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APPLICATION NUMBER:
BLA 125164

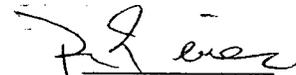
MEDICAL REVIEW

Date: November 7, 2007

From: John Lee, M.D., Medical Officer, DMIHP, OODP



Through: Dwaine Rieves, M.D., Acting Director, DMIHP, OODP



To: BLA File, STN 125164

Subject: Second cycle clinical review of BLA (STN 125164):

Methoxy polyethylene glycol-epoetin beta (Mircera) for the treatment of anemia associated with chronic kidney disease in patients on dialysis or not on dialysis

Review of sponsor response to 18 May 2007 complete review letter

**Second Cycle Clinical Review
Sponsor Response to Complete Review Letter**

Application (Applicant): BLA, STN 125164/0 (Hoffman LaRoche, Inc.)
 Product Name: Methoxy polyethylene glycol-epoetin beta (Mircera)
 Product Class: Erythropoiesis Stimulating Agent
 Proposed Indication: Treatment of anemia associated with chronic kidney disease
 Intended population: Patients with chronic kidney disease on dialysis or not on dialysis
 Complete Review Letter: 18 May 2007

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Product Description

Mircera is a new molecular entity within the class of erythropoiesis stimulating agents (ESAs). The ESA class contains two products marketed in the United States, epoetin alfa and darbepoetin alfa, and both products are manufactured by Amgen, Inc. In evaluating Mircera, the sponsor (Hoffman LaRoche, Inc.) used epoetin alfa, epoetin beta, and darbepoetin alfa as reference comparator agents. Epoetin beta is marketed in Europe and is nearly identical to epoetin alfa.

Mircera is a new molecular entity in that the introduction of a methoxy polyethylene glycol moiety (PEG) into the epoetin beta peptide backbone resulted in a new molecule with an approximate molecular weight of about 60 kilodaltons, about twice the size of epoetin beta. The two-fold increase in size appears to account for the clinically relevant major differences between Mircera and its reference comparator ESAs:

- The chemical modification (introduction of PEG) resulted in a ESA with prolonged circulating half-life, permitting Mircera to be dosed less frequently than the reference ESAs (epoetin alfa, epoetin beta, and darbepoetin alfa).
- The sponsor recommends dosing every two weeks (Q2W) or every four weeks (Q4W) based on clinical data, or every month (QM) based on extrapolation from the Q4W data. As might be expected from pharmacokinetic (PK) considerations, the time to reach the target hemoglobin is significantly longer with Mircera than with the reference agents.
- Unlike the reference erythropoietins, the safety and efficacy of Mircera appears to be less dependent on the administration route; intravenous (IV) or subcutaneous (SC) injection routes appears to be equivalent with respect to safety and efficacy.

Proposed Indication for Use

The sponsor claims that Mircera is effective in correcting anemia and in maintaining the hemoglobin in patients with chronic renal failure (CRF) on dialysis or not on dialysis. The sponsor also claims that Mircera is comparable to the reference erythropoietins (epoetin alfa, epoetin beta, and darbepoetin alfa) with respect to efficacy and safety.

The proposed clinical indication for Mircera is limited to CRF; the sponsor does not seek the "cancer" or the "surgical" indication that are approved for other ESAs. The sponsor proposes the following regimens in using Mircera to treat anemia associated with CRF.

Proposed Treatment Regimen

The sponsor recommends the following specific dosing guidelines in using Mircera to treat anemia associated with CRF, either as de novo therapy in patients not previously treated with an erythropoietin product (anemia correction) or in converting from another erythropoietin in previously treated patients (hemoglobin maintenance).

- For anemia correction in patients not currently treated with an erythropoietin product, the recommended starting dose of Mircera is 0.6 ug/kg Q2W, IV or SC, irrespective of dialysis status (on or not on dialysis). The dose should be titrated to maintain the hemoglobin between 10 and 12 g/dL. At dose stabilization, the Q2W regimen may be converted to a Q4W regimen at twice the stable maintenance dose, and the dose should be again titrated to maintain the hemoglobin between 10 and 12 g/dL.

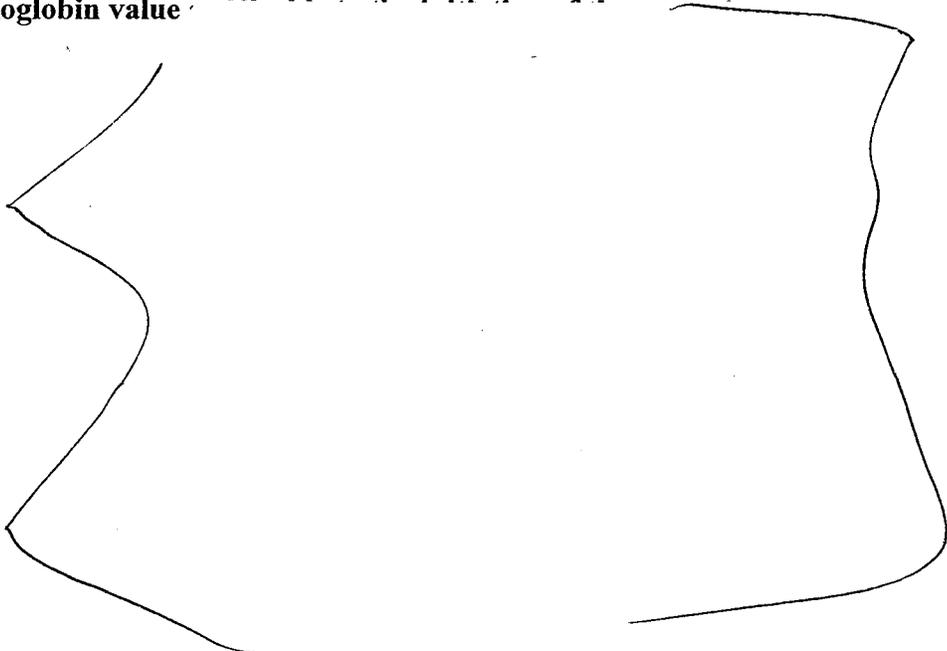
- For hemoglobin maintenance in patients currently treated with an erythropoietin product (epoetin alfa or darbepoetin alfa), the starting dose of Mircera should be determined using a dose conversion ratio specific to the total weekly dose of epoetin alfa or darbepoetin alfa. Mircera may be administered either IV or SC, and either QM or Q2W.

Complete Review Letter (May 18, 2007)

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,

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 baseline hemoglobin value**



1 Page(s) Withheld

 x § 552(b)(4) Trade Secret / Confidential

 § 552(b)(4) Draft Labeling

 § 552(b)(5) Deliberative Process

In brief, the September 2007 FDA Advisory Committee (AC) recommended a target hemoglobin range of 10 to 12 g/dL in using ESAs to treat anemia associated with chronic kidney disease. This recommendation implies that ESA therapy should be initiated when chronic kidney disease (CKD) progresses to a point where the anemia is associated with clinically important consequences and the endogenous hemoglobin level falls below 10 g/dL.

- 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.**

Roche Response

- There is an inverse relation between Hb and dose, confirmed in the literature and in analyses of Mircera-treated and reference-treated patients. Low Hb is associated with increased incidences of infections, serious adverse events and AEs leading to death. Higher doses were documented in these event categories, while the latter were also associated with low hemoglobin levels.
- Analyses of safety by dose quintiles were performed to evaluate safety outcomes with Mircera (and/or reference compound) dosages. At the highest dose quintiles, the safety events seen in both treatment groups (Mircera and reference) were related to infectious events in most cases.
- An analysis of events associated with the highest Mircera dose decile shows that deaths, AEs leading to death, and SAEs were proportionally more common in the highest decile of dose with both Mircera and reference treatment. Of the patients who received doses in the highest decile, 19/177 (10.7%) died in the Mircera group, as compared to 8/61 (13.1%) patients in the epoetin group and 5/24 (20.8%) in the darbepoetin treatment group.
- The highest dose administered in the clinical program was 5129 ug in a patient who completed the study with a hemoglobin value within target range.
- Two of the 20 Mircera-treated patients with the highest dose (more than 938 ug) died, a proportion which is only slightly higher than that found in the whole study population. In both patients, dose was increased in response to low hemoglobin and the fatal event occurred 15 to 25 days after the last dose.
- Based on the analyses of the Mircera renal anemia clinical program, no maximum tolerated dose was identified.
- The draft labeling for Mircera provides recommendation regarding the need to search for causative factors in the event of lack of response or failure to maintain hemoglobin response with Mircera doses in the recommended range. Therefore, no additional changes in labeling are proposed.

