Records	(Y)	N	
◻ Method Validation Package	(Y)	N	
◻ Comparability Protocols	(Y)	N	

CTD Module 3 Contents	Present?		If not, justification, action & status
Module Table of Contents [3.1]	Y	N	
Drug Substance [3.2.S]			
◻ general info	(Y)	N	
o nomenclature			
o structure (e.g. sequence, glycosylation sites)			
o properties			
◻ manufacturers (names, locations, and responsibilities of all sites involved)	(Y)	N	
◻ description of manufacturing process	(Y)	N	
o batch numbering and pooling scheme			
o cell culture and harvest			
o purification			
o filling, storage and shipping			
◻ control of materials	(Y)	N	
o raw materials and reagents			
o biological source and starting materials			
o cell substrate: source, history, and generation			
o cell banking system, characterization, and testing			
◻ control of critical steps and intermediates	(Y)	N	
o justification of specifications			
o analytical method validation			
o reference standards			
o stability			
◻ process validation (prospective plan, results, analysis, and	(Y)	N	

STN Product Part B Page 2

CTD Module 3 Contents	Present?	If not, justification, action & status
conclusions)		
☐ manufacturing process development (describe changes during non-clinical and clinical development; justification for changes)	(Y) N	
☐ characterization of drug substance	(Y) N	
☐ control of drug substance	(Y) N	
○ specification		
○ justification of specs.		
○ analytical procedures		
○ analytical method validation		
○ batch analyses		
○ consistency (3 consecutive lots)		
○ justification of specs.		
☐ reference standards	(Y) N	
☐ container closure system	(Y) N	
☐ stability	(Y) N	
☐ summary		
☐ post-approval protocol and commitment		
☐ pre-approval		
○ protocol		
○ results		
○ method validation		
Drug Product [3.2.P]		
☐ description and composition	(Y) N	
☐ pharmaceutical development	(Y) N	
☐ manufacturers (names, locations, and responsibilities of all sites involved)	(Y) N	
☐ batch formula	(Y) N	
☐ description of manufacturing process for production through finishing, including formulation, filling, labeling and packaging (including all steps performed at outside [e.g., contract] facilities)	(Y) N	
☐ controls of critical steps and intermediates	(Y) N	
☐ process validation including processing & sterility assurance:	(Y) N	
○ 3 consecutive lots		
○ other needed validation data		
☐ control of excipients (justification of specifications; analytical method validation; excipients of	(Y) N	

STN Product Part B Page 3

CTD Module 3 Contents	Present?	If not, justification, action & status
human/animal origin)		
☐ control of drug product (justification of specifications; analytical method validation)	(Y) N	
☐ container closure system [3.2.P.7]	(Y) N	
○ specifications (vial, elastomer, drawings)		
○ availability of DMF		
○ closure integrity		
○ administration device(s)		
☐ stability	(Y) N	
☐ summary		
☐ post-approval protocol and commitment		
☐ pre-approval		
○ protocol		
○ results		
☑ method validation		
Diluent (vials or filled syringes) [3.2.P.1]		
☐ description and composition of diluent	(Y) N	
☐ pharmaceutical development	(Y) N	
☐ manufacturers (names, locations, and responsibilities of all sites involved)	(Y) N	
☐ batch formula	(Y) N	
☐ description of manufacturing process for production through finishing, including formulation, filling, labeling and packaging (including all steps performed at outside [e.g., contract] facilities)	(Y) N	
☐ controls of critical steps and intermediates	(Y) N	
☑ process validation including processing & sterility assurance:	(Y) N	
○ 3 consecutive lots		
○ other needed validation data		
☐ control of excipients (justification of specifications; analytical method validation; excipients of human/animal origin, other novel excipients)	(Y) N	
☐ control of diluent (justification of specifications; analytical method validation, batch analysis, characterization of impurities)	(Y) N	
☐ reference standards	(Y) N	

STN Product Part B Page 4

CTD Module 3 Contents	Present?	If not, justification, action & status
☐ container closure system o specifications (vial, elastomer, drawings) o availability of DMF o closure integrity ☐ stability ☐ summary ☐ post-approval protocol and commitment ☐ pre-approval o protocol o results	(Y) N (Y) N	
Other components to be marketed (full description and supporting data, as listed above): ☐ other devices ☐ other marketed chemicals (e.g. part of kit)	Y N Y N	N/A
Appendices for Biotech Products [3.2.A] ☐ facilities and equipment o manufacturing flow; adjacent areas o other products in facility o equipment dedication, preparation and storage o sterilization of equipment and materials o procedures and design features to prevent contamination and cross-contamination ☐ adventitious agents safety evaluation (viral and non-viral) e.g.: o avoidance and control procedures o cell line qualification o other materials of biological origin o viral testing of unprocessed bulk o viral clearance studies o testing at appropriate stages of production ☐ novel excipients	(Y) N (Y) N (Y) N	
USA Regional Information [3.2.R] ☐ executed batch records ☐ method validation package ☐ comparability protocols	(Y) N (Y) N (Y) N	

STN Product Part B Page 5

CTD Module 3 Contents	Present?	If not, justification, action & status
Literature references and copies [3.3]	(Y) N	

Examples of Filing Issues	Yes?	If not, justification, action & status
content, presentation, and organization sufficient to permit substantive review? □ legible □ English (or translated into English) □ compatible file formats □ navigable hyper-links □ interpretable data tabulations (line listings) & graphical displays □ summary reports reference the location of individual data and records □ all electronic submission components usable	(Y) N (Y) N (Y) N (Y) N (Y) N (Y) N (Y) N (Y) N	
includes appropriate process validation data for the manufacturing process at the commercial production facility?	(Y) N	
includes production data on drug substance and drug product manufactured in the facility intended to be licensed (including pilot facilities) using the final production process(es)?	(Y) N	
includes data demonstrating consistency of manufacture	(Y) N	
includes complete description of product lots and manufacturing process utilized for clinical studies	(Y) N	
describes changes in the manufacturing process, from material used in clinical trial to commercial production lots	(Y) N	
data demonstrating comparability of product to be marketed to that used in clinical trials (when significant changes in manufacturing processes or facilities have occurred)	(Y) N	
certification that all facilities are ready for inspection	(Y) N	
data establishing stability of the product through the proposed dating period and a stability protocol describing the test methods used and time intervals for product assessment.	(Y) N	
if not using a test or process specified by regulation, data is provided to show the alternate is equivalent (21 CFR 610.9) to that specified by regulation. List:	(Y) N	N/A

STN Product Part B Page 6

Examples of Filing Issues	Yes?	If not, justification, action & status
☐ LAL instead of rabbit pyrogen ☐ mycoplasma ☐ sterility ☐ ☐	(Y) N (Y) N (Y) N	
identification by lot number, and submission upon request, of sample(s) representative of the product to be marketed; summaries of test results for those samples	Y N	N/A
floor diagrams that address the flow of the manufacturing process for the drug substance and drug product	(Y) N	
description of precautions taken to prevent product contamination and cross-contamination, including identification of other products utilizing the same manufacturing areas and equipment	Y N	N/A
information and data supporting validity of sterilization processes for sterile products and aseptic manufacturing operations	Y N	N/A
if this is a supplement for post-approval manufacturing changes, is animal or clinical data needed? Was it submitted?	Y N	N/A

List any issue not addressed above which should be identified as a reason for not filing the BLA/BLS. Also provide additional details if above charts did not provide enough room (or attach separate memo).

Recommendation (circle one): (File) RTF

Reviewer: David Plunkett 6/1/06 Type (circle one): (Product (Chair)) Facility (DMPQ)
(signature/ date)

Concurrence:
Branch/Lab Chief: _____ Division. Director: Barry Weiner 6-1-06
(signature/ date) (signature/ date)
for A. Rosenberg

RECORD OF TELEPHONE CONVERSATION

BLA: 125164

Product: PegEpo

Sponsor: Roche

Today's date: June 6, 2007

Speakers:

Krishnan Viswanadhan for Roche

Karen Weiss and Dwaine Rieves for FDA

FDA called Roche in order to obtain Roche's perspective regarding any need for Roche to present their data at a September advisory committee that had been planned to focus upon class issues with the ESAs. FDA noted that if Roche wanted to present at the committee, then the agenda could be modified to include a discussion of Roche safety and efficacy data and to include questions to the committee regarding the data. Roche stated they would discuss the request internally and set up a follow-up discussion with FDA.

Date: 5/18/07
From: Karen Weiss, M.D. Deputy Director, Office of Oncology
Subject: BLA 125164, Mircera,
To: File

Hoffman La-Roche submitted their Biological License Application for Mircera (Pegzeropoeitin alfa), a new Erythropoiesis Stimulating Agent (ESA) on April 18, 2006. The proposed indication is "for the treatment of anemia associated with chronic renal failure including patients on dialysis and patients not on dialysis." A major amendment on December 4 resulted in a 3 month extension; the PDUFA action date is May 18, 2006. The action that the review team, clinical team leader, and acting division director recommend is a Complete Review (CR) letter. I concur with that decision for the reasons stated below and as also described in the Division Director and Clinical Team Leader memos.

Emerging safety issues with ESAs: Two ESA products are marketed in the US, Epogen/Procrit (epoietin alfa) and Aranesp, or darbepoietin alfa; both are indicated for anemia associated with chronic renal failure, including dialysis and pre-dialysis, as well as the anemia associated with cancer chemotherapy in patients with non-myeloid malignancies. Other indications for Epogen/Procrit are: anemia in patients with HIV/AIDS and prior to elective surgery in patients unable or unwilling to donate autologous blood. Post-marketing studies with both products suggest risks that not recognized at the time of FDA approval. Most pertinent to the current application, the emerging safety signals in patients with chronic renal failure who were randomly assigned to a treatment strategy that targeted higher(er) hemoglobin values included higher mortality to patients randomized to a 'lower' hemoglobin target.[1] The hemoglobin targets in the CHOIR study were ~11.3 vs 13.5 g/dl, in the Normal Hematocrit study, hematocrit targets were 30 vs 42%. The former trial enrolled pre-dialysis patients, the latter dialysis patients with underlying cardiovascular disease. While the Mircera dataset (summarized below) did not suggest similar risks, FDA considers all ESA products to have the same mechanism of action and thus, the risks apply similarly across the ESA products.

The 6 active controlled trials of Mircera in support of the BLA involved two approaches: (a) de novo patients – designed to assess the proportion who responded to the agent (response defined as a 1 g/dl hemoglobin increase and achievement of hemoglobin > 11/g/dl) vs another ESA and (b) studies in which patients maintained on another ESA could be switched to and maintained on Mircera. In general, target drug dosing was aimed to maintain hemoglobins within target ranges of 11-13 g/dl. All efficacy trials succeeded in meeting primary endpoints. The safety database of ~ 1700 patients included 84% on hemodialysis. Overall no signals emerged that suggested serious cardiac or thrombotic events. However, the publications above, and a recent meta-analysis[2] all questions remain regarding how best to dose ESAs including optimal hemoglobin target(s). Thus, FDA will discuss this and other issues related to use of ESAs in renal failure patients at a planned meeting of the Cardiorenal Drugs Advisory Committee on September 11, 2007. Final action for the Mircera application will not occur until after the advisory meeting.

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[1] -"CHOIR" study: New England J of Medicine 2006; 355:2085-2098; "Normal Hematocrit" study: New England J of Medicine 1998;339:584-590.

[2] Mortality and target haemoglobin concentrations in anaemic patients with chronic kidney disease; Lancet 2007; 369:381-388

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

Our STN: BL 125164/0

MAY 18 2007

Hoffman La-Roche
Attention: Krishnan Viswanadhan, Pharm.D.
Associate Director, Drug Regulatory Affairs
340 Kingsland Street
Nutley, NJ 07110

Dear Dr. Viswanadhan:

This letter is in regard to your biologics license application for Mircera, submitted under section 351 of the Public Health Service Act.

We have completed the review of your application, including all amendments received through May 14, 2007. Our review finds that the information and data submitted are inadequate for final approval action at this time based on the deficiencies outlined below.

Clinical

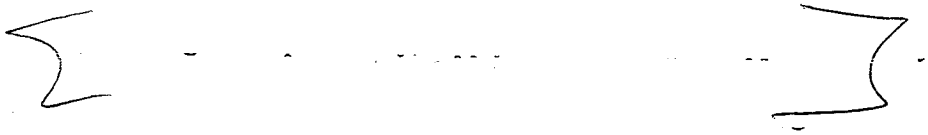
1. Accumulating data from a number of sources have raised concerns regarding the use of Erythropoietin Stimulating Agents (ESAs); see the internet website http://www.fda.gov/cder/drug/infopage/RHE/default.htm. ESAs have the same mechanism of action, and FDA believes these new concerns apply to all ESAs, including Mircera. The main safety concerns with use of ESAs for treatment of anemia in patients with chronic renal failure are increased cardiovascular events, including mortality. Available data appear to indicate that dose selection, specifically the "targeting" of hemoglobin values greater than 12 g/dL, importantly increases the risks for cardiovascular events. The labeling for ESAs, including the proposed Mircera label, state

   The extent to which this dosing recommendation is appropriate or optimal for Mircera is unclear, especially since the pharmacokinetics of Mircera differ from the currently marketed ESAs and the clinical data suggest that the hemoglobin response may be slower in some patients who have not previously been treated with an ESA. More explicit dosing information should be provided in order to minimize cardiovascular risks while retaining the treatment benefits for Mircera. We request that you provide information to address the following items and, as applicable, submit modified product labeling:

a. Provide clinical data and information supporting the choice of a hemoglobin value applicable to the of therapy with Mircera.

b. Provide clinical data and information to identify a maximum safe Mircera dosage. The identification of this maximum dose should be based upon analyses of important safety outcomes and correlations of these outcomes with Mircera dosages.

c. Submit clinical data and information justifying the appropriateness of the proposed dosing recommendations for Mircera,



d. Provide information supporting the choice of a "target" hemoglobin concentration that optimizes Mircera benefits and minimizes risks. Specifically, provide clinical data or information that may be useful to identify a specific hemoglobin value (or range) as the dosing goal for Mircera.

e. Your May 7, 2007 proposed product label included a description of important safety findings from clinical studies of ESA use among certain patients with cancer. Mircera is not proposed for use in the treatment of the anemia due to chemotherapy among certain cancer patients. Please justify the appropriateness of inclusion of the full extent of the proposed product label's description of ESA use among patients with cancer.

2. Your amendment of May 8, 2007 contained a response to our questions regarding thrombocytopenia and hemorrhage.

a. The amendment states that, in the pooled phase 2 and 3 population, 7.5% of Mircera treated patients had at least one post baseline platelet value < 100 x 10^9/L at any time compared to 4.4% among reference ESA treated patients. The proposed product label states

Please reconcile this apparent inconsistency.

b. The amendment appears to indicate that the increased hemorrhage rates for patients receiving Mircera, compared to reference ESAs, may relate to imbalances in baseline characteristics. Please supply a detailed description of these baseline characteristics and supply additional analyses that support this contention.

3. We sent comments and preliminary requests regarding your proposed package insert (PI) and patient package insert (PPI) on April 25, 2007 and May 9, 2007. We acknowledge receipt of your responses to these requests on May 7, 2007 and May 15, 2007. Responses to the information requested above (items 1 and 2) are necessary to complete the review of your proposed labeling. Please provide revised PI and PPI.

4. Some of the issues pertinent to clarifying the safety and effectiveness of Mircera require additional information that may be obtained from postmarketing studies. The information requested above may importantly impact the nature and extent of post-marketing clinical studies. Based upon the available information, we request that you propose studies to address the following issues in patients with the anemia of chronic renal failure:

   a. Provide additional clinical data verifying the safety of Mircera in patients with C-reactive protein concentrations greater than 30 mg/L. In general, these clinical data should be obtained from at least one prospective, randomized clinical study that compares outcomes between patients receiving Mircera and a currently marketed ESA. An alternative proposal may be reasonable, if sufficiently justified.

   b. Provide clinical data assessing major cardiovascular outcomes (death, non-fatal myocardial infarction, stroke, hospitalization for congestive heart failure) from a prospective clinical study that randomizes patients to specific hemoglobin targets less than 12 g/dL (for example: 9 to 10 g/dL; 10 to 11 g/dL and 11 to 12 g/dL). Eligible patients should consist of patients currently maintained on an ESA who are randomized to one of the hemoglobin targets or continued on a current ESA regimen. Alternative study proposals may be considered if the study design features are sufficient to provide the important safety information pertinent to Mircera dosing and the "targeting" of hemoglobin values.

   Please describe your plans to address the above issues in sufficient detail to permit our evaluation of the adequacy of the proposals. We request that your response include:

   - A detailed protocol or, at a minimum, a detailed outline describing all design features of the study including sample size and justification, eligibility criteria with rationale, dosing regimens and duration, clinical assessments to be performed and their timing, and endpoints to be analyzed.

   - Proposed schedule for conducting the study, including all major milestones for the study, e.g. submission of finalized protocol to the FDA, initiation of an animal study, completion of patient accrual, completion of the study, and submission of the final study report, SAS datasets and applicable revised labeling to the FDA.

   Please be advised that submission of complete protocols for review and comment should be made to your IND and may be cross-referenced in your response to this letter.

5. FDA is planning to discuss the risks of ESAs in treatment of anemia in chronic renal failure patients with at an FDA Advisory Committee meeting in early Fall 2007. As discussed in a telephone conversation on May 8, 2007 between FDA representatives, Ms. Florence Moore and Dr. Dwaine Rieves, and your representatives, we anticipate that recommendations from the Advisory Committee will be important to inform both you and us in finalizing product labeling and post-marketing commitments for Mircera. Therefore, we recommend that you request a meeting with us to occur shortly after the Advisory Committee meeting and prior to your BLA resubmission.

6. Provide the final study report for study NH19960, "A multicenter, randomized, open-label dose-finding study of RO0503821 in anemic patients with Stage IIIB or IV non-small cell lung cancer (NSCLC) receiving first-line myelosuppressive chemotherapy" when it is available.

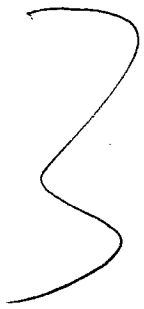
7. Provide a summary of the status of your proposed pediatric clinical study, including a time line for the initiation, completion and submission of the study results.

Chemistry, Manufacturing and Controls

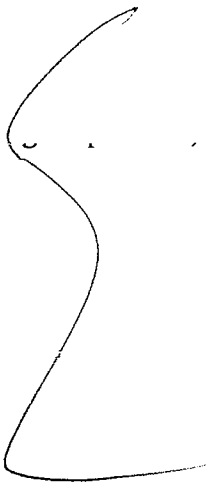
8. Regarding the EPO starting material:

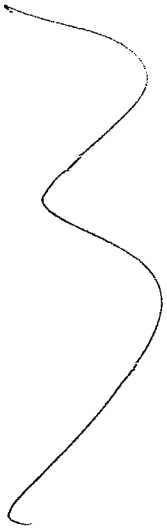
a. 

b. 



c.

d. 



e.

f.

9. Regarding your potency assay, according to the procedures described for the measurement of potency for intermediate, drug substance, and drug product, the same However, the following concerns should be addressed:

a.

b.

10. Regarding drug product (DP) specifications:

a.

b.

c.

d.

e.

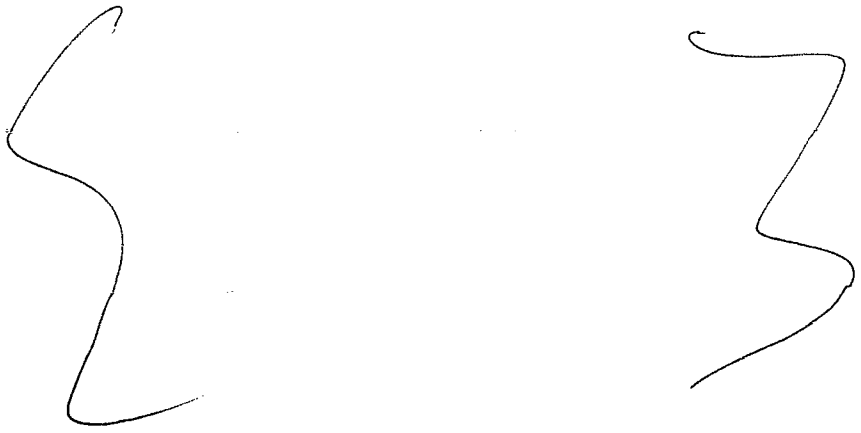
f.

11. With regards to the assays to detect binding antibodies:

a.

b.

c.

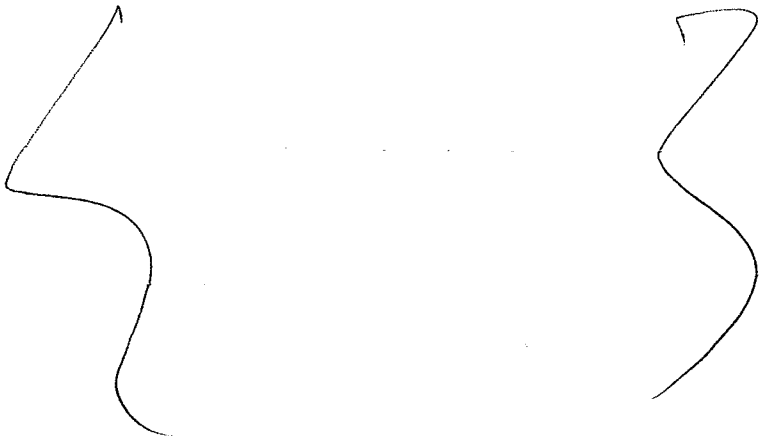


12.

a.

b.

c.



13. We reserve further comment on the proposed carton and container labeling until the application is otherwise acceptable.

You may request a meeting or teleconference with CDER to discuss the steps necessary for approval. Should you wish to have such a meeting, please submit your meeting request as described in the FDA Guidance for Industry: Formal Meetings With Sponsors and Applicants for PDUFA Products – February, 2000 (http://www.fda.gov/cder/guidance/2125fnl.htm).

Within 10 days after the date of this letter, you are requested to take one of the following actions: (1) amend the application; (2) notify us of your intent to file an amendment; (3) withdraw the application; or (4) request an opportunity for a hearing on the question of whether there are grounds for denying approval of the application. In the absence of any of the above responses, we may initiate action to deny the application.

Please note our review clock has been suspended with the issuance of this letter. Note also that any amendment should respond to all deficiencies listed and that a partial reply will not be considered for review nor will the review clock be reactivated until all deficiencies have been addressed.

We acknowledge receipt of your amendment dated May 16, 2007. You may cross reference applicable sections of the amendment(s) in your complete response to this letter and those sections will be reviewed as a part of your complete response.

Should additional information relating to the safety and effectiveness of this drug product become available prior to our receipt of the final printed labeling, revision of that labeling may be required.

Please refer to http://www.fda.gov/cder/biologics/default.htm for information regarding therapeutic biological products, including the addresses for submissions.

If you have any questions, please contact the Regulatory Project Manager, Florence O. Moore, M.S., at (301) 796-2050.

Sincerely,

Richard Pazdur, M.D.
Director
Office of Oncology Drug Products
Center for Drug Evaluation and Research

Moore, Florence O

From: Hughes, Patricia
Sent: Thursday, May 17, 2007 1:37 PM
To: Moore, Florence O
Subject: RE: EER Request

A compliance check was obtained for the BLA (various facilities) and it is in my review at the end. The [redacted] was for a new building in [redacted] and it was inspected in April as part of the [redacted] approval.

Patricia

From: Moore, Florence O
Sent: Thursday, May 17, 2007 1:05 PM
To: Hughes, Patricia
Cc: Clark-Stuart, Michelle; Rieves, Rafel; Harper Velazquez, Tia M
Subject: EER Request

Hi Patricia,

I got your faxed reviews this morning. Thanks again.

Regarding STN 103951/5137 and 125164/0 was EER requested? We need a EER report for the action packages. We are required to request for ERR check for all applications with the exception of labeling. We still have a day left on these application so can we get one from compliance?

Thanks,
Florence

Florence O. Moore, M.S.
Regulatory Health Project Manager
Division of Medical Imaging and Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation Research
Food and Drug Administration
10903 New Hampshire Avenue, Rm 2381
Silver Spring MD 20903

Tel: 301-796-1423
Fax: 301-796-9849

LICENSING ACTION RECOMMENDATION

Applicant: Hoffmann-LaRoche **STN:** STN 125164/0

Product:

Pegeserepoetin alfa

Indication / manufacturer's change :

New BLA for the treatment of anemia associated with chronic kidney disease, including patients on dialysis and patients not on dialysis.

■ Approval:
- ■ Summary Basis For Approval (SBA) included
- ☐ Memo of SBA equivalent reviews included
- ☐ Refusal to File: Memo included
- ☐ Denial of application / supplement: Memo included

RECOMMENDATION BASIS

■ Review of Documents listed on Licensed Action Recommendation Report

■ Inspection of establishment ☐ Inspection report included

☐ BiMo inspections completed ☐ BiMo report included

☐ Review of protocols for lot no.(s) _____

☐ Test Results for lot no.(s) _____

☐ Review of Environmental Assessment ☐ FONSI included ■ Categorical Exclusion

☐ Review of labeling Date completed _____ ☐ None needed

CLEARANCE – PRODUCT RELEASE BRANCH

■ CBER Lot release not required

☐ Lot no.(s) in support – not for release _____

☐ Lot no.(s) for release _____

Director, Product Release Branch _____

CLEARANCE – REVIEW

Review Committee Chairperson: Dov Pluznik, Ph.D. Date: 16 May 20(

Product Office's Responsible Division Director(s)*:

_____ Date: _____

_____ Date: _____

DMPQ Division Director* : Richard Friedman Date: 5/16/07

* If Product Office or DMPQ Review is conducted

CLEARANCE – APPLICATION DIVISION

■ Compliance status checked ■ Acceptable ☐ Hold Date: 16 May 2007

☐ Cleared from Hold Date: _____

☐ Compliance status check Not Required

Regulatory Project Manager (RPM) _____ Date: _____

Responsible Division Director _____ Date: _____
(where product is submitted, e.g., application division or DMPQ)

Form DCC-201 (05/2003)

Hughes, Patricia

Subject: FW: BLA 125164/0 HoffmannLaRoche site

-----Original Message-----
From: Dietrick, John M
Sent: Wednesday, May 16, 2007 3:36 PM
To: Hughes, Patricia
Cc: Friedman, Rick L
Subject: RE: BLA 125164/0 HoffmannLaRoche site

Based on my review of the FDA-483 and the firm's December 8, 2006, January 31, March 9, and April 4, 2007 responses to the FDA-483, the Basel facility is now acceptable and the EIR will be classified VAI.

John Dietrick
Foreign Inspection Team

Moore, Florence O

From: Viswanadhan, Krishnan [krishnan.viswanadhan@roche.com]
Sent: Wednesday, May 09, 2007 12:42 PM
To: Moore, Florence O
Subject: FW: Analyses for Roche
Follow Up Flag: Follow up
Flag Status: Completed
Attachments: CRP.doc

Dear Florence:
See request from FDA in February 2007. The response was submitted to FDA on March 5, 2007 (Amendment 26).
Krishnan

From: Moore, Florence O [mailto:florence.moore@fda.hhs.gov]
Sent: Friday, February 23, 2007 6:28 PM
To: Viswanadhan, Krishnan {PDR~Nutley}
Subject: Analyses for Roche

Hi Krishnan.

This is the information Dr.Rieves had discussed with you earlier this morning. Please let me know if you have any questions.

Regards,
Florence

Analyses for Roche to assess the impact of C-Reactive Protein

Listed below are analyses that we request Roche perform on the randomized, controlled safety database. Please supply the results of these analyses no later than February 28, 2007 (as feasible), along with explanatory text. Additionally, we encourage Roche to provide results of any additional analyses that may help assess the extent, if any, to which C-Reactive protein screening may have importantly limited the enrollment of patients into the clinical studies.

1. Conduct a logistic regression analysis to compare the treatment groups for a composite adverse event outcome (occurrence of death/major CV events/SAE). Specifically, the outcome variable is a composite event of death, CHF hospitalization, non-fatal MI and non-fatal stroke. The input variables should include treatment group (reference group(s) vs Mircera), baseline CRP (≤ 10 vs > 10), interaction of treatment and CRP, baseline hemoglobin, and first treatment dose. Please perform the analysis with pooled reference data and separately for epoetin and darbepoetin..

2. Repeat the logistic analysis described in item (1) above using a composite endpoint expanded to include hospitalizations due to any SAEs, in addition to death, CHF hospitalization, non-fatal MI and non-fatal stroke.

3. Repeat the analysis described in item (2) above using each of the 5 components of the composite endpoint as 5 separate endpoints: hospitalization due to any SAEs, death, CHF hospitalization, non-fatal MI and non-fatal stroke.

4. Repeat the logistic analyses described in items (1), (2), and (3) above with the input variable of baseline CRP changed to maximal CRP during the study. The other variables in the logistic regression model should be kept the same as before.

5. Repeat the logistic analyses described in items (1), (2), and (3) above with the input variable of baseline CRP changed to AUC-CRP, defined as area under the curve in a plot of CRP versus time during the study. The other variables in the logistic regression model should be kept the same as before.

6. Conduct a survival analysis with time to event as the outcome variable for the two composite events and the five component events separately as described in items (1), (2), and (3) above. The analysis should include 4 groups: epoetin with low baseline CRP, epoetin with high baseline CRP, Mircera with low baseline CRP, and Mircera with high baseline CRP. Please also conduct a Cox's regression analysis with baseline CRP as a dichotomous independent variable and as a continuous independent variable.

7. Provide figures that show CRP level alterations during the course of the studies, by treatment group (Mircera, epoetin, darbepoetin, and pooled epoetin and darbepoetin), for all studies with available information.

8. Using linear regression analysis, explore the potential relationship between the change in CRP (from baseline to the last observation) and treatment. CRP should be treated as a

continuous outcome variable. Treatment group, baseline hemoglobin levels, and baseline dose should be used as independent variables in the model.

9. In addition to providing the results via email or facsimile on February 28 (or as soon as possible), please provide an amendment to the BLA including: 1) Analysis results, 2) the SAS codes, 3) a dataset with subject ID, protocol number, and the variables used for the above analyses, and 4) any interpretations for the results.

5. In single dose pharmacokinetic studies with intravenous administration, the mean terminal half-life of Mircera determined in anemic patients not on dialysis (77 ± 54 hour at 0.8 mcg/kg dose, Study BP18034) is similar to the half-life determined in healthy subjects (70 ± 35 hr at 0.4 mcg/kg dose, BP16239), but much shorter than the half-life determined in anemic patients on peritoneal dialysis (134 ± 65 hr at 0.4 mcg/kg dose, BP16779). In contrast, with subcutaneous administration, the half-life in anemic patients not on dialysis (142 ± 64 hr at 1.2 mcg/kg dose, BP18034) is significantly longer than the half-life in healthy subjects (102 ± 62 hour at 0.8 mg/kg dose, BP16198), but similar to the half-life in anemic patients on peritoneal dialysis (139 ± 67 hr at 0.8 mcg/kg dose, BP16779). Please explain these results, especially as they apply to considerations of the consistency of phamacokinetic findings among dialysis or non-dialysis patients.

6. For the phase 3 studies, please pool data by product (epoetin, darbepoetin, or Mircera) and calculate the average time to the following events, for each of the three products:

   a. sudden death

   b. cardiac death

   c. all-cause death

   d. composite of death, non-fatal myocardial infarction, stroke, or congestive heart failure serious adverse events

7. We refer to our recent Public Health Advisory regarding the use of erythropoiesis-stimulating agents (see http://www.fda.gov/cder/drug/advisory/RHE2007.htm). In light of the cardiovascular risks described in this advisory and the revised labels for erythropoiesis-stimulating agents (ESAs), please provide a revised label for Mircera that includes text for a Black Box Warning and your proposed revisions to other sections of the label to maintain consistency, as applicable, with the currently licensed ESA labels. These revisions should apply to both the package insert (PI) and the patient package insert (PPI). Please supply this revision within a week of receiving this letter. We regard these modifications as essential for adequate labeling for Mircera.

Please refer to http://www.fda.gov/cder/biologics/default.htm for important information regarding therapeutic biological products, including the addresses for submissions.

If you have any questions, contact Florence O. Moore, M.S., Regulatory Project Manager, at (301) 796-2050.