FDA Critique of Sponsor Response

- We agree with the sponsor's comments that: (1) higher doses correlate with lower hemoglobin levels and higher rates of deaths, AEs leading to death, and SAEs, for both Mircera and reference agents, (2) these study results are consistent with the ESA literature regarding the complex relationship among baseline hemoglobin, target hemoglobin, achieved hemoglobin, dose, and adverse events including serious cardiovascular events, and (3) a clear maximum dose is difficult to identify using retrospective data. The September 2007 FDA Advisory Committee, however, recommended that ESAs be used in chronic kidney disease according to a dosing strategy consistent with that used in the CHOIR study, which included the specification of an arbitrary maximum dose.
- The AC also recommended that PMC studies be performed to further investigate optimal target hemoglobin ranges as well as to better define a strategy for identifying and managing hyporesponders. In designing the PMC studies, it may be helpful to note that targeting hemoglobin levels may systematically lead to undertreating the hyperresponder and overtreating the hyporesponder. For the hyperresponder reaching a hemoglobin of 10 to 12 g/dL on a very small ESA dose, a hemoglobin level which exceeds 10 to 12 g/dL may be beneficial with little increased adverse outcome. For the hyporesponder requiring a very large ESA dose to achieve a hemoglobin of 10 to 12 g/dL, this hemoglobin level may be associated with a significant risk of adverse outcome. Although the hemoglobin is likely directly involved in the pathogenesis of treatment-related adverse cardiovascular events, the dose may be the predominant driver of cardiovascular toxicity and the hemoglobin may be just one of many variables that are involved in many pathogenetic mechanisms that lead to the overall cardiovascular toxicity.
- Dose titration to desired hemoglobin was a natural consequence of regarding ESA as being free of inherent toxicity (a naturally occurring necessary hormone) AND regarding the normal state (with respect to the hemoglobin level) as being preferable to an abnormal one. The unexpected results of CHOIR and the "Normal Hematocrit" studies indicate that neither assumptions are true. As with most drugs, ESAs may be best administered according to fixed doses shown to improve clinical outcome. If placebo-controlled studies are not ethical, then comparing fixed doses may be an option that avoids extreme overtreatment of hyporesponders while identifying reasonable candidate doses as being "optimal," until additional, more detailed studies can be performed.
- In order to identify the "optimal" dosing strategy, we may ask the sponsor to perform one or more PMC studies to explore the complex relationship among dialysis status, dose, achieved hemoglobin, and targeted hemoglobin. The major design features are described below as item 2 of "FDA Comments to Sponsor."
- The AC recommended that ESAs be used in chronic kidney disease according to a dosing strategy consistent with that used in the CHOIR study, which included the specification of an arbitrary maximum dose. The sponsor should propose a maximum Mircera dose that parallels the maximum epoetin alfa dose in CHOIR:

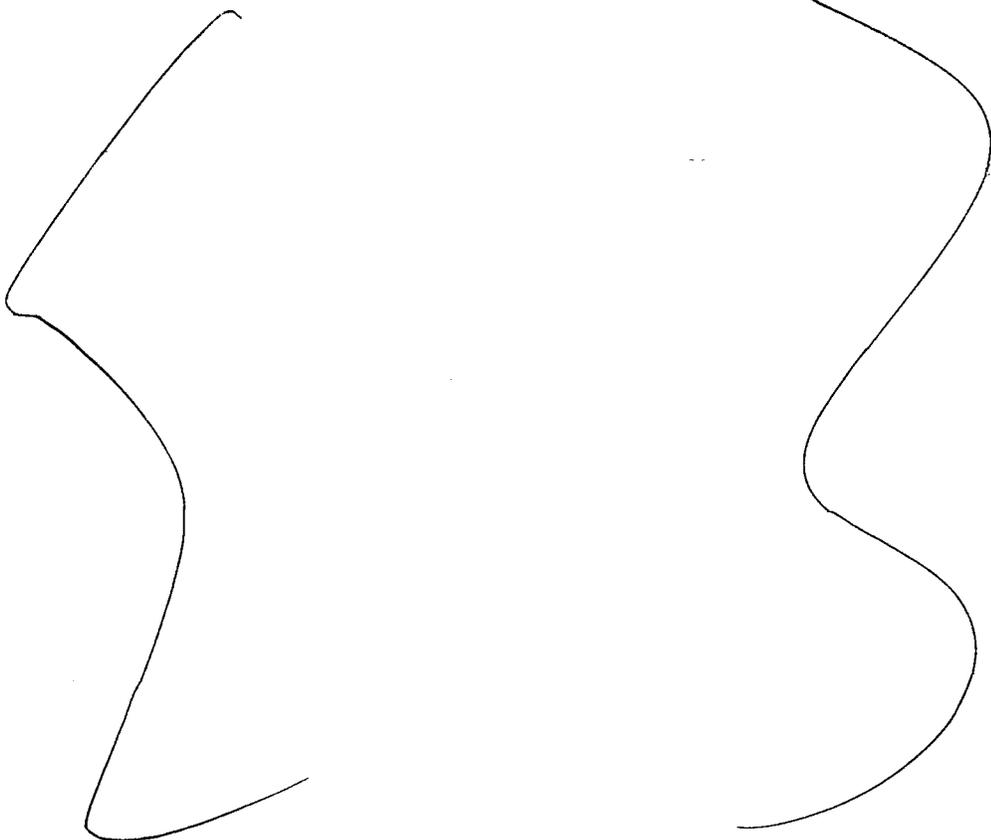
- In the CHOIR study, the mean dose of epoetin alfa in patients achieving the low hemoglobin target (11.3 g/dL) was 6,057 U/week and the protocol-specified maximum dose was 20,000 U/week, for a 3.3-fold "safety" limit (a maximum dose that is 3.3-times the mean dose among responders).
- In Mircera studies, an approximate mean dose of 0.4 ug/kg every two weeks maintained the hemoglobin level at about 12 g/dL, which is higher than the 11.3 g/dL achieved by CHOIR's low-target responders. Applying the 3.3-fold "safety" margin as seen in CHOIR yields 0.6 ug/kg as the weekly maximum dose of Mircera. Conversion to weight-unadjusted dosing (using 70 kg as the average patient weight) yields 42 ug as the total weekly maximum doses of Mircera, or 84 ug every-two weeks.

The sponsor should be asked to comment on this interim approach to using 84 ug every two weeks as the maximum dose, until more definitive data become available.

- c. **Submit clinical data and information justifying the appropriateness of the proposed dosing recommendations for Mircera, including the proposal to administer Mircera in a manner t**
- Specifically, supply clinical data that support the safety of Mircera dosing to target any**

Roche Response

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FDA Critique of Sponsor Comments

- The Mircera pivotal studies show that downward dose adjustments were necessary to achieve and maintain a mean hemoglobin of about 12 g/dL. The starting doses in the pivotal studies were: (1) $\frac{1}{\text{kg}}$ IV for anemia correction in dialysis, (2) 0.6 ug/kg SC for anemia correction in non-dialysis, and (3) as specified by the dose conversion table for hemoglobin maintenance in dialysis. As each pivotal study progressed, the mean dose typically decreased to reach a maintenance dose that is about 30 to 50% lower than the selected starting dose in stably sustaining a mean hemoglobin of about 12 g/dL, a level that is 1 g/dL higher than the midpoint of the 10 to 12 g/dL range recommended by the September 2007 AC.
 - These observations indicate that when physicians prescribe Mircera according to the starting doses used in the pivotal studies (_____), the number of downward dose adjustments necessary to achieve and stably sustain the hemoglobin between 10 and 12 g/dL will be even greater than that observed in Mircera pivotal studies.
- 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.**

Roche Response

- Multiple studies to date have shown an association of Hb < $\frac{1}{\text{g/dL}}$ with mortality and hospitalization in both non-dialyzed CKD and CKD patients on dialysis.
- A review of ESA literature and guidelines, including the recent draft NKF-KDOQI guidelines, indicates that a hemoglobin target range of $\frac{1}{\text{g/dL}}$ minimizes risk and maximizes benefit in patients.
- Exploratory analyses from the two MIRCERA phase III correction studies demonstrate that a relevant transfusion risk was found at an initiation level of Hb < $\frac{1}{\text{g/dL}}$. Avoiding Hb levels $\frac{1}{\text{g/dL}}$ would reduce the incidence of transfusion in these patients. (See response to question 1a.)
- A pooled analysis of ESA treatments from the Phase III studies showed that Hb levels < 11 g/dL were associated with an increased proportion of cardiac events including hypertension, arrhythmia, congestive heart failure, myocardial infarction and cardiac arrest. There was a clear relation of Hb \geq 13 g/dL to an increased incidence of vascular access thrombosis, while cerebrovascular accident, deep venous thrombosis and other thrombovascular events (TVEs) were associated with Hb levels < 10 and \geq 13 g/dL.
- Although specific safety analyses in the Mircera program did not identify a risk at Hb levels up to 13 g/dL, Roche supports treatment initiation at a Hb level of $\frac{1}{\text{g/dL}}$ or less, and the recommendation not to exceed an upper limit of 12 g/dL for all erythropoiesis stimulating agents (class labeling).

FDA Critique of Sponsor Response

See discussion under items 1a, 1b, and 1c above.

- 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.**

Roche Response

In a letter dated March 20, 2007, FDA requested Roche revise the proposed label for Mircera to reflect the recent Public Health Advisory and revised labels for currently marketed ESAs, including text for a Black Box Warning.

- The revised label for Mircera includes all components of the class Black Box Warning, and associated Warnings and Precautions. The current class Black Box Warning includes statements regarding time to progression, overall survival, and increased risk of death in certain patients with cancer. It is Roche's understanding that this warning was derived from the body of evidence outlined in the WARNINGS AND PRECAUTIONS: Increased Mortality and/or Tumor Progression. Roche considers the description of clinical studies in certain patients with cancer to be part of the class label, providing context for the black box warning in cancer patients. As Mircera is a member of the ESA class and the current Black Box Warning for Mircera includes statements pertinent to cancer patients, Roche believes it appropriate to include the study descriptions in the label.
- This approach is consistent with the precedence of Aranesp® (darbepoetin alfa), which is not indicated for the reduction of allogeneic RBC transfusion in anemic pre-operative patients. However, in the current Aranesp USPI, the Warning that corresponds to the Black Box Warning in this patient population includes a description of important safety findings from a clinical study of epoetin alfa ('SPINE' study).
- Furthermore, this approach is consistent with the precedence of Cymbalta® (duloxetine HCl) with respect to its Black Box Warning on suicidality in children and adolescents. Cymbalta is not indicated for the treatment of depression in pediatrics; however, in the current Cymbalta USPI, the Warning that corresponds to the Black Box Warning on suicidality in children and adolescents includes a description of important safety findings from a pooled analysis of clinical studies on other antidepressant medications.