Sincerely,

Dwaine Rieves 3-20-07

Dwaine Rieves, M.D.
Acting Division Director
Division of Medical Imaging and Hematology Products
Office of Oncology Drug Product
Center for Drug Evaluation and Research

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

Our STN: BL 125164/0

Hoffman La-Roche
Attention: Krishnan Viswanadhan, Pharm.D.
Associate Director, Drug Regulatory Affairs
340 Kingsland Street
Nutley, NJ 07110

Dear Dr. Viswanadhan:

This letter is in regard to your biologics license application submitted under Section 351 of the Public Health Service Act.

We have reviewed the label section(s) of your application dated April 18, 2006 Pegzerepoetin alfa (Mircera). We have the following comments and recommendations:

1. We recommend the implementation of the container labels, carton, package insert and patient information labeling revisions outlined below in order to minimize potential errors with the use of this product.

   In the review of the container labels, carton, and insert labeling of Mircera, we have identified the following concerns regarding potential user error:

   a. GENERAL COMMENTS

      i. Several of the colors used to differentiate the package strengths are similar. This raises the concern that the strengths with similar colors could be confused, leading to selection errors and resulting in the dispensing or administration of the wrong dose. We recommend that each syringe/vial strength have a different, distinguishable color which may help practitioners differentiate between the Mircera strengths, and thus reduce the potential for selection errors.

4 Page(s) Withheld

_____ Trade Secret / Confidential

X Draft Labeling

_____ Deliberative Process

Withheld Track Number: Administrative- 13

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

From: Florence O. Moore, M.S.

To: File: STN 125164/0

Subject: Regulatory Briefing Meeting Summary

Sponsor: Hoffman La-Roche

Product: Pegzerepoetin alfa (Mircera)

Meeting Chair: Robert Temple, M.D.

Date, Location, & Time of Meeting: March 16, 2007
WO CSU, Conference Room 2046
1:00 p.m. – 3:00 p.m.

Purpose:

To discuss the sufficiency of safety database: implication of C Reactive Protein Screening (CRP).

FDA Attendees:

Robert Temple
Richard Pazdur
Karen Weiss
Rafel Rieves
Kathy Robie Suh
Patricia Keegan
John Lee
Alice Kacuba
Florence Moore
Kinsey, Vikki S;
Eric Brodsky
Brian Harvey
Hong Zhao
Betsy Scroggs,
Samuel Chan,
Keith Webber,
Helen Winkle,
Gerald Dal-Pan
Jogarao Gobburu
Shiew-Mei Huang
Hylton Joffe
Vikki Kinsey
Larry Lesko
Mehul Mehta
Bob Rappaport
Daniel Shames
Angela Men
Faranak Jamali
Ira Krefting
Victor Santana
Aloka Chakravarty

1.0 PRODUCT AND PROPOSED INDICATION FOR USE

Mircera, a recombinant erythropoietin developed by Hoffman La Roche, is under BLA review for the treatment of anemia due to chronic renal failure (CRF). Mircera is a pegylated form of epoetin beta, an erythropoietin marketed in Europe. Compared to epoetin beta, Mircera has a longer half-life and allowing less frequent dosing.

If licensed, Mircera would be the third FDA-approved erythropoiesis-stimulating agent (ESA). Currently approved ESAs include epoetin alfa (Procrit/Epogen) and darbepoetin alfa (Aranesp), both indicated for the treatment of anemia of chronic renal failure and chemotherapy-induced anemia among certain cancer patients. Epoetin alfa is also approved for peri-operative use to reduce the need for allogeneic blood in non-cardiac/nonvascular surgery and for treatment of Zidovudine-treated HIV-infected patients.

Treatment of anemic CRF patients is the only proposed indication in the BLA.

Roche recently suspended enrollment in a chemotherapy-induced anemia study due to concern regarding excessive mortality.

2.0 REGULATORY CONCERN: SAFETY DATABASE

In developing Mircera, Roche actively screened and excluded patients with elevated levels of C-reactive protein (CRP > 30 mg/L in five of six confirmatory studies, > 15 mg/L in the sixth study) and randomized patients to Mircera or approved ESAs.

Over the past few years, elevated CRP has been recognized as a biomarker for the detection of CRF patients at risk for morbidity and mortality as well as a marker for ESA "hypo-responsiveness." CRP screening was not part of the clinical development program for the FDA-approved ESAs.

Review findings from the Mircera BLA generally support the product's efficacy and safety. DMIHP noted that Roche had recently suspended enrollment in an oncology study of Mircera due to imbalances in mortality (between Mircera and another erythropoietin). With respect to considerations of overall erythropoietin safety, Mircera's relatively prolonged half-life and potential for greater safety concerns due to greater drug exposure, DMIHP is concerned the use of active CRP screening may have resulted in a database insufficiently characteristic of the market population. DMIHP poses two questions:

1. Do you regard the CRP exclusion as an important limitation of the Mircera safety database?

2. Do you regard the database limitation as sufficient to preclude licensure until additional data verify the product's safety?

3.0 BACKGROUND (See Attachment 2)

4.0 DISCUSSION

4.1 The meeting started with brief opening remarks by Dr. Robert Temple, followed by an introduction of the purpose for the meeting by Dr. Dwaine Rieves. Dr John Lee, medical reviewer of the application, gave an overview and a presentation on the product. Dr. Lee concluded the presentation with the two questions (stated above) on which the division was seeking advice on to move forward with their review. The meeting was then opened to the panel for discussions.

Regarding the first question, the panel noted that only 3% of patients were excluded by the CRP extension, so that they could not have affected results to any significant effect had they been included. Moreover, dividing patients by CRP $\leq$ 10 and CRP > 10 showed no tendency for death or CV events to be more affected by Mircera than reference drug in the higher CRP group.

The panel therefore concluded that the inclusion of the extra 2% data regarding CRP will not make a difference and that CRP exclusion is not an important limitation of the Mircera database. However, the panel did think that the CRP screening data should be included in the product label.

Regarding the second question, the panel did not think the CRP limitation of the database was a reason not to approve the application, based upon the presented data. The panel briefly discussed additional analyses that may assist in greater understanding of the role of CRP screening in development of the safety database. The panel suggested that the sponsor should do a PMC study to determine drug effect on patients with high CRP. Regarding FDA development of reviewer tools and guidances, the panel noted that the CRP concern illustrated the importance of eligibility criteria having important review considerations; hence, the guidances/tools should highlight this potential.

5.0 ISSUES REQUIRING FURTHER DISCUSSION

Safety issues regarding all ESAs including Mircera will be discussed at the upcoming ODAC Advisory Committee meeting in May 2007 and Cardio-Renal Advisory Committee in August/September 2007.

6.0 ACTION ITEMS

DMIHP will ask the sponsor to submit to their BLA and IND the following information to assist in further evaluating CRP considerations and safety (including clinical pharmacology correlates):

- a detailed interim report for their Study NH19960 (an oncology study recently reporting mortality imbalances);
- additional information regarding the potential impact of CRP screening to include comparisons between RO0503821 and reference products based upon categorizations of patients into quartiles by baseline CRP;
- a tabular summary of the baseline and any follow-up CRP values for all subjects with "sudden death," in the phase 2/3 studies and the "extended" study;
- source data and statistical methodology used in their analysis of clinical pharmacology-CRP correlates and;
- to provide data for Mircera concentrations measured in each subject before and after hemodialysis;

7.0 ATTACHMENTS AND HANDOUTS

Attachment 1 Regulatory Briefing Agenda
Attachment 2 (DMIHP Clinical Review Background)
Attachment 3 (DMIHP Slide Presentation)

Attachment 4 Meeting Attendee List

Regulatory Briefing Agenda
March 16, 2007

Subject:	BL STN 125164/0 Pegzerepoetin alfa (Mircera™)
Indication:	Treatment of anemia associated with chronic renal failure (CRF)
Purpose:	This meeting is to discuss the sufficiency of safety database: implication of C Reactive Protein Screening (CRP).
Meeting:	Regulatory Briefing
Meeting Date:	March 16, 2007
Meeting Time:	1:00 p.m. – 3:00 p.m.
Meeting Location:	White Oak Central Shared Use (CSU) Building Room 2046
Chair:	Robert Temple M.D.
Facilitator:	Vikki Kinsey, M.S.
Project Manager:	Florence Moore, M.S.

Time	Item #	Agenda Item	Presenter
5 min.	1	Opening Remarks	Robert Temple M.D.
5 min.	2	Introduction	Rafel Dwaine Rieves, M.D.
20 min.	3	Presentation	John Lee, M.D.
80 min.	4	Opinions	Panel
10 min.	5	Wrap-Up	Robert Temple M.D.

Regulatory Briefing, March 16, 2007
Mircera® (Pegzerepoetin beta, Roche) for Anemia of Chronic Renal Failure
Safety Database and C-reactive Protein Screening
Division of Medical Imaging and Hematology Product/Office of Oncology Drug Products

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I. PRODUCT AND PROPOSED INDICATION FOR USE

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II. REGULATORY CONCERN: SAFETY DATABASE

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Over the past few years, elevated CRP has been recognized as a biomarker for the detection of CRF patients at risk for morbidity and mortality as well as a marker for ESA "hypo-responsiveness." CRP screening was not part of the clinical development program for the FDA-approved ESAs.

Review findings from the Mircera BLA generally support the product's efficacy and safety. However, DMIHP is concerned the use of active CRP screening may have resulted in a database insufficiently characteristic of the market population. DMIHP poses two questions:

1. Do you regard the CRP exclusion as an important limitation of the Mircera safety database?

2. Do you regard the database limitation as sufficient to preclude licensure until additional data verify the product's safety?

III. BACKGROUND:

a. C-reactive Protein as a biomarker for adverse cardiovascular events

Blood concentrations of CRP, an "acute phase reactant," increase in response to inflammation. Many publications have cited the prognostic use of CRP values for patients with conditions related to inflammation. In 2003, the CDC and American Heart Association issued a "Statement for Healthcare Professions" that noted:

- CRP assays are sufficiently standardized to support prognostic use of the test in clinical practice; CRP should be measured twice, two weeks apart and values averaged;
- Multiple meta-analyses of prospective databases show a dose-response relationship between CRP levels and the risk of coronary disease;
- In prediction of coronary disease, epidemiological databases support:
  - low risk for CRP < 1 mg/L,
  - average risk for CRP 1.0 to 3.0 mg/L
  - high risk for CRP > 3.0 mg/L
  - CRP of > 10 mg/L indicates "marked elevation;"
- CRP > 10 mg/L has been variously associated with cardiovascular complications (restenosis, death, mycardial infarction).

Many small investigations also suggest that CRP elevation may predict cardiovascular complications among CRF patients. In 2006, the National Kidney Foundation's revised KDOQI guidelines noted that:

- elevated CRP predicts all-cause and cardiovascular mortality in both hemodialysis and peritoneal dialysis patients;
- CRP predicts outcomes and improves risk prediction in CRF patients;
- "it would be beneficial to assess CRP levels in dialysis patients on a regular basis, and to seek sources of infection or inflammation." The guidelines cite a CRP level of > 10 mg/L as elevated for patients with CRF.
- CRP is a biomarker for erythropoietin resistance where "hypo-responsiveness" is defined as: "hemoglobin level persistently less than 11 g/dL and if ESA doses are equivalent to epoetin greater than 500 IU/kg/wk."

One of the largest studies of the prognostic implications for CRP among dialysis patients was performed by Zimmermann (Kidney Int; 1999:648-658). In this study 280 "stable" hemodialysis patients had baseline CRP measured and were followed for two years. Over the two year period, 26% of the patients died; most due to cardiovascular disease. Figure 1 shows the distribution of CRP among the patients at baseline and Figure 2 shows the two year survival.

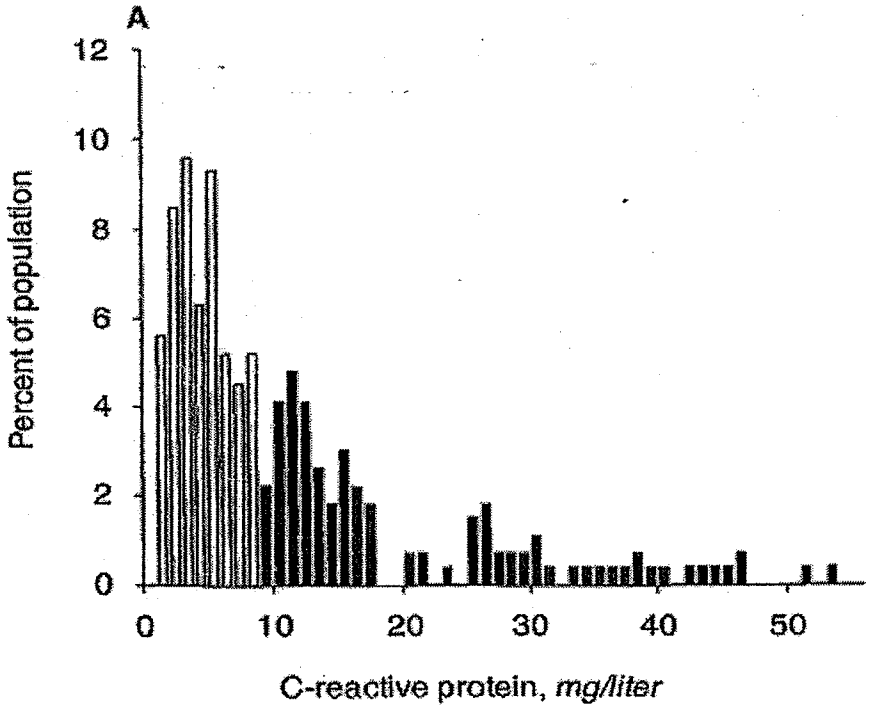

Figure 1. Distribution of CRP among 280 "stable" hemodialysis patients

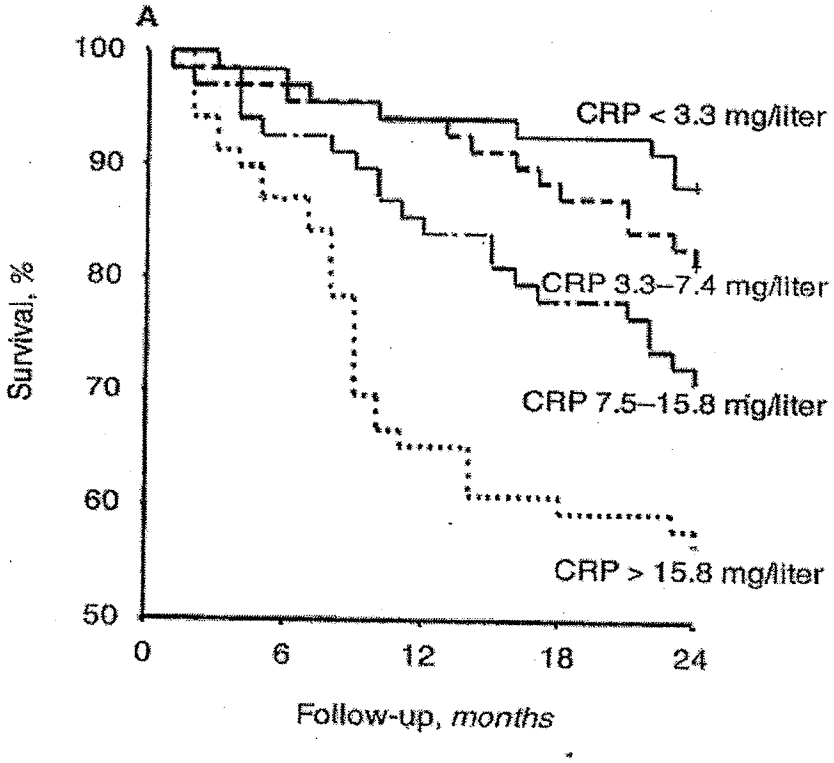

Figure 2. Survival among 280 "stable" hemodialysis patients by baseline CRP level

In the Zimmermann study, nearly half of all "stable" hemodialysis patients with CRP > 16 mg/L had died by the end of the two year follow-up period.

b. ESAs and adverse cardiovascular reactions

Two randomized, controlled clinical studies compared the targeting of higher hemoglobin levels to lower levels and both studies found significantly more cardiovascular toxicity among patients assigned to the higher hemoglobin level targets.

In the "Normal Hematocrit Study" of hemodialysis patients (1998):

- 1265 anemic patients with clinically evident cardiac disease were randomized to either a target hematocrit of 42% or 30%, with titration of Epoetin alfa
- Study was terminated early due to excessive mortality in high hematocrit group (35% vs 29%)
- 2/3 of all deaths among the patients in the high hematocrit group were among "hypo-responders"--ie., failed to achieve the target hemoglobin despite no maximum epoetin dose.

In the "CHOIR Study" of non-dialysis patients (2006):

- 1432 anemic non-dialysis CRF patients were randomized to either target hemoglobin of 13.5 g/dL or 11.3 g/dL
- Study was terminated early due to excessive toxicity in high hemoglobin group (18% vs 14% for a composite endpoint of: death, myocardial infarction, stroke or hospitalization for heart failure)
- Maximum dose was limited to no more than 285 U/kg/week

In both studies, more patients failed to achieve the higher target than the lower target.

c. Eligibility criteria in the Darbepoietin alfa clinical development programs

Roche proposes that their use of active screening with C-reactive protein (CRP) was an attempt to eliminate "hypo-responders" from the database in order to optimize demonstration of a treatment effect. Roche notes that Amgen also used stringent eligibility criteria in the clinical development of darbepoietin that may have also eliminated "hypo-responders" due to the exclusion of patients with:

-systemic infection
-active inflammatory disease,
-malignancy
-hepatic enzymes > 2X ULN

Roche maintains that exclusion of patients based upon the presence of "active inflammatory disease" or "systemic infection" is tantamount to screening with CRP. No data are available to verify this contention.

IV. MIRCERA CONFIRMATORY STUDIES: EFFICACY AND SAFETY

a. Efficacy

Roche has provided persuasive of Mircera efficacy and these findings are briefly summarized.

Phase 3 Studies for Anemia Correction

Two randomized, open-label, multicenter studies were conducted among 505 patients undergoing anemia correction. The results indicated that the adjusted mean change in hemoglobin from baseline with Mircera (2.12 g/dL) was not inferior to that with darbepoetin alfa (1.95 g/dL).

Phase 3 Studies for Hemoglobin Maintenance (Dose Conversion)

Four randomized, open-label, non-inferiority studies were conducted among 1894 patients to confirm the efficacy of Mircera in maintaining the hemoglobin (after converting from epoetin alfa, epoetin beta, or darbepoetin alfa to Mircera), all in patients with CRF on dialysis. The four studies followed the same basic design, and the primary efficacy endpoint in each study was defined as the mean change in hemoglobin from baseline to evaluation. The results showed that Mircera treatment was not inferior to treatment with epoetin or darbepoetin alfa. The median hemoglobin did not appreciably change from baseline to evaluation. In all studies (Mircera and reference), the majority of patients (66 - 76%) were able to maintain the hemoglobin within ±1 g/dL of baseline value, and the monthly hemoglobins (mean and median) remained within a clinically acceptable range (11 - 13 g/dL) throughout the study.

b. Safety

The Mircera safety database consisted of pooled results from four phase 2 and six phase 3 clinical studies involving 2737 (1789 receiving Mircera and 948 receiving a reference ESA). Baseline characteristics were similar across treatment groups. Baseline co-morbidities reflected those expected in the CRF population.

The results of the primary analyses of adverse events (AE) for the pooled phase 2 and 3 studies showed generally similar results between the Mircera and reference groups for the incidence of serious AE, severe AE, and AE leading to withdrawal.

- Across the clinical studies, the death rate was low and generally similar between groups, although numerically higher in the Mircera group (Table 1). The causes of death were varied and none of the events were uncommon for a CRF population.
- No consistent pattern of individual AE, SAE, or AE leading to withdrawal was observed.
- There were no appreciable safety findings related to regimen, route of administration, correction or maintenance setting, stage of renal disease, or to any pre-specified subpopulations.

- An apparent greater incidence of sudden deaths with Mircera than with reference agents was initially a major review concern. The degree of imbalance, however, decreased with extended safety follow up beyond the period of the index studies, and an adjudicated evaluation of all deaths by a blinded cardiac panel indicated no imbalance in the incidence of sudden deaths as defined more rigorously by the cardiac panel. The sponsor's report of the investigation into potential cardiac toxicity, however, does not include an adequate determination of the QT effect. An adequate determination of the QT effect is considered to be an important component of evaluating sudden deaths for drugs although the utility for biologic products is less clear.

It is important to note that all studies terminated at 52 weeks and after 52 weeks, subjects were allowed to enroll in a long term extension. Approximately half of all the patients enrolled in the long term extension.

Table 1. Deaths in Mircera Studies

Outcome	Phase 2/3 Studies		Phase 2/3 studies + patients who chose to continue in extended f/u	
	Micera n = 1789	Comparator n = 948	Mircera n = 1789	Reference n = 948
Deaths	130 (7.3%)	64 (6.8%)	182 (10.2%)	103 (10.9%)
Sudden deaths	9 (0.5%)	0	14 (0.8%)	5 (0.5%)

Overall, the Mircera safety profile did not remarkably differ from reference erythropoietin products although the numerical mortality rate appears slightly higher and, during the controlled studies, 9 sudden deaths were detected among Mircera patients but none among the group of patients receiving a comparator erythropoetin.

V. MIRCERA C-REACTIVE PROTEIN (CRP) EXCLUSION CRITERIA

Subject selection criteria in all phase 2 and phase 3 studies specified exclusion for elevated CRP. In five of the six phase 3 studies (BA16736, BA16739, BA16740, BA17283, and BA17284), patients were excluded for CRP > 30 mg/L; in the remaining phase 3 study (BA16738), patients were excluded for CRP > 15 mg/L. In the phase 2 studies, dialysis patients were excluded for CRP > 50 mg/L (BA16285, BA16286, BA16260) and non-dialysis patients were excluded for CRP > 15 mg/L (BA16528).

Exclusion for elevated CRP was based on active laboratory screening (with patients returning for repeat tests if the initial CRP was elevated), which was subsequently repeated every 8 weeks in all phase 3 studies as part of scheduled subject monitoring. Table 2 shows the proportions of patients excluded based on elevated CRP, and Table 3 compares the patient distribution across different CRP levels at study baseline. Overall, approximately 75% of all subjects had baseline CRP < 10 mg/mL.

Table 2: CRP Exclusion in Phase 3 Studies

Study	Description	Screened	Excluded Solely for Elevated CRP
BA16736	anemia correction in dialysis, exclude for CRP > 30 mg/L	234	1 (0.4%)
BA16738	anemia correction in non-dialysis, exclude for CRP > 15 mg/L	498	17 (3.4%)
BA16739	hemoglobin maintenance in dialysis, conversion from epoetin, exclude for CRP > 30	1115	39 (3.5%)
BA16740	hemoglobin maintenance in dialysis, conversion from epoetin, exclude for CRP > 30	817	15 (1.8%)
BA17283	hemoglobin maintenance in dialysis, conversion from darbepoetin, exclude for CRP >	444	5 (1.1%)
BA17284	hemoglobin maintenance in dialysis, conversion from epoetin, exclude for CRP > 30	519	17 (3.3%)
All Phase 3 Studies		3627	94 (2.6%)

Table 3: CRP Distribution at Baseline in Safety Database

EPO	Baseline Levels of C-Reactive Protein			
	NA	< 10 mg/L	> 10 & < 30 mg/L	> 30 mg/L
Mircera	43 (2.4%)	1319 (74%)	398 (22%)	29 (1.6%)
Reference	24 (2.5%)	720 (76%)	190 (20%)	14 (1.5%)

EPO = erythropoietin product; CRP = C-reactive protein; NA = value not available

c. Roche Justifications for active CRP screening and exploratory analyses

As previously noted, Amgen excluded patients with systemic inflammation/infection from their studies of darbepoietin. Roche regards active CRP screening as accomplishing the same goal.

Roche notes that subject exclusion based on active CRP screening was intended to improve upon the efficiency of subject exclusion. The cut-off of 30 mg/L or 50 mg/L was chosen based on the distribution of CRP levels in CRF patients on dialysis such that the added laboratory exclusion did not "significantly alter the overall exclusion rate." Based upon the use of CRP alone as an exclusion criterion, the number of patients excluded from participation in the phase safety database studies was a relatively small fraction of those screened (~ 3%).

Roche notes that 23% of all enrolled patients in Mircera studies had CRP values > 10 mg/L at baseline and that 28% of all enrolled patients developed a CRP of > 30 mg/L while on treatment, with no differences between Mircera and the reference group.

Roche provides tables comparing important outcomes between non-dialysis and dialysis patients enrolled in anemia correction studies, both for Mircera as well as the findings from Amgen studies used to support the approval of Darbepoetin (DA). Tables 4 and 5 compare safety outcomes from the older darbepoetin correction studies and the Mircera correction studies among non-dialysis and dialysis patients, respectively. Safety problems may be more evidence in anemia correction studies since these patients have never previously been treated with an ESA.

Table 4. Comparison of Safety Outcomes between Darbepoietin and Mircera in Non-dialysis Patients

	Darbepoietin study (24 wk)		Mircera study (28 wk)	
	DA n = 129	Epo n = 37	Mircera n = 162	DA n = 162
AE	83%	65%	84%	85%
SAE	33%	22%	20%	23%
Death	2%	3%	4%	2%

Table 5. Comparison of Safety Outcomes between Darbepoietin and Mircera in Dialysis Patients

	Darbepoietin study (22 wk)		Mircera study (26 wk)	
	DA n = 91	Epo n = 31	Mircera n = 135	DA n = 46
AE	98%	100%	72%	78%
SAE	41%	35%	22%	15%
Death	6%	3%	1%	0%

While the comparison of the correction studies between non-dialysis patients (Table 4) appears to show no important differences between the Darbepoietin and Mircera studies, the dialysis correction studies (Table 5) indicate fewer SAE and deaths in the Mircera study even though the Mircera observation period was longer. This observation suggests that the Mircera study may have enrolled healthier subjects (perhaps based on CRP screening).

Roche performed logistic regression analyses on the Mircera safety database to assess the correlation of baseline CRP with safety outcomes. These analyses showed:

- Baseline CRP showed a significant effect on multiple composite cardiovascular toxicity endpoints as well as the components of the composites, including death.
- No significant treatment by CRP interaction.
- Kaplan-Meier survival analyses generally confirmed the impact of baseline CRP > 10 mg/L on composite endpoints and on individual endpoints.

Figure 3 shows the median CRP over time for Mircera patients versus pooled reference patients in all the phase 3 studies (phase 2 studies showed a similar pattern).

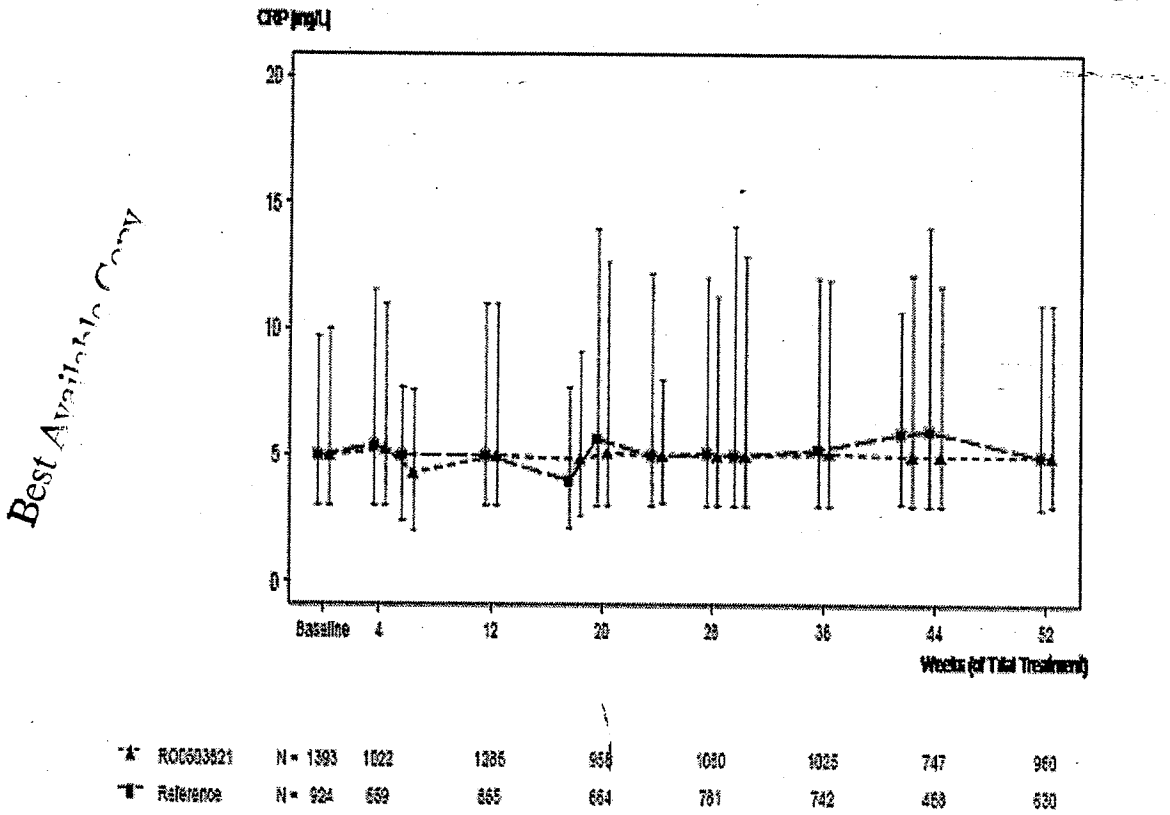

Figure 3. Time Course of CRP by Treatment group (Mircera vs pooled Epoetin and Darbepoetin)

As shown in Tables 6 and 7 below, higher baseline CRP levels (> 10 mg/L) correlated with death and more composite cardiovasular events (death, congestive heart failure, non-fatal myocardial infarction or stroke), in both Mircera and comparator groups with similar effects.

Table 6. Incidence (proportion) of composite endpoint events (death, CHF, MI, stroke) by baseline CRP and treatment

	Baseline CRP (mg/L)	
	<=10	> 10
Epoetin/ darbepoetin	10.7% (77/720)	14.7% (30/204)
Mircera	9.4% (101/1070)	16.8% (54/322)

Table 7. Incidence (proportion) of death by baseline CRP and treatment

	Baseline CRP (mg/L)	
	<=10	> 10
Epoetin/ darbepoetin	6.0 % (43/720)	10.3% (21/204)
Mircera	5.8% (62/1070)	10.6% (34/322)

Overall, only approximately 3% of CRF patients were excluded from Mircera confirmatory clinical studies because of elevated CRP.

Estimating the potential worst possible outcome for the 3% of patients excluded from Mircera studies may illustrate the extent of the consideration. Overall, exclusions of 3% of the patients solely due to CRP would have eliminated 82 potential patients from the final database size of 2737 patients. Of these 82 patients, assuming all patients assigned to Mircera died and all patients assigned to the comparator survived, table 8 shows the outcome.

Table 8. Worst Case: estimated mortality rates in phase 2/3 studies assuming addition/proportioning of 3% additional deaths within the database; assuming all Mircera patients died and all comparator patients survived

Outcome	Mircera n = 1789	Comparator n = 948
Deaths	130 (7.3%)	64 (6.8%)
3% of 2737 = 82 additional subjects, of whom only the 54 assigned to Mircera died while the 28 assigned to comparator survived	54 (3%)	0
Deaths + estimated deaths	184 (10.3%)	64 (6.8%)

Given the overall Mircera safety pattern and assuming extreme outcomes for fatalities as a result of CRP screening, the sufficiency of the Mircera safety database appears unclear.

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

IND 10158

Hoffman La-Roche
Attention: Jennifer Dudinak, Ph.D
Director, Regulatory Affairs
340 Kingsland Street
Nutley, NJ 07110

Dear Dr. Dudinak:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Pegylated Erythropoietin beta (human, recombinant, CHO cells, Hoffmann La-Roche).

We also refer to the meeting held on March 6, 2006, between representatives of your firm and this agency. A copy of the official minutes of the meeting is attached for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 796-2050.