Therefore, Roche proposes to include the description of important safety findings from clinical studies of ESA use among certain patients with cancer.

FDA Critique of Sponsor Response

Sponsor response is logical and the proposed approach to labeling is consistent with preventing off-label use of Mircera in cancer, provided that the scope of labeling is clearly indicated in the black box class label with reference to cancer study description elsewhere in each product label. As part of class labeling, Mircera cancer studies should be described along with other ESA cancer studies and the class black box should indicate the scope of approval for each approved ESA.

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 $\leq 100 \times 10^9/L$ at any time compared to 4.4% among reference ESA treated patients. The proposed product label states that platelet counts below $100 \times 10^9/L$ were observed in $\frac{7.5}{4.4}$ of patients treated with Mircera and $\frac{4.4}{7.5}$ of patients treated with ESAs. Please reconcile this apparent inconsistency.**

Roche Response

- The statement in the proposed product label regarding the percent of patients with low platelet counts in the Mircera and reference ESA treatment groups (respectively) was based on the following definition of marked laboratory abnormalities for platelets: proportion of patients with at least one post baseline platelet value $< 100 \times 10^9/L$ and at least *below baseline* (italics added).
- In the pooled phase 2 and 3 population, 7.5% of Mircera treated patients had at least one post baseline platelet value $< 100 \times 10^9$ at any time compared to 4.4% among reference ESA treated patients. The product labeling, therefore, has been revised as follows to be consistent:

“At least one post baseline platelet value below $100 \times 10^9/L$ at any time was observed in 7.5% patients treated with Mircera compared to 4.4% patients treated with other ESAs.”

- In order to evaluate the impact of Mircera on platelet function, Roche is conducting an in-vitro study of the effects of Mircera on platelet function in platelet enriched plasma and blood from healthy subjects and patients with chronic kidney disease under dialysis. The study is currently ongoing and the clinical study report will be submitted upon completion of the study.

FDA Critique of Sponsor Response

The sponsor's explanation and proposal for course of action are acceptable.

- 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.**

Roche Response

- In the pooled Phase II and Phase III population, serious hemorrhagic events occurred in 5.2% and 4.0% of patients treated with Mircera and reference, respectively. Corresponding findings for the randomized Phase III studies were 4.8% and 4.0%, respectively.
- History of hemorrhage was demonstrated to be a statistically significant risk factor in patients with serious hemorrhage, based on a multivariate Cox regression analysis using baseline risk factors in patients from Phase III studies. Examination of the medical history for patients in both treatment groups indicated that a history of bleeding was documented more often in patients treated with Mircera than with reference.

- An analysis of concomitant medications affecting coagulation, platelet function or mucosal integrity among patients with serious hemorrhagic events showed that these agents were given more frequently in patients treated with Mircerca than in patients treated with a reference drug.
- These imbalances in factors associated with bleeding risk contribute to the observed differences in serious hemorrhagic events between the Mircerca and reference treatment groups in the pooled Phase II and Phase III population.

FDA Critique of Sponsor Response

The sponsor's description and analyses about patient characteristics and anticoagulant use are acceptable, in view of the small difference seen in rates of hemorrhage in open-label studies. The sponsor's contention that the small difference in rates of hemorrhage is "spurious" should be confirmed in a prospective study.

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 Mircerca 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 Mircerca 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 Mircerca 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 10g/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 Mircerca 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.

Roche Response

In accordance with the Agency's request, Roche submitted a draft synopsis to BB-IND 10158 (Submitted on July 27, 2007 S-295).

FDA Critique of Sponsor Response



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.**

Roche Response

In accordance with the Agency's request, Roche submitted the clinical 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."

FDA Critique of Sponsor Comments

Sponsor submitted a clinical study report for study NH19960. The sponsor should describe this study in the label for Mircerca. The label should clearly state that Mircerca is not indicated in cancer. See comments about cancer labeling under item 1e above.

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.**

Roche Response

On October 10, 2005, Roche submitted draft synopses for the following pediatric clinical studies to FDA for review:

- Study NH19707 – Dose finding pediatric study
- Study NH19708 – Confirmatory efficacy/safety study in pediatric patients

FDA provided comments on both study synopses February 22, 2006. Roche updated both protocols to address FDA's comments, and resubmitted full protocols on December 20, 2006. On March 15, 2007, Roche received an e-mail from FDA stating that the pediatric pharmacokinetic assessment plan was acceptable from a clinical pharmacology standpoint, and that FDA had no further comments at that time.

- Proposed Timelines for Pediatric Clinical Study NH19707
 - Study Title (NH19707): An open-label multi-center, multiple dose study to determine the optimum starting dose of intravenous RO0503821 for maintenance treatment of anemia in pediatric patients with chronic kidney disease on dialysis.
 - Study Initiation: Roche intends to initiate the dose finding study following approval of the BLA. Based on an anticipated BLA approval date of December 2007 and an approximately 6 month site initiation timeframe, Roche anticipates study initiation by June 2008.
 - Study Completion and Final Study Report: Study completion date will be approximately 1 year following study initiation, and therefore Roche anticipates study completion by June 2009 and a final study report by October 2009.
- Proposed Timelines for Pediatric Clinical study NH19708
 - Study Title (NH19708): An open-label randomized, controlled, multi-center, parallel group study to confirm the optimal starting dose of RO0503821 for the maintenance treatment of anemia in pediatric patients with chronic kidney disease who are not yet on dialysis and those who are on dialysis.
 - Study Initiation: The timelines for initiation of study NH19708 is dependent on the results of the dose finding study NH19707. Following discussions and agreement with

FDA on the final protocol for NH19708 and an anticipated 6 month recruitment time, Roche anticipates study initiation by May 2010.

- Study Completion and Final Study Report: Roche anticipates study completion by December 2011 and a final study report by April 2012.

FDA Critique of Sponsor Comments

The sponsor's summary of the status of the pediatric clinical study and the proposed time line are acceptable.

Efficacy

The data submitted in support of this BLA clearly demonstrates the efficacy of Mircera in increasing the hemoglobin level in patients with anemia associated with CRF.

Raising the hemoglobin level from below 10 g/dL to a range between 10 and 12 g/dL is assumed to result in clinical benefit, and the pivotal studies were not designed to show clinical efficacy beyond raising the hemoglobin level. Direct evidence of clinical benefit were not shown, including transfusion avoidance or reduction, decreased morbidity and mortality, slower disease progression, or enhanced health-related quality of life.

Safety

Multiple studies (including six large phase 3 studies, each about one year in duration) in patients with CRF receiving or not receiving dialysis did not show that the safety profile of Mircera (nearly 1800 patients) is significantly different from those of reference ESAs (epoetin alfa, epoetin beta, or darbepoetin alfa; nearly 1000 patients).

A high background incidence of adverse events in CRF makes it difficult to discern "small" potential safety differences inherent to product. The study designs do not permit an evaluation of safety related to the ways in which the products are used; Mircera and all reference ESAs were used to achieve and maintain the same hemoglobin target level using product-specific dose titration schemes. See Appendices 1-3.

The potential for off-label use of Mircera to treat anemia associated with cancer chemotherapy remains a major safety concern. How aggressively the sponsor should pursue efforts to mitigate this concern (e.g., surveillance of the off-label use and/or new studies to address this concern) would depend on how the risk from using Mircera off-label in cancer is reflected in final product labeling. See item 9 in Appendix F below, *List of New Studies Recommended by FDA*.

Appendix A

Major Residual Safety Concerns Specific to Mircera

The following is a list of safety concerns for Mircera identified to date (October 2007). These safety concerns should be reflected in product labeling and/or further investigated in new studies.

1. Potentially inadequate representation of the intended treatment population:

Laboratory screening for elevated levels of C-reactive protein (CRP) systematically excluded from phase 2 and phase 3 studies some patients who may receive Mircera in clinical practice. In the pivotal studies, patients with CRP levels above 30 mg/dL were not represented, and the safety (and efficacy) data may not apply to CRF patients with CRP levels above 30 mg/dL.

2. Mortality (probable cardiovascular toxicity):

a. Sudden death: A statistically significant greater incidence of sudden death with Mircera than with the reference agents in the phase 2 and phase 3 (safety) study population, as well as a statistically significant difference in the mean time to sudden death upon extended safety follow up of the phase 2 and phase 3 study populations.

(1) The imbalance in sudden deaths was statistically significant ($p = 0.03$). Upon extended safety follow up, the degree of imbalance decreased to a statistically non-significant level ($p = 0.4$). Upon adjudication by a blinded cardiac panel, the incidence of sudden deaths was comparable between Mircera and the reference agents. Results obtained at extended follow up or cardiac adjudication, however, do not demonstrate that the initially observed imbalance in sudden deaths is spurious; the definition of "sudden death" may have changed from one that is specific but unstated (by the clinical investigators) to one that is rigorously defined (by the cardiac adjudication panel) but less specific.

(2) Sudden deaths on Mircera were observed at all time points. Sudden deaths on a reference agent were observed only after the initial data lock. Although the difference between Mircera and the reference agents in the incidence of sudden death decreased to a statistically non-significant level upon continued follow up, the duration of survival after initiating Mircera therapy was shorter (statistically significant) than after initiating therapy using a reference agent.

(3) Lack of an adequate determination of a QT effect regarding cardiac safety: Malignant cardiac arrhythmia is a possible mechanism of sudden death. Given the concern about sudden death, a cardiac toxicity assessment should include a complete evaluation of a potential QT effect.

b. Overall mortality:

(1) A statistically significant greater overall mortality with Mircera than with epoetin (alfa or beta) at approximately treatment day 190:

In two of the three phase 3 hemoglobin maintenance studies in dialysis in which epoetin (alfa or beta) was used as the comparator agent (BA16739, BA16740), greater mortality was suggestive for Mircera, maximally at about treatment day 190. In the third study (BA17284) in which a statistically significant difference was not observed, the use of Mircera in pre-filled syringes may have resulted in hemoglobin titration to a

level lower than the maximum level permitted in the study protocol. Greater mortality was not seen in BA17283, a phase 3 hemoglobin maintenance study in dialysis in which a long-acting agent was used as the reference agent (darbepoetin alfa).

- (2) A statistically non-significant trend to a greater overall mortality with Mircerca than with the reference agents in the phase 2 and phase 3 (safety) study population
- (3) A statistically significant lower mean time to death with Mircerca than with the reference agents in all four phase 3 hemoglobin maintenance studies in dialysis:

Although overall mortality was not significantly different between Mircerca and the reference agents, the duration of survival after initiating Mircerca therapy was appreciably shorter than after initiating a reference agent.

3. Adverse events:

a. Treatment-related adverse events:

- (1) A statistically significant greater proportion of patients experiencing a treatment-related adverse event (as assessed by the clinical investigators) with Mircerca than with epoetin (alfa or beta) at any given time in all four phase 3 hemoglobin maintenance studies in dialysis.
- (2) A statistically significant lower mean time to first treatment-related adverse event with Mircerca than with the reference agents in all four phase 3 hemoglobin maintenance studies in dialysis

b. Potential for thrombotic events:

- (1) A statistically significant greater reduction in the mean platelet count with Mircerca than with the reference agents after initiating treatment:

This reduction in platelet count after initiating Mircerca therapy may increase the risk for thrombosis (including acute coronary syndrome) and may be mechanistically related to the increased incidence of sudden deaths and the trend to increased overall mortality.

- (2) A statistically significant greater proportion of patients experiencing arterial-venous graft thrombosis with Mircerca than with the reference agents:

This observation is consistent with the reduction in platelet count after initiating Mircerca therapy and the potential for increased risk for thrombosis.

- (3) Small but statistically increased risk of hemorrhage relative to reference ESAs:

In the safety population (pooled phase 2 and phase 3 studies), serious hemorrhage occurred in 5.2% and 4.0% of patients treated with Mircerca and reference, respectively. Corresponding rates for the controlled pivotal studies were 4.8% and 4.0%, respectively.

The sponsor attributes these differences in rates of serious hemorrhage to imbalances in baseline patient characteristics (bleeding history) and the use of anticoagulant and antiplatelet agents during the studies, with both factors favoring increased hemorrhage in patients randomized to receive Mircerca.

The sponsor's explanation supports the view that Mircera and reference ESAs are not different with respect to the potential for causing serious hemorrhage. However, the same explanation increases the concern about potentially greater risk for Mircera for causing serious thrombotic events: if the presumed imbalances had not been present, the rates of thrombosis-related events (sudden death, cardiovascular events including death, arterial-venous graft thrombosis) in patients receiving Mircera may have been even greater than observed.

4. Results of Mircera cancer study (mortality):

Although the results of a cancer study may not be applicable to CRF, the safety concern raised by the cancer study is consistent with, and reinforces, the safety concerns in CRF:

- Study NH19960 was a multicenter, randomized, open-label dose-finding study of Mircera in anemic patients with stage III-B or stage IV non-small cell lung cancer (NSCLC) receiving first-line myelosuppressive chemotherapy. This study was terminated early when interim results showed a statistically significant increase in mortality in patients receiving Mircera relative to those receiving an active comparator (darbepoetin alfa).
- This observed Mircera-related increased mortality in cancer may be mechanistically related to ESA-related mortality in CRF. Mortality was NOT increased for Mircera in CRF, however, possibly because much lower (10-fold) doses were used in CRF than in cancer and the lower doses were given to slowly achieve the same hemoglobin level over an extended period of time, irrespective of the ESA used. With slow dose titration to achieve the same hemoglobin, all ESAs are used at the same level of erythropoietic (and potentially other) stimulation resulting in similar safety (and efficacy) profiles.
- These considerations suggest that the degree of erythropoietic (and potentially other) stimulation may be causally related to mortality and other serious events (safety), as well as directly causing an increase in the hemoglobin level (efficacy). When relatively low doses of ESAs are titrated to achieve the same hemoglobin level, all ESAs may share a similar risk-benefit ratio.
- In using ESAs to treat anemia in CRF, however, longer-acting preparations (like Mircera) may have a greater potential for transient overdose during an early treatment period in which the hemoglobin level cannot increase rapidly enough to reflect overdosing. This view is consistent with the observations about sudden death, arteriovenous graft thrombosis, and other adverse events which show a trend towards increased rates of serious adverse events in patients receiving Mircera relative to shorter-acting reference ESAs (see discussion under item 2 above).

These considerations suggest the following hypotheses about ESAs: (1) toxicity and efficacy may be inseparable, (2) ESAs share similar toxicity-efficacy (risk-benefit) profiles, (3) toxicity is related to transient overtreatment, (4) In CRF, the potential for transient overtreatment is minimized owing to slow titration of relative low ESA doses using continuous hemoglobin monitoring (and hence the lack of a strong safety signal as in Mircera cancer study), (5) longer-acting ESAs carry a greater potential for transient overtreatment, particularly early in treatment before dose stabilization, (and hence the trend for increased rates of serious adverse events seen with Mircera), and (6) in CRF, hemoglobin levels between 10-12 g/dL may be associated with greater toxicity than are lower hemoglobin levels.

4. Duration between successive dose adjustments:

The proposed Mircera label specifies a minimum duration between successive dose adjustments that is the same as in other ESA labels (4 weeks).

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Appendix C

Safety Concerns for Product Class

The September 2007 FDA Advisory Committee (AC) recommended that ESA class label be revised to indicate a treatment target hemoglobin range of 10 to 12 g/dL, and to describe the published study results that supported this target hemoglobin range. The AC recommended new studies to address the following residual concerns about ESA therapy in CRF:

1. The risk of serious adverse events at target hemoglobin levels below 13.3 g/dL (including the AC-recommended range of 10 to 12 g/dL) has not been evaluated.
2. How ESA-resistant patients should be identified and managed.

The following concerns were not specifically discussed at the AC meeting. These concerns, identified at review of Mircera BLA, are applicable to the entire ESA product class. Class labeling should reflect these concerns:

3. The desirable hemoglobin target may be different for each patient.
4. In hemodialysis patients, the target hemoglobin should be selected with an awareness of periodic fluid overload and potential sudden hemoconcentration at dialysis procedure.
5. Infection or inflammation may increase the risk of serious adverse events, particularly in patients requiring hemodialysis, and particularly during (or following) a hemodialysis procedure. The effect of ESA therapy (including increased hemoglobin) in a patient with active inflammation is not known. In comparison with no therapy, ESA therapy in inflammation may increase the risk for serious thrombotic events.
6. Long-acting preparations may have an increased potential for excessive treatment that may result in serious adverse events. Excessive treatment will be typically unintentional from insufficient hemoglobin monitoring, but may also be "intentional" from inadequate knowledge about how to use ESAs in CRF. This risk increases with circulating half-life, in the order of epoetin alfa, darbepoetin alfa, and Mircera.
7. Current ESA labels specify the same minimum duration between successive dose adjustments (4 weeks). A more appropriate guidance may be to relate this duration to a product's circulating half-life.

Appendix D

Points to Consider in Designing New Studies

The safety concerns identified above should be described in ESA product labels (as a product class and as applicable specifically to Mircera). As the results of additional studies become available, the labels should be periodically revised to replace these descriptions with more definitive information that provides "more adequate" directions in using an ESA to treat anemia associated with CRF. The following points should be considered in designing new studies:

1. Compare the safety of different hemoglobin targets below 12 g/dL.

CHOIR and "Normal Hematocrit" studies suggest that lower hemoglobin targets are safer than higher ones, and it remains unknown whether a hemoglobin level of 12 g/dL is sufficiently low for optimum risk-benefit ratio.

2. Compare the safety of different fixed ESA doses.

ESA therapy using fixed doses would be a new treatment strategy that permits relatively high hemoglobin levels in those that can tolerate it while guarding against overtreatment of hyporesponders most prone to serious treatment-related adverse events. It may be possible to identify an "optimal" dose that maximizes benefit while minimizing risks. Results of studies performed with one ESA generally will not be applicable to other ESAs with a different dosing strategy.