Sincerely yours,

{See appended electronic signature page}

Florence O. Moore, M.S.
Regulatory Health Project Manager
Division of Medical Imaging and Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

Enclosure - Meeting Minutes

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: March 22, 2006

From: Florence O. Moore, M.S., DMIHP, HFD-160

To: Hoffman La- Roche

Subject: Pre-BLA Meeting Summary

Meeting Date:	**March 6, 2006 Time: 2:00 - 3:30 PM**
Location:	**CDER White Oak Bldg 22 Conference Room 1421**
Sponsor:	**Hoffman La-Roche (HLR)**
Product:	**Pegylated Erythropoietin beta (human, recombinant, CHO cells, Hoffmann La-Roche)**
Proposed Use:	**Treatment of anemia associated with chronic renal failure, including patients on dialysis and patients not on dialysis.**
Type of Meeting:	**Type B (Pre-BLA)**
Meeting Chair:	**Kathy Robie-Suh, M.D., Ph.D.**
Meeting Lead:	**John Lee, M.D.**
Meeting Recorders:	**Florence Moore, M.S.**
External Participant Lead:	**Cynthia Dinella, Ph.D./Jennifer Dudinak, Ph.D**
Meeting Purpose:	**To discuss the primary safety and efficacy data from the pivotal supportive correction and maintenance studies as well as to obtain scientific feedback on the adequacy of these data to support a BLA filing.**

Note: *FDA provided draft responses to the questions submitted in the meeting package by Hoffman La-Roche via facsimile transmission on March 1, 2006.*

Meeting Summary

At the beginning of the meeting, Hoffman La-Roche acknowledged receiving the FDA's responses to the submitted questions. Roche gave a brief slide presentation to clarify some of FDA's questions from the facsimile (see Attachment 1). What follows is a summary of the sponsor's questions, FDA's response by facsimile and specific discussions and clarifications sought by Hoffman La-Roche regarding FDA's responses.

Sponsor Questions, FDA Response and Discussions

Question 1:

Based on information presented in the package, please comment on the following:

Part 1

A. *What are the Agency's perspectives on the overall safety and efficacy results from studies BA16736 and BA16738 to support the use of RO0503821 in the treatment of anemia for CKD patients not currently treated with an erythropoiesis stimulating agent?*

FDA Response (by facsimile):

As presented in the pre-BLA meeting briefing material, the safety and efficacy results from studies BA16736 and BA16738 appear to support the filing of the BLA, for the use of RO0503821 in the treatment of anemia for CKD patients not currently treated with an erythropoiesis stimulating agent.

B. *What are the Agency's perspective on the approach to support a dosing recommendation of 0.6 mcg/kg IV or SC once every two weeks for the treatment of anemia in CKD patients on dialysis and not on dialysis?*

FDA Response (by facsimile):

The results presented in the pre-BLA meeting briefing material appear to support the filing of the BLA, for a dosing recommendation of 0.6 mcg/kg IV or SC once every two weeks for the treatment of anemia in CKD patients on dialysis and not on dialysis.

Discussions at the meeting:

Roche acknowledged FDA's comments regarding the overall safety and efficacy results and asked if FDA had any further comments. FDA stated there were no further comments to be added to the above responses.
FDA indicated that a more detailed examination of the submitted information will be performed in order to determine the acceptability of the BLA for filing. However, based upon the supplied information, the plans appear reasonable.

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D. Datasets

For the clinical study reports two datasets will be provided. One dataset will include the core correction/evaluation phase. Another dataset will include data for those patients who completed the study at the time of the November 2005 database closure.

Does the Agency agree with this approach?

FDA Response (by facsimile):

We reiterate our comments about the unclarity in the data submission plans. Please focus your pre-BLA presentation upon resolving this unclarity. As noted above, we encourage you to describe the basis for any data truncation, the extent of truncated data and the data you will supply in order to address the potential consequences of submitting truncated data.

Discussions at the meeting:

See "Discussion," above. Roche clarified that there will be two data sets at time of filing which will not be altered. The safety data for the 141 patients from the rollover extension study will be sent in as an amendment for review.

E. Case Report Forms

In the BLA submission, Case Report Forms from the correction studies will be provided for all deaths and withdrawals due to an adverse event at the time of database closure.

In addition, Case Report Forms will be provided for patients who had a serious adverse event associated with a study drug regimen alteration and patients who had a RBC transfusion that occurred in the correction/evaluation phase of the study and for those who completed the long-term safety extension phase at the time of the November 2005 database closure.

Does the Agency agree with this approach?

FDA Response (by facsimile):

Yes.

Discussions at the meeting:

There were no further comments made or clarification sought on this section.

F. *Four Month Safety Update*

The four month safety update will include data from patients who were ongoing in the long term safety extension phase at the time of the November 2005 database closure. Case Report Forms for these patients will be consistent with those provided in the BLA.

Does the FDA agree with this approach?

FDA Response (by facsimile):

Some of your studies include "extension periods" and some include "long term safety periods." Please clarify what you regard as the "long term extension phase" for the applicable clinical studies. Conceivably, you are referring to the 28 week extension period for Study BA16736 and the 24 week extension period for Study BA16738. A four month safety update should include all important safety data as an update to the data providing substantial evidence of safety and efficacy. We reiterate the unclarity within your data submission plans and request that you more explicitly describe the extent of any "truncated" or unsubmitted clinical data.

Discussions at the meeting:

There were no further comments made or clarification sought on this section. As noted above, FDA generally regarded the plans for data submission as reasonable.

Question 2:

A. *What are the Agency's perspectives on the overall safety and efficacy results from studies BA16739 and BA16740 to support conversion from epoetin to R00503821?*

FDA Response (by facsimile):

As presented in the pre-BLA meeting briefing material, the safety and efficacy results from studies BA16739 and BA16740 appear to support the filing of a BLA, for maintenance therapy after converting from epoetin to R00503821.

Discussions at the meeting:

There were no further comments made or clarification sought on this section.

B. *What are the Agency's perspectives on the approach to recommend the once every two-weeks and once every-four weeks (monthly) regimen for patients converting from epoetin to R00503821?*

FDA Response (by facsimile):

As presented in the pre-BLA meeting briefing material, the results appear to support the filing of a BLA, for the use of R00503821 once every two-weeks or once every-four weeks after converting from epoetin alfa. Whether either or both dosing regimens are approvable remains a review issue, which may require analyses that directly compare the two regimens for safety and efficacy, in addition to comparing each R00503821 regimen to a reference therapy. The draft labeling should provide guidance to the use with respect to the relative risks and benefits associated with the two dosing regimens. An opportunity to examine detailed draft labeling early in the review period would be helpful.

Discussions at the meeting:

There were no further comments made or clarification sought on this section.

Question 3:

A. *What are the Agency's perspectives on the overall safety and efficacy results from study BA17283 to support the use of R00503821 in patients currently treated with darbepoetin?*

FDA Response (by facsimile):

As presented in the pre-BLA meeting briefing material, the safety and efficacy results from study BA17283 appear to support the filing of a BLA, for the use of R00503821 in patients currently treated with darbepoetin alfa.

Discussions at the meeting:

FDA commented that the overall safety and efficacy results appear sufficient to support the submission of the BLA.

B. *What are the Agency's perspectives on the approach to recommend a once every two-weeks and once every four-week (once monthly) regimen when converting from darbepoetin alfa?*

FDA Response (by facsimile):

As presented in the pre-BLA meeting briefing material, the results appear to support the filing of a BLA, for the use of R00503821 once every two-weeks or once every-four weeks after converting from darbepoetin alfa.

Whether either or both dosing regimens are approvable remains a review issue, which may require analyses that directly compare the two regimens for safety and efficacy, in addition to comparing each R00503821 regimen to a reference therapy.

Discussions at the meeting:

Roche intends to seek approval for both regimens so that the users (patients) may flexibly choose one of the regimens. FDA commented that even if both regimens are found to be safe and effective, Roche should provide information (in the BLA submission and also in the eventual product labeling) about any differences in safety or efficacy between the two regimens that may be important for a patient in selecting a regimen. If there are no appreciable differences between the two regimens in terms of safety or efficacy, FDA commented that the sponsor may wish to consider seeking approval only for the more convenient (e.g., every 4-week) regimen. Roche acknowledged.

Question 4

What are the Agency's perspectives on the overall approach to support the once monthly claim?

FDA Response (by facsimile):

Whether the once "monthly" regimen is approvable is a review issue. Among many review issues, the approvability of the once monthly regimen would depend on the safety and efficacy of the every four-week regimen and the justification for citing the usage as a once monthly regimen.

Discussions at the meeting:

FDA stated that the rationale remains a review issue. Data should be provided to support the differences in administrating once monthly vs. once every four weeks.

Roche clarified that the available date for the once a month and once every four weeks regimen shows no differences, but the change in terminology is proposed for convenience.

Question 5

Based on the information presented in the package, what are the Agency's perspectives on the overall safety and efficacy results from study BA17284 to support to support the use of pre-filled syringes as an alternative dosage form to vials?

FDA Response (by facsimile):

As presented in the pre-BLA meeting briefing material, the safety and efficacy results from study BA17284 appear to support the filing of a BLA, for the use of pre-filled syringes as an alternative dosage form to vials. Among many review issues, the approvability of using pre-filled syringes would depend on analyses that individually compare each starting dose (low, intermediate, high) with the reference (weight-based) starting dose, for the potential need to make more frequent dosage adjustments, in addition to overall relative safety and efficacy.

Discussions at the meeting:

Roche clarified that the presented safety and efficacy results in the briefing material was to support administration and does not intend to propose different approaches to dosing.

Question 6

What are the Agency's perspectives on the overall pooled safety results and the Sponsor's plans to address safety in the BLA?

FDA Response (by facsimile):

- As presented in the pre-BLA meeting briefing material, the pooled safety results and your plans to address safety appear to support the filing of a BLA.
- The BLA should include safety analyses that examine the extent of the ranges for the hemoglobin safety parameters (hemoglobin excursions and rates of rise) in view of the dosing regimen and dose adjustment guideline used in the studies, correlation between fractions of the range (e.g., each quintile) and the occurrence of clinical adverse events (including thromboembolic adverse events and other events of particular interest). Based on these analyses and other safety analyses, the proposed product label should describe the types of monitoring procedures necessary for safe use of the product.

Discussions at the meeting:

FDA discussed the importance of analyzing hemoglobin rate of rise (ROR) within the clinical studies and correlating these rates with the occurrence of important adverse events.

Roche stated that they have previously looked at the ROR as part of their analysis for adverse events in relation to their propose dose and have not seen any notable correlations in ROR with the occurrence of adverse events.

Question 7

What are the Agency's perspectives on the risk minimization action plan for R00503821?

FDA Response (by facsimile):

As presented in the pre-BLA meeting briefing material, the risk minimization action plan for R00503821 appears to support the filing of a BLA.

Discussions at the meeting:

There were no further comments made or clarification sought on this section.

Question 8:

Based on the overall safety and efficacy results of the Phase 3 development program, does the Agency agree that the overall results support a BLA filing?

FDA Response (by facsimile):
As presented in the pre-BLA meeting briefing material, the overall safety and efficacy results of the Phase 3 development program appear to support the filing of a BLA. We note that safety experience about immunogenicity is not described adequately in the meeting briefing material. The BLA should contain detailed analyses and discussion regarding the immunogenic potential of R00503821.

Discussions at the meeting:

Roche explained that they have not seen any antibodies in their immunogenicity assays and will provide data in the dossier.

FDA expressed concern that there were no antibodies detected in the immunogenicity assays and noted that the robustness of the immunoassay should be evaluable from the data submitted within the BLA.

Question 9:

What are the Agency's perspectives on the overall phase 3 results to support the following indication: R00503821 is indicated for the treatment of anemia associated with chronic kidney disease including patients on dialysis and not on dialysis"?

FDA Response (by facsimile):

As presented in the pre-BLA meeting briefing material, the overall safety and efficacy results of the Phase 3 development program appear to support the filing of a BLA, for the proposed indication for use. The approvability of the proposed indication remains a review issue.

Discussions at the meeting:

There were no further comments made or clarification sought on this section.

CONTENT/FORMAT QUESTIONS

Question 10:

In light of the results presented in the Briefing Package, does the Agency have any additional comments on the Content/Format of the upcoming BLA?

FDA Response (by facsimile):

We take this opportunity to inform you that you can meet with the Office/Division staff in a post-submission meeting shortly following the submission of your BLA.

We anticipate that this meeting will consist of an overview of the application, with a focus upon describing those aspects of the submission critical to supporting your product's safety and efficacy. Presentations are generally one hour, followed by a half-hour question and answer session. The applicant, not consultants, presents important information on each technical aspect (i.e., clinical statistical, CMC or product information, pre-clinical pharmacology and toxicology, and clinical pharmacology and biopharmaceutics) of the application. These meetings are generally held after the BLA submission and prior to the filing date.

We also wish to inform you that, contingent upon our review findings, we may seek a discussion of your BLA findings at an Advisory Committee (AC). Additional information regarding this option will be discussed with you during the BLA review.

Discussions at the meeting:

Roche acknowledged the FDA response regarding the post-BLA submission meeting and asked for further clarification why Office of Oncology Products (OODP) has implemented this opportunity. FDA explained that OODP (and other Offices in the agency might probably follow in suite) implemented this opportunity to allow sponsors to share information regarding their product and BLA submission in an informal manner in order to facilitate the review. This meeting is also an opportunity for sponsors to highlight important subjects in their application. Nevertheless, this meeting is an invitation and sponsors do not have to present at these meetings if they feel they have nothing else to share with the Office.

Roche stated that they will like to take this opportunity to present at the meeting and would prefer an earlier date prior to the 60 day filing.

FDA Attendees:
Office of Oncology Drug Products
Division of Medical Imaging and Hematology Products
Rafel Dwaine Rieves, M.D., Deputy Division Director
Kathie Robie-Suh, M.D., Ph.D., Medical Team Leader
John Lee, M.D., Medical Reviewer
Florence Moore, M.S., Regulatory Health Project Manager

Office of Biostatistics
Division of Biometrics V
Mike Welch, Ph.D. Deputy Director

Office of Clinical Pharmacology and Biopharmaceutics
Division of Clinical Pharmacology and Biopharmaceutics V
Hong Zhao, Ph.D., Team Leader
Anil Rajpal, Ph.D., Clinical Pharmacology Reviewer

Sponsor Attendees:
Dr. Cynthia Dinella, Vice President, Regulatory Affairs
Dr. Jennifer Dudinak, Group Director, Regulatory Affairs
Dr. Krishnan Viswanadhan, Associate Driector, Regulatory Affairs
Ms. Lisa Luther, Executive Director, Regulatory Affairs
Dr. Bruno Osterwalder, Vice President, Clinical Science
Dr. Ulrich Beyer, Statistics
Mr. Chrys Kokino, Vice President, US Business
Ms. Zoe Morgan, Statistics
Ms. Allison Mueller, Regulatory Affairs
Mr. Fabrice Steible, Senior Global Project Manager

The following participated via teleconference:
Dr. Chris Dougherty, Clinical Science Leader
Dr. Bruno Reigner, Clinical Pharmacology

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

Our STN: BL 125164/0

MAR 02 2007

Hoffman La-Roche
Attention: Krishnan Viswanadhan, Pharm.D.
Associate Director, Drug Regulatory Affairs
340 Kingsland Street
Nutley, NJ 07110

Dear Dr. Viswanadhan:

Please refer to your biologics license application (BLA) submitted under section 351 of the Public Health Service Act.

We also refer to the meeting held on February 13, 2007, between representatives of your firm and this agency. A copy of the official minutes of the meeting is attached for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 796-2050.

Sincerely yours,

Florence O. Moore, M.S.
Regulatory Health Project Manager
Division of Medical Imaging and Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

Enclosure - Meeting Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

Meeting Type:	Type A
Meeting Category:	Safety Data Assessment
Meeting Date and Time:	February 13, 2007
Meeting Location:	CDER WO 1421 Conf Room Bldg 22
Application Number:	STN 125164/0
Product Name:	Pegylated Erythropoietin beta (human, recombinant, CHO cells, Hoffmann La-Roche)
Received Briefing Package:	January 4, 2007
Sponsor Name:	Hoffman La-Roche
Meeting Requestor:	Krishnan Viswanadhan, Pharm.D.
Meeting Chair:	Rafel Rieves, M.D.
Meeting Recorder:	Florence Moore, M.S.

Meeting Attendees:

FDA Attendees

Office of Oncology Drug Products
Immediate Office
Richard Pazdur, M.D., Director

Office of Oncology Drug Products
Division of Medical Imaging and Hematology Products
Rafel (Dwaine) Rieves, M.D., Deputy Director
Kathy Robie-Suh, M.D., Ph.D., Medical Team Leader
John Lee, M.D., Medical Reviewer

Yanli Ouyang, Ph.D., Pre-Clinical Reviewer
Florence Moore M.S., Regulatory Health Project Manager

Office of Biotechnology Products
Division of Therapeutic Proteins (DTP)
Emily Shacter, Ph.D., Laboratory Chief
Dov Pluznik, Ph.D.., Product Quality Reviewer
Susan Kirshner, Ph.D.., Product Quality Reviewer

Office of Compliance
Division of Manufacturing and Product Quality (DMPQ)
Patricia Hughes, Ph.D.., Product Quality Reviewer

Office of Clinical Pharmacology
Division of Clinical Pharmacology V
Hong Zhao, Ph.D., Clinical Pharmacology Team Leader
Jang-Ik Lee, Ph.D., Clin Pharmacology Reviewer
Hao Zhu, Ph.D., Clinical Pharmacology Reviewer
Pravin Jadhav, Ph.D., Pharmacometrics Reviewer

Office of Biostatistics
Division of Biometrics V
Jyoti Zalkikar, Ph.D., Team Leader
Richard Chen, Ph.D. Biostatistics Reviewer

Sponsor Attendees
Global Regulatory Affairs CMC:

Krishnan Viswanadhan, Regulatory Affairs
Cindy Dinella, Regulatory Affairs
Lisa Luther, Regulatory Affairs
Uli Beyer, Statistics
Bruno Reigner, Clinical Pharmacology
Chris Dougherty, Clinical Science
Bruno Osterwalder, Clinical Science
Ute Dugan, Medical Affairs
Chrys Kokino, US Business
Philippe Van der Auwera, Life Cycle Leader
Julianne Essig, Drug Safety

1.0 BACKGROUND

- Hoffman La-Roche submitted a Biologic License Application (BLA) on April 18, 2006 to support the use of Mircera for the treatment of anemia associated with chronic kidney disease (CKD), including patients on dialysis and not on dialysis.

Roche submitted a major amendment to their application on December 4, 2006, which included a September 1, 2006 safety update report, a cardiovascular mortality adjudication report, datasets, case report forms and an updated labeling.

- Roche requested this Type A meeting to obtain feedback from the agency on how the safety information has impacted the Division's previous assessment of the safety profile of Mircera, especially with regards to cardiovascular events, sudden death, and over all mortality.

- Further more, Roche requested that the public health advisory issued on November 17, 2006 regarding the agency's concerns on the results of the CHOIR and CREATE studies and erythropoietin stimulating agents (ESA) safety impact on Mircera be addressed at this meeting to better understand the safe and effective use of these products in the management of anemia associated with CKD.

2.0 DISCUSSION

FDA provided draft responses to the questions submitted in the meeting package by Roche by email communication on February 8, 2007. Roche provided an overview of their understanding of FDA's preliminary comments for the meeting (see attached Roche presentation).

2.1 Clinical

Question 1: *The September 1 Safety Update Report (Attachment 2: submitted December 4, 2006, Amendment 15,) demonstrated that there were no new safety findings with MIRCERA with longer treatment duration, and that differences between treatment arms have generally become smaller or show an imbalance in the reference treatment arm. In comparison to the 4MSU, small imbalances between MIRCERA and reference treatment arms have decreased for sudden death (from 0.5% to 0.3%), or shifted to a very slight imbalance in the reference compared to MIRCERA arm in the incidence of all cardiac deaths (5.4% and 5.3%, respectively) and overall mortality (10.9% and 10.2%, respectively):*

	4MSU Population		September 1 Extended Population	
	RO0503821 (N=1789) No. (%)	Reference (N=948) No. (%)	RO0503821 (N=1789) No. (%)	Reference (N=948) No. (%)
Deaths	130 (7.3)	64 (6.8)	182 (10.2)	103 (10.9)
Sudden Deaths	9 (0.5)	0 (0.0)	14 (0.8)	5 (0.5)
Cardiac Arrest Deaths	39 (2.2)	13 (1.4)	51 (2.9)	25 (2.6)
Cardiac Deaths	71 (4)	30 (3.2)	95 (5.3)	51 (5.4)

Based on this new Safety Update Report, does the Division agree with Roche's assessment that the safety profile of MIRCERA is similar to that of other ESAs, especially with regard to cardiovascular events, sudden death, and overall mortality?

FDA Response to Question 1: Please be aware that FDA granted this meeting in order to enhance the review of the most recent clinical data submissions. This review is ongoing and would benefit from Roche spending the bulk of the meeting time summarizing the content within the submissions and responding to any FDA questions. FDA will not provide preliminary or definitive feedback upon the results of the review since the process is continuing.

Question 2: *The results of an expert Cardiovascular Adjudication Committee blinded evaluation and adjudication of all deaths in MIRCERA clinical trials as of March 15, 2006 demonstrated a nearly equal distribution of sudden deaths with MIRCERA (1.96%) and reference (1.90%) treatments (Attachment 3: submitted December 4 2006, Amendment 15, 2006).*
When taken together with the additional patient source documentation for sudden death cases (see Amendment 9, submitted November 10, 2006) that described in greater detail the severity and decline in health status attributed to progression of end-stage renal disease or pre-existing cardiovascular risk factors, do the results of the independent mortality adjudication alleviate the Division's concern about the treatment imbalance in sudden deaths in the original BLA?

FDA Response to Question 2: As noted above, FDA will not provide preliminary or definitive feedback regarding conclusions from the review since the review is on-going.

Question 3: *On the basis of your review to date including the newly submitted data in the major amendment, does the Agency believe that the data presented in the MIRCERA application demonstrate a favorable risk/benefit profile when this product is used in accordance with the proposed labeling (Attachment 4 & 5: submitted December 4, 2006, Amendment 15)?*
Specifically, does the Agency believe that the clinical trial program support the proposed indication for the treatment of anemia associated with chronic kidney disease including patients on dialysis and not on dialysis?
Does the Agency believe that external consultation, such as an external Advisory Committee, should be pursued and if so, what committee and what projected timeframe?

FDA Response to Question 3: FDA plans presentation to the Cardio-renal advisory committee on April 17. Roche will be contacted regarding the logistical plans for this meeting.

Question 4: *Based on the results of the phase III clinical studies, Roche proposed the following starting dose recommendation for labeling (See Attachment 5).*
Roche recognizes the regulatory precedent with darbepoetin alfa in which further refinements in the dosing recommendations were made in labeling in order to ensure safe and effective use. Based on the Agency's review of the data, what are the Agency's

perspectives on the proposed dosing recommendations for the correction and conversion setting? Does the Agency have any specific recommendations or requests for additional analyses?

FDA Response to Question 4: FDA reiterates the educational/facilitation purpose of the meeting. At the upcoming meeting, FDA will not provide either preliminary or definitive feedback of review outcomes.

Question 5: *Based on the recently published results of the CHOIR study that showed a significantly increased risk for serious and life-threatening cardiovascular complications in patients dosed with epoetin alfa to higher target Hb concentrations (13.5 g/dL vs 11.3 g/dL), FDA advised physicians and other healthcare professionals to adhere to dosing with ESAs to maintain a target Hb range of 10 to 12 g/dL. In response to this Advisory, Roche has proactively updated the proposed labeling for MIRCERA in accordance with this recommendation.*

Does the Division plan to convene an Advisory Committee meeting in 1-2Q2007 to discuss new class labeling for ESAs consistent with recommendations in the November 17, 2006 Public Health Advisory?

FDA Response to Question 5: See above comments regarding the April 17, 2007 meeting.

Question 6: *The new action date for the MIRCERA BLA application is May 19, 2006. In anticipation of meeting these timelines can the Agency comment on planned timing for the following key milestones:*

- ***Clinical site audits****. The originally scheduled site audits were cancelled by FDA based on the anticipated Major Amendment.*
- ***Trade name confirmation****. Roche received preliminary approval of the tradename MIRCERA on October 27, 2006.*
- ***FDA assessment of Roche response to FDA Form 483, Inspectional Observations, submitted on December 8, 2006****. As a result of the November 13-17 inspection of the Basel site, FDA Form 483 was issued to Roche. Roche had two verbal discussions with FDA for clarity and to ensure Roche responded appropriately to the observations. Roche submitted responses to the observations on December 8, 2006.*
- ***Timeframe and process for labeling discussions***
- ***Timeframe and process for discussions on post-approval commitments***

FDA Response to Question 6: FDA reiterates the educational/facilitation purpose of the meeting. At the upcoming meeting, FDA will not provide either preliminary or definitive feedback of review outcomes.

Question 7: *Roche would like to work with FDA in the development of potential post-approval commitment studies. Roche is currently in discussions with the EU Rapporteurs on the development of post approval commitment studies as per their request.*

Roche recognizes the fact that studies like the CHOIR study have been conducted to further investigate the risk of complications from cardiovascular causes and death at different hemoglobin targets. Roche is receptive to discussing the impact of CHOIR and CREATE results on the design of future clinical trials to assess safety. Specifically, Roche would like to get the Division's preliminary thoughts on potential areas that the Agency believes would warrant further investigation through a post approval commitment study.

FDA Response to Question 7: See above comments regarding the April 17, 2007 meeting.

2.2 Discussions

After Roche's presentation FDA stated that the review of the application is still on-going and the information presented during the meeting needs to be considered further. FDA noted that Mircera will not be taken to an Advisory Committee (AC) in April as previously indicated. The additional data submitted in the major amendment were sufficient to conclude that an AC meeting is not needed. The sudden death concerns have lessened based upon the information submitted following submission of the BLA. However, FDA reiterated the on-going nature of the review, including concerns regarding the use of C-reactive protein screening of subjects. FDA noted subsequent actions will concern finalizing reviews, include the review of draft labeling and potential post-marketing considerations. FDA noted that the sponsor should not regard the review as completed.

[redacted] FDA noted that even though that might be the case, there will be a different population that would be introduced to the drug. FDA is concerned that clinicians will give Mircera to patients who are not stable and those who have no experience with erythropoietin. Roche explained that the stability of target hemoglobulin is dependent on baseline and indicated that patients with issues were not excluded from the studies. FDA reiterated that patients with no previous experience with ESA may be more susceptible to a product with longer duration and this presents a safety concern. FDA encouraged Roche to supply data analyses that support the contention that the overall safety database was not importantly altered by actively screening potential subjects with C-Reactive Protein tests.

Roche inquired about the approvalability of their application. FDA reiterated that guidance cannot be given on the approvalability of the application until the PDUFA date.

3.0 ISSUES REQUIRING FURTHER DISCUSSION

- C-Reactive Protein concerns

4.0 ACTION ITEMS

- Roche to provide CRP data
- FDA to provide Roche analysis

5.0 ATTACHMENTS AND HANDOUTS

Roche's slide presentation

RECORD OF TELEPHONE CONVERSATION

BLA 125164

Today's date: February 23, 2007

Speakers: Dwaine Rieves for FDA; Krishnan Viswwanadhan for Roche

Phone: 973-235-6241

I called Roche to let them know that we are providing a list of requested data analyses and that we request a response to these items by February 28, if possible. I stated that the requests would be provided either by email or fax.

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug
Administration
Rockville, MD 20857

IND 10158

Hoffman La-Roche
ATTENTION: Jennifer Dudinak, PharmD.
Program Director, Drug Regulatory Affairs
340 Kingsland Street
Nutley, NJ 07110

Dear Dr. Dudinak:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Pegylated Erythropoietin beta (human, recombinant, CHO cells, Hoffmann La-Roche).

We also refer to your amendment dated October 10, 2005, containing a request for perspectives on your proposed Pediatric Research Equity Act development plan.

We have the following comments and recommendations:

Questions:

1. Does the Agency agree that the proposed pediatric development program fulfills the requirements of the pediatric Research Equity Act of 2003?

   FDA Response: With acceptable study modifications (as outlined below) the proposed clinical studies represent a reasonable approach to fulfilling the requirements of the Pediatric Research Equity Act of 2003.

2. Does the Agency agree to a waiver of pediatric assessment in neonates up to age 5?

   FDA Response: Yes.

3. Does the Agency agree to a deferral of pediatric assessment in ages 5 to 18 given that the product will be ready for approval in adults before pediatric studies are complete?

   FDA Response: Yes. Please see our comments (below) regarding ages.

5 Page(s) Withheld

X Trade Secret / Confidential

_____ Draft Labeling

_____ Deliberative Process

Withheld Track Number: Administrative- 17

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

Our STN: BL 125164/0

Hoffman La-Roche
Attention: Krishnan Viswanadhan, Pharm.D.
Associate Director, Drug Regulatory Affairs
340 Kingsland Street
Nutley, NJ 07110

Dear Dr. Viswanadhan:

This letter is in regard to your biologics license application submitted under Section 351 of the Public Health Service Act.

We also refer to your January 3, 2007 correspondence requesting a meeting to discuss the safety information submitted to assess the safety profile of Mircera regarding the cardiovascular events, death and overall mortality. We consider the meeting a type A meeting.

The meeting is scheduled as follows:
Date: February 13, 2007
Time: 11:30 AM -1:00 PM (Eastern Time)
Location: CDER White Oak Building 22

CDER Participants:
Richard Pazdur, M.D., Director (OODP)
Karen Weiss, M.D., Deputy Director (OODP)
Rafel Rieves, M.D., Deputy Director
Kathy Robie-Suh, M.D., Ph.D., Clinical Team Leader
John Lee, M.D., Clinical Reviewer
Hong Zhao, Ph.D., Clinical Pharmacology Team Leader
Jang-Ike Lee, Ph.D., Clinical Pharmacology Reviewer
Yanli, Ouyang, Ph.D., Preclinical Reviewer
Jyoti Zalikikar, Ph.D., Biometrics Team Leader
Richard Chen, Ph.D., Biometrics Reviewer
Pravin Jadhav, Ph.D., Clinical Pharmacology Reviewer
Florence Moore, M.S., Regulatory Health Project Manager (DMIHP)

In addition, as discussed in the telephone conversation of January 11, 2007 between you and Drs. John Lee, Kathy Robie Suh and Dwaine Rieves, FDA anticipates discussion of Pegzerepoetin alfa (Mircera) at the scheduled April, 2007 meeting of the Cardiovascular and Renal Drug Products Advisory Committee. The definitive date for this meeting is pending and you will be notified the date, along with additional logistical information, once the date is confirmed.

If you have any questions, call me at (301) 301-796-2050.

Sincerely yours,

Florence O. Moore, M.S.
Regulatory Health Project Manager
Division of Medical Imaging and Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

Due Date 12/2/06

BLA Letter Routing Slip

SEN # 125464/0

Letter Type NME

FINAL ROUTING AND SIGNATURES

TYPIST
/date final typed

RPM
/date file box signed

CPMS
/date file box signed

CDER DMPQ BRANCH CHIEF
/date file box signed

CDER DMPQ DIRECTOR
/date file box signed

COMMITTEE CHAIR
/date file box signed

DBOP/PRODUCT DIRECTOR
/date file box signed

OODP DIRECTOR
/date file box signed

DBOP TYPIST
/date sent to sponsor

Milestone Entered

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

Our STN: BL 1251664/0

DEC 15 2006

Hoffman La-Roche
Attention: Krishnan Viswanadhan, Pharm.D.
Associate Director, Drug Regulatory Affairs
340 Kingsland Street
Nutley, NJ 07110

Dear Dr. Viswanadhan:

Please refer to your biologics license application submitted under section 351 of the Public Health Service Act for Mircera (Pegzerepoetin alfa).

We received your December 4, 2006 amendment to this application on December 5, 2006 and consider it to be a major amendment. Because the receipt date is within three months of the user fee goal date, we are extending the goal date by three months to May 19, 2007, to provide time for a full review of the amendment.

Please refer to http://www.fda.gov/cder/biologics/default.htm for important information regarding therapeutic biological products, including the addresses for submissions.

If you have any questions, please contact the Regulatory Project Manager, Florence O. Moore, M.S., at (301) 796-2050.

Sincerely,

Dwaine R. Lewis MD for

George Q. Mills, M.D., M.B.A. Acting
Director
Division of Medical Imaging and Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

6 Page(s) Withheld

_____ Trade Secret / Confidential

X Draft Labeling

_____ Deliberative Process

Withheld Track Number: Administrative- 18

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

From: Florence O. Moore, M.S.

Subject: First Committee for STN 125164/0

Sponsor: Hoffman La-Roche

Product: Pegserepoetin alfa

Date, Location, & Time of Meeting: **May 9, 2006**
WO Bldg 22 Conference Room 2376
11:00 a.m. – 11:30 a.m.