3. Compare the safety of two treatment strategies: fixed hemoglobin target versus fixed dose.

The fixed hemoglobin approach will generate a wide range of titrated doses that support the selected hemoglobin range. The fixed dose approach will generate a wide range of achieved hemoglobin levels depending on patient responsiveness to treatment. Mean doses and mean achieved hemoglobin levels can be compared across the two approaches. A comparable benefit (similar mean hemoglobins) may be associated with significantly different risks (serious events less frequent with fixed dose than with fixed hemoglobin target).

4. Perform placebo-controlled studies.

The clinical benefit of increasing the hemoglobin in patients with anemia of CRF has been accepted uncritically, without clinical evidence, and ESA therapy has emerged as the current standard of care in managing patients with CRF. Placebo-controlled studies about the use of ESAs in CRF have been considered unethical. The results of CHOIR and "Normal Hematocrit" studies, two best studies about the safety of ESAs in CRF, indicate that placebo-controlled studies are NOT unethical. Given the results of these studies, NOT performing placebo-controlled studies may be considered unethical, particularly in non-dialysis CRF. Many patients not on dialysis have baseline hemoglobin levels that are sufficiently high without ESA support to permit a hemoglobin target study that is also a placebo-controlled study.

5. Perform blinded studies.

Open-label studies have been the rule in the past as the result of uncritical acceptance of the hemoglobin level as a surrogate for clinical benefit. CHOIR and "Normal Hematocrit" studies show that raising the hemoglobin level is NOT risk-free, and underscores the importance of evaluating adverse events. Even with relatively "objective" safety endpoints, an open-label

design is inadequate for evaluating important serious events. A blinded design will make it possible to evaluate important clinical decisions with a significant subjective component, such as when to report a death as "sudden death" and when to hospitalize a patient for heart failure. The blinded design is no longer "unduly" burdensome.

6. Establish that raising the hemoglobin above 9 to 10 g/dL is associated with clinical benefit.

ESA therapy is a major alternative to transfusion in managing anemia associated with CRF. Transfusion is administered only when anemia is clinically intolerable, and only to a minimum hemoglobin level sufficient to manage serious clinical consequences of severe anemia. This minimalist approach stems from concerns about infectious disease transmission and alloimmunization, two major potential adverse outcomes of transfusion therapy in CRF.

ESAs are not unlike transfusion in that it is also associated with important serious adverse outcomes. CHOIR and "Normal Hematocrit" studies have shown that raising the hemoglobin increases the risk for serious cardiovascular events including death. In the absence of evidence to indicate otherwise, ESAs and transfusion should be used similarly in clinically intolerable anemia using "transfusion triggers," and to raise the hemoglobin only to a minimum level sufficient to manage serious clinical consequences of severe anemia, without using transfusion.

Given the serious risks associated with ESA therapy, it is no longer unethical to perform blinded studies comparing ESA use intended to achieve a hemoglobin target currently recommended in ESA class labeling (10 to 12 g/dL) to a more stringent ESA use intended to achieve a significantly lower target that incurs a significantly greater risk of requiring transfusion "rescue" (8 to 10 g/dL).

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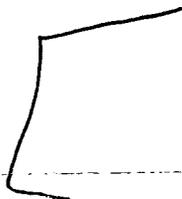
Appendix E

List of Additional Mircera Studies Proposed by the Sponsor

The sponsor proposes the following post-marketing commitment (PMC) studies to further investigate concerns about ~~_____~~ C-reactive protein (CRP) exclusion, and transition to dialysis. These concerns are discussed above under *Complete Review Letter*, items 1c and 1d (hemoglobin target), 4a (CRP exclusion), and 4b (transition to dialysis).

1. Study NH20052: An open-label randomized study to compare the safety and efficacy of every four week subcutaneous Mircera with darbepoetin alfa in correcting anemia up to a hemoglobin of 10-12 g/dL in 300 CRF patients (1:1 randomization) not on dialysis and not previously treated with an ESA (projected completion in July 2010). A major secondary objective of this study will be to study CRP. This study will not exclude patients with high CRP and patients will be stratified by baseline CRP above or below 30 mg/L.

2.



3. Study ML20337: An open-label randomized study to demonstrate the safety and efficacy of monthly intravenous Mircera in maintaining the hemoglobin within 10-12 g/dL in 2121 patients (2:1 Mircera/reference randomization) transitioning from non-dialysis to dialysis (projected study completion in April 2012). The study will examine the proportions of patients able to maintain the hemoglobin within 10-12 g/dL after initiating dialysis. This study is currently on-going.

Appendix F

List of New Studies Recommended by FDA

The sponsor had already planned on conducting the three "new" studies described above (Appendix E) to support Mircera product development, independent of FDA's charge to the sponsor to consider studies that advance the field of ESA use in CRF. The sponsor revised existing study designs to reflect changing consensus opinion about hemoglobin target and to address two of many FDA's many specific safety concerns. The studies do not adequately address FDA's safety concerns and do not advance the field. The sponsor may consider the following new studies.

1. A "dose study" in which patients with CRF not on dialysis are randomized to different fixed ESA doses instead of hemoglobin targets:
 - Since the recent CHOIR study served as the basis for much of the September 2007 FDA AC recommendations, it may be useful to design such a "dose study" in a way that parallels and complements CHOIR: randomize ESA-naïve non-dialysis patients to two ESA dose levels that correspond with the mean doses for the responders in the high and low groups of the CHOIR study (approximately 11,000 and 6,000 U/wk).
 - The "non-dialysis dose study" will involve two dose levels but three study arms. For the high dose group, epoetin alfa SC may be given at 150 U/kg/wk (11,000 U/wk converted to weight-adjusted dosing). For the low dose group, epoetin alfa SC may be given at 90 U/kg/wk (6,000 U/wk converted to weight-adjusted dosing). In addition, a third Mircera SC arm at a dose of 0.3 ug/kg/2-wk should permit a comparison of Mircera with epoetin alfa. The selected Mircera dose is 25% lower than 0.4 ug/kg/2-wk, a dose which corresponds with a mean hemoglobin of about 12 g/dL in pivotal Mircera studies).
 - In all three arms, dose cannot be adjusted upward but must be adjusted downward (in increments of 25% of previous dose) if the hemoglobin exceeds 14 g/dL. Between two successive dose adjustments, at least 4 weeks should elapse for epoetin alfa and at least 8 weeks should elapse for Mircera. The sample size for each arm should approximate that that used in CHOIR. Patients should be monitored for 1 year.
 - The three arms should be compared for the following safety analyses: (1) primary: incidence of composite endpoint events consisting of death, non-fatal myocardial infarction, non-fatal stroke, and congestive heart failure requiring hospitalization, and (2) secondary: incidence of composite endpoint events in subgroups achieving the following hemoglobin levels: (a) < 12 g/dL, (b) \geq 12 g/dL, (c) \geq 12 g/dL WITHOUT dose adjustment, and (d) \geq 12 g/dL WITH dose adjustment. For the hemoglobin subgroups, the incidence of composite endpoint events should be compared across the dose arms for comparable achieved hemoglobin levels, as well as across the hemoglobin subgroups within each dose arm.
 - The three arms should be compared for the following efficacy analyses: (1) mean increase in hemoglobin at stabilization (plateau hemoglobin), (2) the hemoglobin range containing 95% of patients, (3) time to reach stable hemoglobin, (4) number/fraction of patients achieving hemoglobin \geq 12 g/dL, (5) number/fraction of patients achieving hemoglobin \geq 14 g/dL, for which the dose of the study medication was decreased, and (6) number/fraction of patients not achieving a pre-specified minimum hemoglobin response.

- The three arms should be compared for the following exploratory analyses: (1) number/fraction of patients requiring initiation of dialysis, and (2) number/fraction of patients requiring initiation of dialysis for the subgroups achieving the following hemoglobin levels: (a) < 12 g/dL, (b) ≥ 12 g/dL, (c) ≥ 12 g/dL WITHOUT dose adjustment, and (d) ≥ 12 g/dL WITH dose adjustment. For the hemoglobin subgroups, the incidence of disease progression to require dialysis should be compared across the dose arms for comparable achieved hemoglobin levels, as well as across the hemoglobin subgroups within each dose arm.
2. A "dose study" in patients with CRF on dialysis using design features for the "non-dialysis dose study" as described above. In this study, IV dosing in patients on dialysis replaces SC dosing in patients not on dialysis. The dose levels and study arms remain the same. All analyses for the non-dialysis study apply also to the dialysis study, except for the exploratory analyses about progression to dialysis.
 3. A study which compares the safety and efficacy of two treatment strategies: fixed hemoglobin target versus fixed dose. In this study, a fixed dose treatment strategy using Mircera may be compared with "standard therapy": a fixed hemoglobin strategy using reference ESAs (combination of epoetin and darbepoetin alfa).
 - The fixed dose of Mircera should be selected such that it supports a mean hemoglobin of 11 g/dL. The fixed dose approach using Mircera will generate a wide range of achieved hemoglobin levels depending on patient responsiveness to treatment. The fixed hemoglobin approach using reference ESAs will generate a wide range of titrated doses that support the selected hemoglobin range. Mean doses and mean achieved hemoglobin levels can be compared across the two approaches. A comparable benefit (similar mean hemoglobins) may be associated with significantly different risks (serious events less frequent with fixed dose than with fixed hemoglobin target).
 - The increase in hemoglobin will be a minor efficacy endpoint, reserving the major efficacy endpoint for a clinical measure of benefit (e.g., transfusion reduction). The primary endpoint will be one of safety -- adverse cardiovascular outcome similar to that used in CHOIR. The anticipated study results are that the fixed dose strategy using Mircera is as effective as, and safer than, the "standard" fixed hemoglobin strategy using reference ESAs. The results of this study will support a labeling advantage for Mircera.
 4. A study which compares the safety and efficacy of different hemoglobin targets below 12 g/dL. In this study, targeting a conservative hemoglobin level of 8-10 g/dL using Mircera may be compared with "standard therapy": targeting a hemoglobin level of 10-12 g/dL using reference ESAs (combination of epoetin and darbepoetin alfa).
 - CHOIR and "Normal Hematocrit" studies suggest that lower hemoglobin targets are safer than higher ones, and it remains unknown whether a hemoglobin level of 12 g/dL is sufficiently low for optimum risk-benefit ratio.
 - The increase in hemoglobin will be a minor efficacy endpoint, reserving the major efficacy endpoint for a clinical measure of benefit (e.g., transfusion reduction). The primary endpoint will be one of safety -- adverse cardiovascular outcome similar to that used in CHOIR. The anticipated study results are that targeting a hemoglobin level of 8-10 g/dL using Mircera is as effective as the "standard" therapy in reducing transfusion use despite lower hemoglobin levels, and is safer than the "standard" therapy with respect to mortality and adverse