Purpose:

To introduce review team and discuss the timelines for the review process of the BLA submission.

Summary:

The review team met to discuss Hoffman La Roche's submission of a BLA for the treatment of anemia associated with chronic kidney disease, including patients on dialysis and patients not on dialysis. This supplement has been assigned 125164/0. The review schedule is a standard BLA submission with a 10-month review clock (Action Due Date: **February 17, 2007**).

The review team also discussed the following topics:

- Consults
- Timeline of the application review process.
- Filing Meeting
- Post Submission Meeting
- Labeling Meeting
- Advisory Committee
- Midcycle Meeting

A filing decision needs to be made by **June 15, 2006** (Filing action due date: **6/18/06**). The review team was advised to forward the signed-off filing review memo to the RPM by interoffice mail (HFD-160) before **6/15/06.**

First Action Due: February 17, 2007

Review Committee:

Clinical -John Lee, DMIHP
CMC - Dov Pluznik, DTP
P/T - Yanli Ouyang, DMIHP
PK - Jang-Ik Lee, DCPB
Stats - Richard Chen, OPSS
DMPQ- Patricia Hughes. DMPQ
RPM - Florence Moore, DMIHP

Other FDA Representatives:

Dwaine Rieves, DMIHP
Emily Shacter, DTP
Hong Zhao, DMPQ
Jyoti Zalkikar, OPSS
Lynn Henley, DMIHP

Regulatory Filing Review Memo for BLAs and Supplements

The filing review should seek to identify all omissions of clearly necessary information such as information required under the statute or regulations or omissions or inadequacies so severe that a meaningful review cannot be accomplished. CBER may refuse to file (RTF) an application or supplement as provided by 21 CFR 601.2, and 21 CFR 314.101, including those reasons consistent with the published RTF policy (http://www.fda.gov/cber/regsopp/8404.htm). An RTF decision may also be appropriate if the agency cannot complete review of the application without significant delay while major repair or augmentation of data is being done. To be a basis for RTF, the omissions or inadequacies should be obvious, at least once identified, and not a matter of interpretation or judgement about the meaning of data submitted. Decisions based on judgments of the scientific or medical merits of the application would not generally serve as bases for RTF unless the underlying deficiencies were identified and clearly communicated to the applicant prior to submitting a license application, e.g., during the review of the IND or during pre-BLA communications. The attached worksheets, which are intended to facilitate the filing review, are largely based upon the published RTF policy and guidance documents on the ICH Common Technical Document (CTD) (see http://www.fda.gov/cber/ich/ichguid.htm).

Where an application contains more than one indication for use, it may be complete and potentially approvable for one indication, but inadequate for one or more additional indications. The agency may accept for filing those parts of the application that are complete for a particular indication, but refuse to file those parts of the application that are obviously incomplete for other indications.

CBER management may, for particularly critical biological products, elect not to use the RTF procedure, even where it can be invoked, if it believes that initiating the full review at the earliest possible time will better advance the public health.

STN: 125164/0 Product: Pegserepoetin Alfa Applicant: Hoffman La-Roche

Final Review Designation (circle one): (Standard) Priority

Submission Format (circle all that apply): Paper (Electronic) Combination

Submission organization (circle one): (Traditional) CTD

Filing Meeting: Date _____ Committee Recommendation (circle one): (File) RTF

RPM: _____ 5/19/06
(signature/date)

Attachments:

- ☐ Discipline worksheets (identify the number of lists attached for each part and fill-in the name of the reviewer responsible for each attached list):
  - X Part A – RPM
  - X Part B – Product/CMC/Facility Reviewer(s): D. Pluznik P. Hughes
  - X Part C – Non-Clinical Pharmacology/Toxicology Reviewer(s): _____
  - X Part D – Clinical (including Pharmacology, Efficacy, Safety, and Statistical) Reviewers J. Lee R. Chen J. Lee Y. Ouyang
- ☐ Memo of Filing Meeting

Part A. Regulatory Project Manager (RPM)

CTD Module 1 Contents	Present?	If not, justification, action & status
Cover Letter	Y N	
Form 356h completed	Y N	
❑ including list of all establishment sites and their registration numbers	Y N	
❑ If foreign applicant, US Agent signature.	Y N	NA
Comprehensive Table of Contents	Y N	
Debarment Certification with correct wording (see * below)	Y N	
User Fee Cover Sheet	Y N	
User Fee payment received	Y N	
Financial certification &/or disclosure information	Y N	
Environment assessment or request for categorical exclusion (21 CFR Part 25)	Y N	
Pediatric rule: study, waiver, or deferral	Y N	
Labeling:	Y N	
❑ PI –non-annotated	Y N	
❑ PI –annotated	Y N	
❑ PI (electronic)	Y N	
❑ Medication Guide	Y N	
❑ Patient Insert	Y N	
❑ package and container	Y N	
❑ diluent	Y N	
❑ other components	Y N	
❑ established name (e.g. USAN)	Y N	
❑ proprietary name (for review)	Y N	

* The Debarment Certification must have correct wording , e.g. "I, the undersigned, hereby certify that XXX Co. did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food Drug, and Cosmetic Act in connection with the studies listed in Appendix XXX." Applicant may not use wording such as "To the best of my knowledge,.."

Examples of Filing Issues	Yes?	If not, justification, action & status
Content, presentation, and organization of paper and electronic components sufficient to permit substantive review?:	Y N	
Examples include:		
❑ legible	Y N	
❑ English (or translated into English)	Y N	
❑ compatible file formats	Y N	
❑ navigable hyper-links	Y N	
❑ interpretable data tabulations (line listings) & graphical displays	Y N	
❑ summary reports reference the location of individual data and records	Y N	

Examples of Filing Issues	Yes?	If not, justification, action & status
❑ protocols for clinical trials present ❑ all electronic submission components usable (e.g. conforms to published guidance)	Y N Y N	
companion application received if a shared or divided manufacturing arrangement	Y N	NA
if CMC supplement: ❑ description and results of studies performed to evaluate the change ❑ relevant validation protocols ❑ list of relevant SOPs	 Y N Y N Y N	
if clinical supplement: ❑ changes in labeling clearly highlighted ❑ data to support all label changes ❑ all required electronic components, including electronic datasets (e.g. SAS)	 Y N Y N Y N	NA
if electronic submission: ❑ required paper documents (e.g. forms and certifications) submitted	 Y N	

List any issue not addressed above which should be identified as a reason for not filing the BLA/BLS. Also provide additional details if above charts did not provide enough room (or attach separate memo).

Has orphan drug exclusivity been granted to another drug for the same indication?
If yes, review committee informed? NA

Does this submission relate to an outstanding PMC? NO

If an Advisory Committee (AC) discussion may be needed, list applicable AC meetings scheduled to occur during the review period:

- Name:
- Dates:

Recommendation (circle one) File RTF

RPM Signature: Branch Chief concurrence:

Part D – Clinical (Pharmacology, Efficacy, Safety,and Statistical) Reviewers

CTD Module 2 Contents	Present?	If not, justification, action & status
Overall CTD Table of Contents [2.1]	(Y) N	
Introduction to the summary documents (1 page) [2.2]	(Y) N	
Clinical overview [2.5]	(Y) N	
Clinical summary [2.7] (summary of individual studies; comparison and analyses across studies)	(Y) N	
▫ Biopharmaceutics and associated analytical methods	(Y) N	
▫ Clinical pharmacology [includes immunogenicity]	(Y) N	
▫ Clinical Efficacy [for each indication]	(Y) N	
▫ Clinical Safety	(Y) N	
▫ Synopses of individual studies	(Y) N	

CTD Module 5 Contents	Present?	If not, justification, action & status
Module Table of Contents [5.1]	(Y) N	
Tabular Listing of all clinical studies [5.2]	(Y) N	
Study Reports and related information [5.3]	(Y) N	
▫ Biopharmaceutic	(Y) N	
▫ Studies pertinent to Pharmacokinetics using Human Biomaterials	(Y) N	
▫ Pharmacokinetics (PK)	(Y) N	
▫ Pharmacodynamic (PD)	(Y) N	
▫ Efficacy and Safety	(Y) N	
▫ Postmarketing experience	(Y) N	
▫ Case report forms	(Y) N	
▫ Individual patient listings (indexed by study)	(Y) N	
o electronic datasets (e.g. SAS)	(Y) N	
Literature references and copies [5.4]	(Y) N	

Examples of Filing Issues	Yes?	If not, action & status
Content, presentation, and organization sufficient to permit substantive review?	(Y) N	
▫ legible	(Y) N	
▫ English (or certified translation into English)	(Y) N	
▫ compatible file formats	(Y) N	
▫ navigable hyper-links	(Y) N	
▫ interpretable data tabulations (line listings) & graphical displays	(Y) N	

Examples of Filing Issues	Yes?	If not, action & status
▫ summary reports reference the location of individual data and records	(Y) N	
▫ protocols for clinical trials present	(Y) N	
▫ all electronic submission components usable	(Y) N	
statement for each clinical investigation: ▫ conducted in compliance with IRB requirements	(Y) N	
▫ conducted in compliance with requirements for informed consent	(Y) N	
adequate and well-controlled clinical study data (e.g. not obviously inappropriate or clinically irrelevant study design or endpoints for efficacy)	(Y) N	
adequate explanation of why results from what appears to be a single controlled trial (or alternate method for demonstrating efficacy) should be accepted as scientifically valid without replication	(Y) N	
study design not clearly inappropriate (as reflected in regulations, well-established agency interpretation or correspondence) for the particular claim	(Y) N	
study(ies) assess the contribution of each component of a combination product [21 CFR 610.17]	(Y) N	
total patient exposure (numbers or duration) at relevant doses is not clearly inadequate to evaluate safety (per standards communicated during IND review, or ICH or other guidance documents)	(Y) N	
adequate data to demonstrate safety and/or effectiveness in the population intended for use of the biological product based on age, gender, race, physiologic status, or concomitant therapy	(Y) N	
drug interaction studies communicated as during IND review as necessary are included	(Y) N	
assessed drug effects whose assessment is required by well established agency interpretation or communicated during IND review	(Y) N	
comprehensive analysis of safety data from all current world-wide knowledge of product	(Y) N	

Examples of Filing Issues	Yes?		If not, action & status
data supporting the proposed dose and dose interval	(Y)	N	
appropriate (e.g. protocol-specified) and complete statistical analyses of efficacy data	(Y)	N	
adequate characterization of product specificity or mode of action	(Y)	N	
data demonstrating comparability of product to be marketed to that used in clinical trials when significant changes in manufacturing processes or facilities have occurred	(Y)	N	
inadequate efficacy and/or safety data on product to be marketed when different from product used in clinical studies which are the basis of safety and efficacy determinations	Y	(N)	
all information reasonably known to the applicant and relevant to the safety and efficacy described?	(Y)	N	

List of Clinical Studies (protocol number)	Final study report submitted?		Financial disclosure or certification submitted?			SAS & other electonic datasets complete & usable?		BiMo sites identified? (Dates)		
	Y	(N)	(Y)	N	NR	(Y)	N	Y	N	NR
	Y	(N)	(Y)	N	NR	(Y)	N	Y	N	NR
	Y	(N)	(Y)	N	NR	(Y)	N	Y	N	NR
BA 16260	(Y)	N	(Y)	N	NR	(Y)	N	Y	N	NR
BA 16740	(Y)	N	(Y)	N	NR	(Y)	N	Y	N	NR
BA 16739	(Y)	N	(Y)	N	NR	(Y)	N	Y	N	NR
BA 17283	(Y)	N	(Y)	N	NR	(Y)	N	Y	N	NR
BA 17284	(Y)	N	(Y)	N	NR	(Y)	N	Y	N	NR
	Y	(N)	(Y)	N	NR	(Y)	N	Y	N	NR
	Y	(N)	(Y)	N	NR	(Y)	N	Y	N	NR

Y= yes; N=no; NR=not required

List any issue not addressed above which should be identified as a reason for not filing the BLA/BLS. Also provide additional details if above charts did not provide enough room (or attach separate memo).

None

Is clinical site(s) inspection (BiMo) needed?

(Dalen)

Is an Advisory Committee needed?

No issues for an Advisory Committee identified at filing.

Recommendation (circle one): (File) RTF

Reviewer: [signature] 5/8/'06 Type (circle one): (Clinical) Clin/Pharm Statistical
(signature/ date)

Concurrence:

Branch Chief: [signature] 5-9-06 Division. Director: _____
(signature/ date) (signature/ date)

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20852

MAY 0 8 2006

Hoffman La-Roche
Attention: Krishnan Viswanadhan, Pharm.D.
Director, Regulatory Affairs
340 Kingsland Street
Nutley, NJ 07110

Dear Dr. Viswanadhan:

We have received your biologics license application (BLA) submitted under section 351 of the Public Health Service Act for the following biological product:

Our Submission Tracking Number (STN): BL 125164/0

Name of Biological Product: Pegserepoetin alfa

Indication: Treatment of anemia associated with chronic kidney disease, including patients on dialysis and patients not on dialysis

Date of Application: April 18, 2006

Date of Receipt: April 19, 2006

User Fee Goal Date: February 17, 2007

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We reference the deferral granted on February 21, 2006, for the pediatric study requirement for this application.

We request that you submit all future correspondence, supporting data, or labeling relating to this application in triplicate, citing the above STN number. Please refer to http://www.fda.gov/cder/biologics/default.htm for important information regarding therapeutic biological products, including the addresses for submissions.

Effective August 29, 2005, the new address for all submissions to this application is:

Food and Drug Administration
Center for Drug Evaluation and Research
Therapeutic Biological Products Document Room
5901-B Ammendale Road
Beltsville, MD 20705-1266

We will notify you within 60 days of the receipt date if the application is sufficiently complete to permit a substantive review.

If you have any questions, please contact the Regulatory Project Manager, Florence O. Moore, M.S., at (301) 796-2050.

Sincerely,

Kyong "Kaye" Kang, Pharm.D.
Chief, Project Management Staff
Division of Medical Imaging and Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

CONCURRENCE PAGE

Letter Type: Acknowledgement Letter (ACK)
Summary Text: STN Assignment - Application

SS & RIS Data Check:

- **If "Unacceptable for Filing" add 2nd LETTER TYPE "UN".**
- **Communication**

RIS Data Check:

- **Submission Screen: In Arrears Box Is Checked**
- **Milestone: Confirm "UN" Entry & User Fees Not Paid -- The Clock Has Stopped. First Action Due Close Date And The New "UN" Entry Date Should Match**
- **No Action Due Date**
- **STN Status – Unacceptable for Filing**

cc: F. Moore
J. Lee
HFD-141/Ayoub Suliman
DMIHP BLA file (hard copy)
HFD-020/OND Immediate Office if original BLA (hard copy)

History:

File Name: S:\BLA\Letters\Acknowledgement\125164\0ACK.doc

Office	Name/Signature	Date
DMIHP		5/2/06
DMI4P		5/8/06

STN 125164/0 Product Pegserepoetin-α

Part D – Clinical (Pharmacology, Efficacy, Safety,and Statistical) Reviewers

CTD Module 2 Contents	Present?		If not, justification, action & status
Overall CTD Table of Contents [2.1]	~~Y~~	(N)	not eCTD format but reviewable
Introduction to the summary documents (1 page) [2.2]	(Y)	N	
Clinical overview [2.5]	(Y)	N	
Clinical summary [2.7] (summary of individual studies; comparison and analyses across studies)	(Y)	N	
☑ Biopharmaceutics and associated analytical methods	(Y)	N	
☑ Clinical pharmacology [includes immunogenicity]	(Y)	N	
☑ Clinical Efficacy [for each indication]	(Y)	N	
☑ Clinical Safety	(Y)	N	
☑ Synopses of individual studies	(Y)	N	

CTD Module 5 Contents	Present?		If not, justification, action & status
Module Table of Contents [5.1]	(Y)	N	
Tabular Listing of all clinical studies [5.2]	(Y)	N	
Study Reports and related information [5.3]	(Y)	N	
☑ Biopharmaceutic	(Y)	N	
☑ Studies pertinent to Pharmacokinetics using Human Biomaterials	(Y)	N	
☑ Pharmacokinetics (PK)	(Y)	N	
☑ Pharmacodynamic (PD)	(Y)	N	
☑ Efficacy and Safety	(Y)	N	
☐ Postmarketing experience	Y	N	N/A
☑ Case report forms	(Y)	N	
☑ Individual patient listings (indexed by study)	(Y)	N	more
o electronic datasets (e.g. SAS)	(Y)	~~N~~	will request if necessary
Literature references and copies [5.4]	(Y)	N	

Examples of Filing Issues	Yes?		If not, action & status
Content, presentation, and organization sufficient to permit substantive review?	(Y)	N	
☑ legible	(Y)	N	
☑ English (or certified translation into English)	(Y)	N	
☑ compatible file formats	(Y)	N	
☑ navigable hyper-links	(Y)	N	
☑ interpretable data tabulations (line listings) & graphical displays	(Y)	N	

Examples of Filing Issues	Yes?	If not, action & status
☑ summary reports reference the location of individual data and records	(Y) N	
☑ protocols for clinical trials present	(Y) N	
☑ all electronic submission components usable	(Y) N	
statement for each clinical investigation: ☑ conducted in compliance with IRB requirements	(Y) N	
☑ conducted in compliance with requirements for informed consent	(Y) N	
adequate and well-controlled clinical study data (e.g. not obviously inappropriate or clinically irrelevant study design or endpoints for efficacy)	Y N	N/A to Clinical Pharmacology (CP)
adequate explanation of why results from what appears to be a single controlled trial (or alternate method for demonstrating efficacy) should be accepted as scientifically valid without replication	Y N	N/A to CP
study design not clearly inappropriate (as reflected in regulations, well-established agency interpretation or correspondence) for the particular claim	Y N	N/A to CP
study(ies) assess the contribution of each component of a combination product [21 CFR 610.17]	Y N	N/A (not combo product)
total patient exposure (numbers or duration) at relevant doses is not clearly inadequate to evaluate safety (per standards communicated during IND review, or ICH or other guidance documents)	Y N	N/A to CP
adequate data to demonstrate safety and/or effectiveness in the population intended for use of the biological product based on age, gender, race, physiologic status, or concomitant therapy	Y N	N/A to CP
drug interaction studies communicated as during IND review as necessary are included	(Y) N	
assessed drug effects whose assessment is required by well established agency interpretation or communicated during IND review	(Y) N	
comprehensive analysis of safety data from all current world-wide knowledge of product	Y N	N/A to CP

STN 125164/0 Product Pegserepoetin-α Part D Page 3 A

Examples of Filing Issues	Yes?		If not, action & status
data supporting the proposed dose and dose interval	(Y)	N	
appropriate (e.g. protocol-specified) and complete statistical analyses of efficacy data	Y	N	N/A to CP
adequate characterization of product specificity or mode of action	(Y)	N	
data demonstrating comparability of product to be marketed to that used in clinical trials when significant changes in manufacturing processes or facilities have occurred	(Y)	N	
inadequate efficacy and/or safety data on product to be marketed when different from product used in clinical studies which are the basis of safety and efficacy determinations	(Y)	N	
all information reasonably known to the applicant and relevant to the safety and efficacy described?	(Y)	N	

List of Clinical Studies (protocol number)	Final study report submitted?		Financial disclosure or certification submitted?			SAS & other electonic datasets complete & usable?		BiMo sites identified?		
BP16964	(Y)	N	Y	N	NR	(Y)	N	Y	N	(NR)
BP16198	(Y)	N	Y	N	NR	(Y)	N	Y	N	(NR)
BP16239	(Y)	N	Y	N	NR	(Y)	N	Y	N	(NR)
JP16417	(Y)	N	Y	N	NR	(Y)	N	Y	N	(NR)
JP16690	(Y)	N	Y	N	NR	(Y)	N	Y	N	(NR)
BP16346	(Y)	N	Y	N	NR	(Y)	N	Y	N	(NR)
WP16422	(Y)	N	Y	N	NR	(Y)	N	Y	N	(NR)
WP16383	(Y)	N	Y	N	NR	(Y)	N	Y	N	(NR)
BP18035	(Y)	N	Y	N	NR	(Y)	N	Y	N	(NR)
BP17278	(Y)	N	Y	N	NR	(Y)	N	Y	N	(NR)

Y= yes; N=no; NR=not required

Examples of Filing Issues	Yes?	If not, action & status
data supporting the proposed dose and dose interval	Y N	
appropriate (e.g. protocol-specified) and complete statistical analyses of efficacy data	Y N	
adequate characterization of product specificity or mode of action	Y N	
data demonstrating comparability of product to be marketed to that used in clinical trials when significant changes in manufacturing processes or facilities have occurred	Y N	
inadequate efficacy and/or safety data on product to be marketed when different from product used in clinical studies which are the basis of safety and efficacy determinations	Y N	
all information reasonably known to the applicant and relevant to the safety and efficacy described?	Y N	

List of Clinical Studies (protocol number)	Final study report submitted?	Financial disclosure or certification submitted?	SAS & other electonic datasets complete & usable?	BiMo sites identified?
BP17570	(Y) N	Y N NR	(Y) N	Y N (NR)
BP16779	(Y) N	Y N NR	(Y) N	Y N (NR)
BP18034	(Y) N	Y N NR	(Y) N	Y N (NR)
	Y N	Y N NR	Y N	Y N NR
	Y N	Y N NR	Y N	Y N NR
	Y N	Y N NR	Y N	Y N NR
	Y N	Y N NR	Y N	Y N NR
	Y N	Y N NR	Y N	Y N NR
	Y N	Y N NR	Y N	Y N NR
	Y N	Y N NR	Y N	Y N NR

Y= yes; N=no; NR=not required

List any issue not addressed above which should be identified as a reason for not filing the BLA/BLS. Also provide additional details if above charts did not provide enough ~~room~~ (or attach separate memo).

Is clinical site(s) inspection (BiMo) needed?

no from a clinical Pharmacology standpoint

Is an Advisory Committee needed?

no from a clinical Pharmacology standpoint

Recommendation (circle one): (File) RTF

Reviewer: Jayne Lee Type (circle one): Clinical (Clin/Pharm) Statistical
(signature/ date)

Concurrence:

~~Branch Chief~~ Team leader: [signature] 5/8/06 Division. Director: [signature] May 8, 2006
(signature/ date) (signature/ date)

STN 125164/0 Product Pegserepoetin alfa (MIRCERA)

Part D – Clinical (Pharmacology, Efficacy, Safety,and Statistical) Reviewers

CTD Module 2 Contents	Present?	If not, justification, action & status
Overall CTD Table of Contents [2.1]	(Y) N	
Introduction to the summary documents (1 page) [2.2]	(Y) N	
Clinical overview [2.5]	(Y) N	
Clinical summary [2.7] (summary of individual studies; comparison and analyses across studies)	(Y) N	
❑ Biopharmaceutics and associated analytical methods	Y N	
❑ Clinical pharmacology [includes immunogenicity]	Y N	
❑ Clinical Efficacy [for each indication]	(Y) N	
❑ Clinical Safety	(Y) N	
❑ Synopses of individual studies	(Y) N	

CTD Module 5 Contents	Present?	If not, justification, action & status
Module Table of Contents [5.1]	(Y) N	
Tabular Listing of all clinical studies [5.2]	(Y) N	
Study Reports and related information [5.3]	(Y) N	
❑ Biopharmaceutic	Y N	
❑ Studies pertinent to Pharmacokinetics using Human Biomaterials	Y N	
❑ Pharmacokinetics (PK)	Y N	
❑ Pharmacodynamic (PD)	Y N	
❑ Efficacy and Safety	(Y) N	
❑ Postmarketing experience	Y N	
❑ Case report forms	(Y) N	
❑ Individual patient listings (indexed by study)	(Y) N	
○ electronic datasets (e.g. SAS)	(Y) N	
Literature references and copies [5.4]	Y N	

Examples of Filing Issues	Yes?	If not, action & status
Content, presentation, and organization sufficient to permit substantive review?	(Y) N	
❑ legible	(Y) N	
❑ English (or certified translation into English)	(Y) N	
❑ compatible file formats	(Y) N	
❑ navigable hyper-links	(Y) N	
❑ interpretable data tabulations (line listings) & graphical displays	(Y) N	

STN 125164/0 Product Pegsarepoetin Alfa Part D Page 2

Examples of Filing Issues	Yes?	If not, action & status
❑ summary reports reference the location of individual data and records	(Y) N	
❑ protocols for clinical trials present	(Y) N	
❑ all electronic submission components usable	(Y) N	
statement for each clinical investigation:		
❑ conducted in compliance with IRB requirements	(Y) N	
❑ conducted in compliance with requirements for informed consent	(Y) N	
adequate and well-controlled clinical study data (e.g. not obviously inappropriate or clinically irrelevant study design or endpoints for efficacy)	(Y) N	
adequate explanation of why results from what appears to be a single controlled trial (or alternate method for demonstrating efficacy) should be accepted as scientifically valid without replication	(Y) N	
study design not clearly inappropriate (as reflected in regulations, well-established agency interpretation or correspondence) for the particular claim	(Y) N	
study(ies) assess the contribution of each component of a combination product [21 CFR 610.17]	(Y) N	
total patient exposure (numbers or duration) at relevant doses is not clearly inadequate to evaluate safety (per standards communicated during IND review, or ICH or other guidance documents)	(Y) N	
adequate data to demonstrate safety and/or effectiveness in the population intended for use of the biological product based on age, gender, race, physiologic status, or concomitant therapy	(Y) N	
drug interaction studies communicated as during IND review as necessary are included	Y N	N/A
assessed drug effects whose assessment is required by well established agency interpretation or communicated during IND review	Y N	
comprehensive analysis of safety data from all current world-wide knowledge of product	Y N	

Examples of Filing Issues	Yes?	If not, action & status
data supporting the proposed dose and dose interval	(Y) N	
appropriate (e.g. protocol-specified) and complete statistical analyses of efficacy data	(Y) N	
adequate characterization of product specificity or mode of action	(Y) N	
data demonstrating comparability of product to be marketed to that used in clinical trials when significant changes in manufacturing processes or facilities have occurred	Y N	
inadequate efficacy and/or safety data on product to be marketed when different from product used in clinical studies which are the basis of safety and efficacy determinations	Y N	
all information reasonably known to the applicant and relevant to the safety and efficacy described?	(Y) N	

	List of Clinical Studies (protocol number)	Final study report submitted?		Financial disclosure or certification submitted?			SAS & other electonic datasets complete & usable?		BiMo sites identified?		
◊	BA 16260	(Y)	N	Y	N	NR	Y	N	Y	N	NR
◊	BA 16528	(Y)	N	Y	N	NR	Y	N	Y	N	NR
*	BA 16736	(Y)	N	Y	N	NR	Y	N	Y	N	NR
*	BA 16738	(Y)	N	Y	N	NR	Y	N	Y	N	NR
◊	BA 16285	(Y)	N	Y	N	NR	Y	N	Y	N	NR
◊	BA 16286	(Y)	N	Y	N	NR	Y	N	Y	N	NR
*	BA 16739	(Y)	N	Y	N	NR	Y	N	Y	N	NR
*	BA 16740	(Y)	N	Y	N	NR	Y	N	Y	N	NR
*	BA 17823	(Y)	N	Y	N	NR	Y	N	Y	N	NR
*	BA 17824	(Y)	N	Y	N	NR	Y	N	Y	N	NR

Y= yes; N=no; NR=not required

* = phase III study

◊ = phase II study

List any issue not addressed above which should be identified as a reason for not filing the BLA/BLS. Also provide additional details if above charts did not provide enough room (or attach separate memo).

NONE

Is clinical site(s) inspection (BiMo) needed?

A

Is an Advisory Committee needed?

NO

Recommendation (circle one): (File) RTF

May 3, 2006

Reviewer: [signature] Type (circle one): Clinical Clin/Pharm (Statistical)
(signature/ date)

Concurrence:

Branch Chief: Tyoh Zalkika Division. Director: Alaka Chakravarty
(signature/ date) (signature/ date) 5/3/06

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville, MD 20852

Our Reference: BB-IND 10158

OCT 31 2003

Hoffmann-La Roche, Incorporated
Attention: Jennifer A. Dudinak, Pharm.D.
Director, Regulatory Affairs
340 Kingsland Street,
Nutley, NJ 07110-1199

Dear Dr. Dudinak:

Please refer to your **Investigational New Drug Application (IND)** for "Pegylated Epoetin beta (human, recombinant CHO cells, Hoffmann-La Roche)" and to the meeting held on October 2, 2003, between representatives of your firm and this agency. A copy of our memorandum of that meeting is attached for your information.

If you have any questions, please contact me at (301) 827-4358.

Sincerely yours,

Karen Winestock

Karen Winestock
Regulatory Project Manager
Division of Review Management and Policy
Office of Drug Evaluation VI
Office of New Drugs
Center for Drug Evaluation and Research

Enclosure

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: OCT 31 2003

From: *Karen D. Winestock, DARP, DTPP, HFM-585*

To: BB-IND 10158

Subject: Type B, IND End of Phase 2/PrePhase 3 Meeting Summary

Meeting: October 2, 2003 **Time:** 3:00 to 4:30 p.m.

Location: WOC 1, Conference Room 2

Meeting Sponsor: Hoffmann-La Roche, Incorporated

Product: Pegylated Epoetin beta

Proposed Use: Treatment of anemia associated with chronic renal failure

Type of meeting: End of Phase 2/PrePhase 3

Meeting Purpose: To obtain FDA feedback on the preclinical, clinical pharmacology and clinical development programs that will be used to support initiation of the Phase 3 dialysis program and eventual registration of Pegylated Epoetin beta to treat anemia in chronic renal failure patients, including patients on dialysis and patients not on dialysis (i.e. chronic kidney disease)

Prior to the start of the meeting, Hoffmann-La Roche provided the FDA with population exposure and safety data base information for the Phase 2 and 3 trials.

Hoffmann-La Roche informed the FDA that the [redacted] material produced at the pilot facility would be used in the Phase 3 clinical trials.

Sponsor questions and FDA response:

Clinical Development Program

1. *Please comment on the acceptability of the Phase I and II clinical pharmacology program to support Phase III and ultimate registration of ROO503821 for the treatment of anemia in patients with chronic renal failure. The Sponsor is proposing no additional clinical pharmacology studies other than completing the ongoing Phase I studies in healthy volunteers and patients, and assessing the pharmacokinetics and the concentration-effect relationship of ROO503821 in some patients in Phase III studies. Does the Agency agree?*

   The FDA found the current proposal acceptable. The final decision on acceptability will depend on the data submitted. Hoffmann-La Roche should consider including the pre-dialysis Phase 3 study subjects in the population pharmacokinetic analysis.

   a. *Please comment on the acceptability of the Sponsor s interpretation/plans for addressing the pharmacokinetic variability noted with ROO503821.*

      The FDA found this proposal acceptable. The final decision on acceptability will depend on the data submitted.

   b. *Please comment on the overall acceptability of the Sponsor's proposal not to conduct formal drug-drug interaction (DDI) studies but to use a population pharmacokinetic approach to explore the effect of other drugs on the pharmacokinetics and pharmacodynamics of ROO503821.*

      The FDA stated that if the results of the exploratory studies suggest there is a drug-drug interaction, then formal drug-drug interaction studies might be needed.

      Hoffmann-La Roche informed the FDA that the data from the exploratory studies would not be available for review prior to filing the BLA. Hoffmann-La Roche asked if the formal drug-drug interaction studies could be performed post marketing, if a decision was made by the FDA that these studies were necessary.

      The FDA stated that the decision of whether a study can be done post marketing would depend on the data submitted.

5 Page(s) Withheld

0 Trade Secret / Confidential

_____ Draft Labeling

_____ Deliberative Process

Withheld Track Number: Administrative- 19

Issues Requiring Further Discussion:

- The size of the patient safety data base
- The additional tissue types that should be included in the in vitro cell proliferation study

Action Items:

- FDA will schedule a follow-up telephone conference to discuss the size of the safety database.
- The FDA will schedule a follow-up telephone conference to discuss the additional tissue types that should be included in the vitro cell proliferation study.

FDA Attendees: Marc Walton, Ellis Unger, John Hyde, Ilan Irony, Barbara Wilcox, Dov Pluznik, Anil Rajpal, Marc Walton, and Ferrin Harrison

Sponsor Attendees: F.C. Dougherty, Robert Provenzano, Jennifer Dudinak, Uli Beyer, Jian-ping Tang, Hee-joong Kim, Robin Conrad, John Michailidis, Martin Huber, Randall Stevens, Delphine Oguey, Nathalie Schultze, Anne Pannier, Ronald Gieschke, Bruno Reigner