cardiovascular outcome. The results of this study will support a labeling advantage for Mircerca, and directly fulfills the previous FDA charge to sponsor to perform studies that explore hemoglobin targets below 12 g/dL.

5. A study in which the current dosing guidelines are compared against a revised guideline which "adjusts" for: (1) phase 3 study results which show decreasing mean doses as the studies progressed and stabilizing at a dose about 30% than the starting dose, and (2) new recommendations about hemoglobin target (a range of 10 to 12 g/dL, which is lower than 11 to 13 g/dL used in your studies). The results of this study should be used to either confirm or revise the current Mircerca dosing recommendations.
6. A study designed to guard against the variables that presumably account for the observed differences in rates of hemorrhage between Mircerca and reference ESA arms, to confirm that Mircerca does not increase the risk for hemorrhage in patients with chronic kidney disease. See comments above about "dose studies." Comparing hemorrhage rates in the "dose studies" conducted under a blinded study design may be adequate to achieve this objective.
7. A "CRP" study to confirm that elevated CRP levels > 30 mg/L do not adversely affect the safety and efficacy of Mircerca relative to other ESAs, and to confirm that treatment-related adverse outcome, if any, are not magnified by elevated CRP levels.
 - A placebo-controlled study or at least a "dose study" may be necessary to adequately evaluate the potential for Mircerca and other ESAs to cause adverse safety outcome.
 - The adverse outcome may be: unaffected by the CRP level, more frequent with elevated CRP levels, or limited to patients with high CRP levels.
 - A study that uses different ESA and the same hemoglobin target (Study NH20052) will not be able to confirm that treatment-related adverse outcome, if any, are not magnified by elevated CRP levels (a potential class effect).
8. Given the residual concern about sudden death, a cardiac toxicity assessment should include an adequate evaluation of a potential QT effect.
9. A cancer study comparing Mircerca with darbepoetin alfa as in Study NH19960, but in which Mircerca is administered earlier and in smaller doses than in Study NH19960 and the hemoglobin target with Mircerca is lower than that with darbepoetin alfa. A third placebo arm will "ground" the safety and efficacy of the "standard" darbepoetin therapy, as well as the new investigational Mircerca regimen.

The aim of this study will be to show that: (1) the previous negative outcome of Study NH19960 reflects a class effect common to all ESAs, (2) ESA safety outcome in cancer chemotherapy is driven by ESA dosing strategies, (3) the previous negative outcome of Study NH19960 implicates only the specific Mircerca dosing strategy used in that study, and not Mircerca itself, and (4) the use of an alternate Mircerca dosing strategy can result in safety and efficacy outcomes that are similar or superior to those obtained with darbepoetin alfa.

The anticipated study results are that the Mircerca regimen is as effective as darbepoetin alfa in reducing the need for transfusion despite a conservative hemoglobin target, and is safer than darbepoetin alfa with respect to overall mortality. The results of this study will advance the field of ESA use in cancer, addresses a major safety concern about potential off-label use of Mircerca in cancer, and may prove important in further product development for use in cancer.

2). The survival curves typically merged towards the end of each study at about one year. Factors associated with the suggestive decreased survival during 3 to 9 months after initiating the comparison between Mircera and reference ESAs appear to be: longer (versus shorter) ESA half-life, hemoglobin maintenance setting (versus anemia correction setting), subcutaneous (versus intravenous) route of administration, and more frequent (versus less frequent) dosing interval for a given ESA with more than one dosing interval option. The common feature for all of these observations may be higher total drug exposure. Additional exploratory analysis about dosing regimen (drug exposure per unit time) may provide more direct support for this hypothesis.

Figure 1: Kaplan-Meier Plot of BA16740
Mircera versus Epoetin
Hemoglobin Maintenance, Dialysis, Subcutaneous Dosing

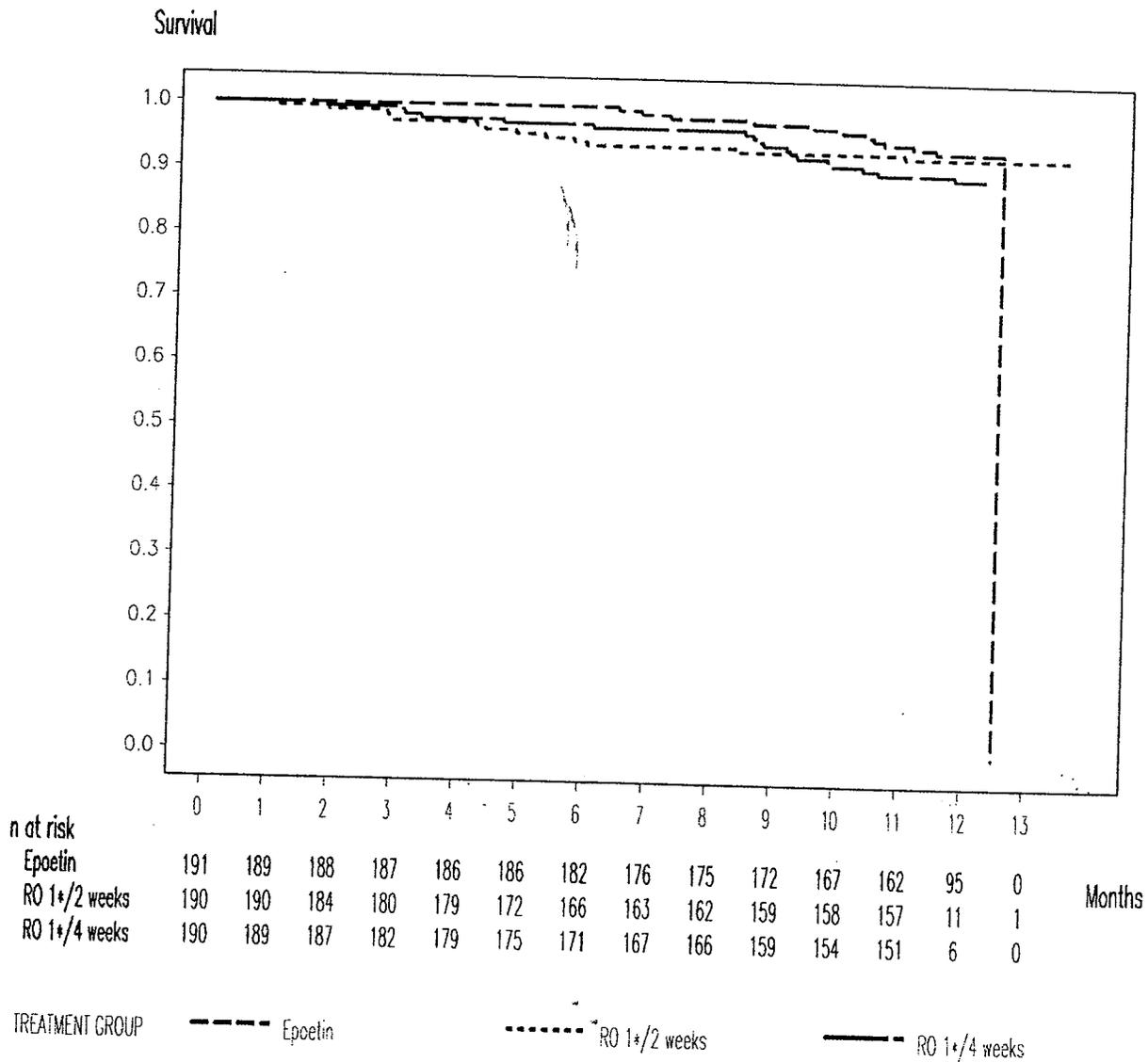
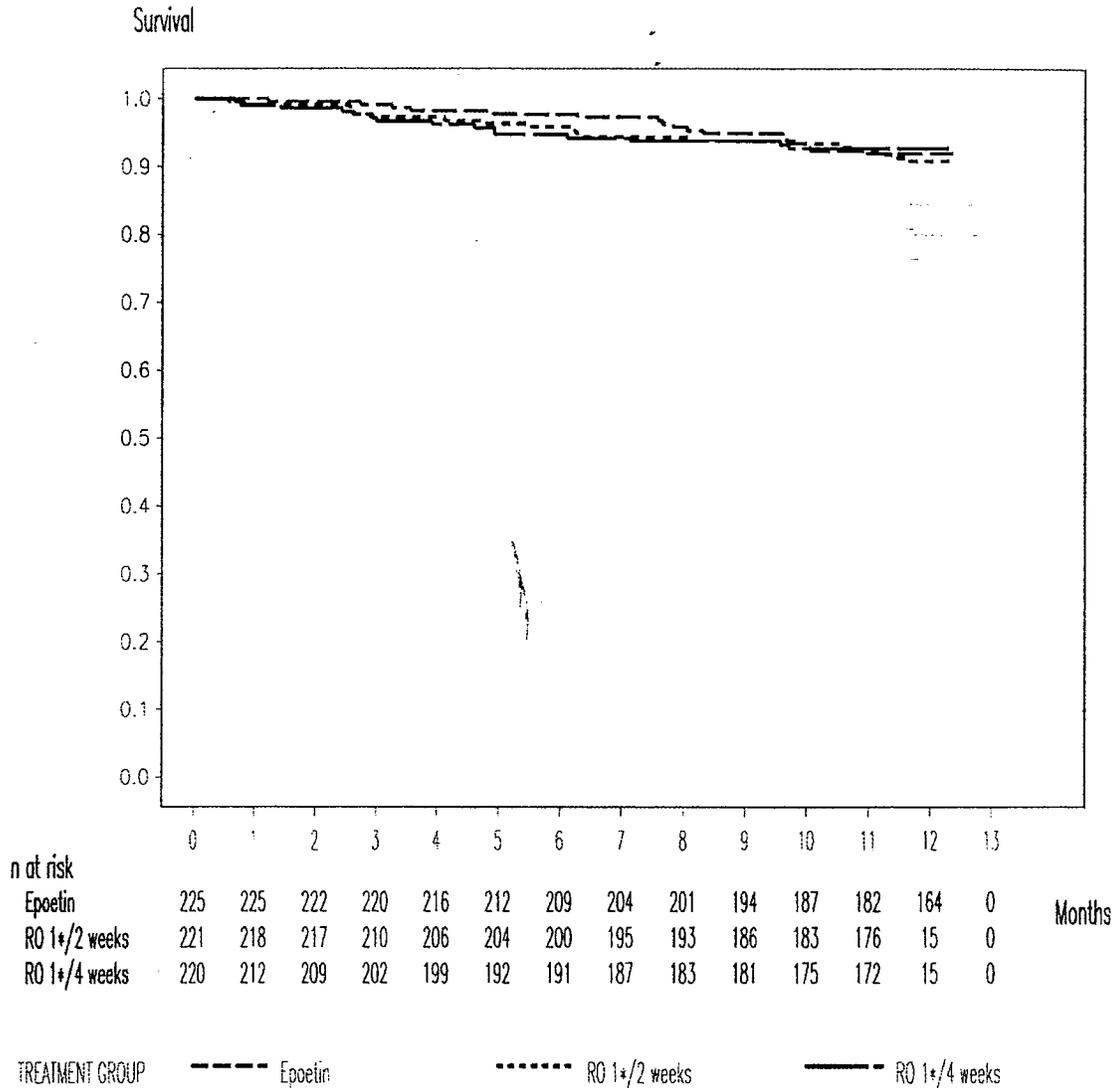


Figure 1: Kaplan-Meier Plot of BA16739
Mircera versus Epoetin
Hemoglobin Maintenance, Dialysis, Intravenous Dosing



The findings of CHOIR and "Normal Hematocrit" studies are consistent with this hypothesis: higher hemoglobin targets result in greater drug exposure per unit time and greater incidence of serious adverse events including death; and within each hemoglobin target group, the high drug exposure among ESA-resistant patients achieving low hemoglobin levels drive the overall safety outcome. The CHOIR and "Normal Hematocrit" study results and this "drug exposure" hypothesis suggest that ESA therapy is indicated in CRF only when the expected ESA toxicity is less serious than the adverse clinical consequences of severe anemia or other options for treating severe anemia. It is no longer "apparent" that ESAs are preferable to transfusion therapy in managing anemia. As with transfusion practice, ESA therapy may evolve to reserve its use for increasingly more stringent "anemia triggers," and perhaps only when transfusion-related adverse outcome is clearly not acceptable.

- Amendment 26 (March 5, 2007): Additional data and analyses about CRP exclusion in Mircera phase 3 studies (see Amendment 22 above).
- Amendment 27 (March 22, 2007): Additional CMC information about product vials and pre-filled syringes manufacturing facilities from a microbiology product quality perspective.
- Amendment 28 (March 23, 2007): Revised Mircera labeling consistent with Public Health Advisory and class labeling for ESAs.
- Amendment 29 (March 26, 2007): Responses to Questions 4 and 5 of March 20, 2007 FDA letter about pharmacokinetics of Mircera.
- Amendment 30 (March 29, 2007): Additional CMC information about product vials and pre-filled syringes manufacturing facilities from a microbiology product quality perspective.
- **Amendment 31 (March 30, 2007):** Additional information about major safety endpoints analyzed by ESA (epoetin alfa, darbepoetin alfa, Mircera); additional information about CRP exclusion. No new review observations.
- **Amendment 32 (April 3, 2007):** Information about phase 2 oncology NH19960
 Study NH19960 evaluated 3 doses of Mircera against darbepoetin alfa as the reference ESA for the treatment of anemia in patients with stage IIIB or IV non-small cell lung cancer receiving chemotherapy. An interim safety review suggested an imbalance in the rate of all cause mortality during the study (within 28 days from the last dose of study medication) among the 4 treatment groups, with the highest rate seen in the 9 ug/kg Q3W Mircera group. Multivariate regression analyses of death or time-to-death showed higher hazard ratios in the Mircera groups relative to the darbepoetin alfa group after adjusting for the potential risk factors.
- Amendment 33 (April 13, 2007): Results of CMC studies regarding the _____ method used to determine the _____ of Mircera drug substance.
- Amendment 34 (May 3, 2007): Creatinine clearance values determined in each patient enrolled in study BP18034 to support FDA's pharmacokinetic review.
- Amendment 35 (May 7, 2007): Revised draft labeling.
- **Amendment 36 (May 8, 2007):** Subgroup analyses regarding hemorrhage and thrombocytopenia. See discussion above under *Complete Review Letter*, item 2.
- Amendment 37 (May 14, 2007): Revised labeling, patient package insert.
- Amendment 38 (May 16, 2007): Revised labeling per PLR format.
- Amendment 39 (May 17, 2007): Additional CMC data about product stability.
- Amendment 40 (May 17, 2007): Sponsor's summary of telephone conversation with FDA about timeliness of CMC review.
- Amendment 41 (May 29, 2007): Intent to file an amendment to BLA to address all items outlined in complete review letter.
- Amendment 42 (June 20, 2007): Sponsor's summary of telephone conversation with FDA about review timelines and the impact of FDA Advisory Committee on FDA review process.

- Amendment 43 (July 18, 2007): Sponsor's response to FDA's May 18, 2007 complete review letter regarding CMC.
- Amendment 44 (July 27, 2007): Sponsor's response to complete review letter.
- **Amendment 45 (August 13, 2007):** Safety update as of May 1, 2007 (additional 8 months since last update) and meeting request. No new safety observations.
- Amendment 46 (August 17, 2007): Response to complete review letter regarding CMC.
- Amendment 47 (September 13, 2007): Revised labeling and request to restart the review clock.
- **Amendment 48 (October 5, 2007):** Additional analyses regarding hemoglobin target, maximum dose, and transfusion use. No new safety observations.
- Amendment 49 (October 9, 2007): Sponsor responses to October 3, 2007 FDA letter regarding container and carton labeling.
- Amendment 50 (October 15, 2007): Proposed language regarding oncology use, revisions to information about platelet counts and hemorrhage rate, sponsor comments regarding immunogenicity section, and presentation of clinical studies in tabular format.
- Amendment 51 (October 16, 2007): Additional information about product shelf life.
- Amendment 52 (October 16, 2007): Proposal on post-marketing commitments and timelines for study initiation and completion.

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MEMORANDUM

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

DATE: 5/4/2007

FROM: Ruyi He, MD
Acting Medical Team Leader
Division of Medical Imaging & Hematology Products

TO: Rafel Rieves, MD
Acting Director
Division of Medical Imaging & Hematology Products

SUBJECT: Team Leader CR Comments
BLA-STN 125164

APPLICANT: Hoffmann-La Roche Inc.

PRODUCT: Established name: pegserepoetin alfa
Proprietary name: MIRCERA
Chemical name: methoxy polyethylene glycol-epoetin beta
Code designations: RO0503821 (drug substance),
Ro 050-3821 (drug product)

RECOMMENDATIONS:

The effectiveness of Mircera (pegserepoetin beta) was established in 6 clinical studies. All studies show consistent success in correction/maintaining hemoglobin levels within the defined threshold. However, the risk-benefit of Mircera and overall erythropoiesis-stimulating agents (ESAs) is questionable. At this time, it is not possible to optimize the treatment given uncertainties in hemoglobin target, hemoglobin minimum to start ESA treatment, and whether ESAs would improve the quality of life in patients with chronic renal failure (CRF). These issues should be studied, evaluated further and will be discussed at the Cardiorenal Drugs Advisory Committee in September 2007.

I concur with Dr. John Lee's recommendations that at this time a Complete Review Letter be issued for BLA-STN 125164, Mircera (pegserepoetin alfa), for the indication of treatment of anemia associated with CRF including patients on dialysis and patients not on dialysis pending further evaluation above issues and discussion at the Cardiorenal Drugs Advisory Committee scheduled in September 2007.

In accordance with the pediatric research equity act of 2003, Roche submitted to BB-IND 10158, a pediatric development plan, a request for waiver and deferral of pediatric assessment for MIRCERA (S-198). The Division granted a waiver of pediatric assessment in neonates up to age of 5 as well as a deferral of pediatric assessment for ages 5 – 16 (February 2006) until the efficacy and safety data are available in adults. The sponsor is required to submit a pediatric study plan for ages 5-16 to fulfill the requirement for this application within 120 days of the date of approval of the application.

I also concur with Dr. John Lee's recommendations that the sponsor be encouraged to perform a study to validate current labeling statements about the target hemoglobin (g/dL). The study can be conducted either pre-approval or as a Phase 4 commitment.

There is no risk management step recommended.

I. BACKGROUND:

Mircera (pegserepoetin alfa), a stimulator of erythroid progenitor cells in the bone marrow, is a polymer-based erythropoietic compound that is synthesized by chemically conjugating one linear methoxy-polyethylene glycol molecule (PEG), with an average molecular weight of approximately 30 kDa, to Epoetin beta (EPO, RO2053859), an erythropoietin marketed in Europe. Compared to Epoetin beta, Mircera has a longer half-life and allows less frequent dosing.

Currently, FDA-approved erythropoiesis-stimulating agents (ESA) include Epoetin alfa (Procrit/Epogen) and Darbepoetin alfa (Aranesp). Both indicated for the treatment of anemia of chronic renal failure (CRF) and chemotherapy-induced anemia among certain cancer patients. Epoetin alfa is also approved for perioperative use to reduce the need for allogeneic blood and for treatment of Zidovudine-treated HIV-infected patients.

In this BLA, the sponsor provided 2 clinical studies for anemia correction and 4 clinical studies for hemoglobin maintenance to support Mircera (pegserepoetin alfa) for the indication of treatment of anemia associated with CRF including patients on dialysis and patients not on dialysis.

This chemotherapy-induced anemia study was terminated on March 2007 as recommended by the DSMB due to concern regarding excessive mortality.

II. DISCIPLINE REVIEW SUMMARY AND COMMENTARY:

A. OPDRA/DDMAC/DMETS:

C. Pre-Clinical Pharmacology/Toxicology:

Pharmacology Reviewer, Dr. Yanli Ouyang, recommended that the application be approved for the proposed indication and no recommendation for further nonclinical studies. Please see her review for detail.

No significant drug related cardiovascular and respiratory effects were observed at doses up to 50 mcg/kg with a total cumulative dose up to 70 mcg/kg when compared to the controls in a dog study. No significant drug related neurological effects were observed at doses up to 3 mcg/kg in a rat 26 wk study.

The bioavailability after SC dosing in rats was 31% and 45% in the 2.5 and 25 mcg/kg dose groups, respectively, and was 80% and 46% in the 3 and 10 mcg/kg dose groups in dogs, respectively.

¹⁴C-labeled RO0503821 was detected as radioactivity in almost all analyzed matrices and the highest tissue radioactivity was found in the injection site (SC), lymph nodes, testis, blood, adrenal gland, and spleen. The radioactivity was also detected in cerebellum, cerebrum, and CSF at very low level (0-0.947 mcg equivalent/g). In addition, there was limited penetration (<0.3% of administered dose) of RO0503821 through the placenta and was excreted into the milk.

In summary, the pharmacological, pharmacokinetic and toxicological profile demonstrate that RO0503821 has the acceptable pharmacological and pharmacokinetic properties, and does not indicate serious toxicity liabilities that would preclude its use in humans for the treatment of anemia associated with chronic kidney disease.

D. Biopharmaceutics:

From a clinical pharmacology standpoint, this BLA is acceptable for the approval of the indication for the treatment of anemia associated with chronic renal failure. No Phase 4 commitment studies are recommended in the area of clinical pharmacology.

The mean total body clearance (CL) of pegserepoetin beta is slow (approx. 60 mL/hr) in healthy subjects and CRF patients not on dialysis, and even slower (approx. 35 mL/hr) in patients on peritoneal dialysis. Pegserepoetin beta appears to be distributed mainly intravascularly: the mean volume of distribution at steady state is similar to or slightly larger than the serum volume in adults. Following an IV dose, the mean terminal half-life ($t_{1/2}$) value determined in CRF patients on peritoneal dialysis (approx. 130 hr) is longer than the values determined in healthy subjects or CRF patients not on dialysis (approx. 70 - 80 hr). Following an SC dose, the maximum concentration (C_{max}) was achieved approximately 3 days after dose in the majority of subjects. The mean $t_{1/2}$ values determined in CRF patients are longer (approx. 140 hr) than the values determined in healthy subjects (approx. 100 hr) at similar doses.

The reticulocyte response was characterized by an increase with a rapid onset and a peak 8 to 10 days following a single IV or SC dose of pegserepoetin beta to CRF patients on peritoneal dialysis. Thereafter, reticulocyte counts declined and returned to values near baseline 20 - 30 days post dose. The reticulocyte count response remained nearly constant over time after IV dosing every three weeks. For both SC and IV dosing, the relationship between reticulocyte response and dose was nearly linear.

Hemoglobin increase defined as an increase > 0.4 g/dL from baseline was observed after 7 to 15 days. After multiple dose administrations of pegserepoetin beta to healthy volunteers, a cumulative increase in hemoglobin levels over time with a rough dose-dependent fashion was observed. Please see Dr. Jang-ik Lee's review for details.

E. Clinical/Statistical:

Efficacy:

In this BLA, the sponsor provided 2 clinical studies for anemia correction and 4 clinical studies for hemoglobin maintenance to support Mircera (pegserepoetin alfa) for the indication of treatment of anemia associated with CRF including patients on dialysis and patients not on dialysis. In all clinical studies patients were assessed as clinical stable at baseline and without evidence of infection or inflammation as determined by history and laboratory data including C-reactive protein (CRP ≤ 15 mg/L for study 2 and CRP ≤ 30 mg/L for Study 1, 3-6).

Phase III Anemia Correction Studies

The sponsor provided 2 Phase III anemia correction studies:

Study 1 (BA16736): 0.4 μ g/kg/2 weeks IV, in dialysis patients, vs epoetin alfa or beta

Study 2 (BA16738): 0.6 μ g/kg/2 weeks SC, in patients not on dialysis, vs darbepoetin alfa

The studies were randomized, open-label, multicenter studies, and each had a reference group. The study designs were similar. A primary objective of both studies was to demonstrate the efficacy of Mircera treatment in the correction of anemia based on the Hb response rate (the primary parameter). The Hb response rate was defined as an increase in Hb ≥ 1.0 g/dL from baseline and a Hb concentration ≥ 11 g/dL without red blood cell (RBC) transfusion during the correction period (24 weeks, Study 1) or correction and evaluation periods (28 weeks, Study 2). Study 1 was intended to demonstrate that the response rate was at least 60% in the Mircera group and the results observed in the Mircera group were comparable to those seen in an approved compound (IV epoetin alfa or beta). Study 2 was intended to demonstrate that the response rate was greater than 60% in the Mircera group and that the Mircera group was clinically non-inferior to the darbepoetin alfa reference group.

A total of 505 patients were randomized into the studies, of which, 462 completed the correction or correction/evaluation period.

The efficacy results, the Hb response rates are summarized in Table 1 below.

Table 1: Summary of Responders, Primary Efficacy Parameter (ITT Population)

Study	Treatment	Total number	Number of Responder	Response rate (%)	p-value* (95% CI)
1	Mircera	135	126	93.3	<0.0001 (87.7; 96.9)
	Epoetin	46	42	91.3	<0.0001 (79.2; 97.6)
2	Mircera	162	158	97.5	<0.0001 (93.8; 99.3)
	Darbepoetin	162	156	96.3	<0.0001 (79.2; 98.6)

* H0: $r \leq 0.6$ versus H1: $r > 0.6$

In the ITT population, the response rates in the Mircera group were 93% and 98%, and the lower limit of the confidence interval (CI) was well above 60%, confirming that Mircera resulted in the correction of anemia. The response rates were comparable in the epoetin group, 91% and in the darbepoetin alfa group, 96%.

However, the correction of anemia was slower in the Mircera groups compared with the epoetin and the darbepoetin groups (median time to response was 57 and 43 days in the Mircera groups, and 31 days in the epoetin group and 29 days in the darbepoetin group). The percentage of patients who required blood transfusions were 5% and 3% in the Mircera groups and 4% in the epoetin group and 7% in the darbepoetin alfa group. In addition, the majority of patients in both treatment arms had dose adjustments (90% and 96% in the Mircera groups and 98% in both epoetin and darbepoetin groups).

An analysis of covariance (ANCOVA) comparing the Mircera dosing regimen to the darbepoetin alfa group showed that the adjusted mean change from baseline Hb in the Mircera group (2.12 g/dL) was non-inferior to that of the darbepoetin alfa group (1.95 g/dL), in the ITT population. The results were consistent in the PP, ITT, and eligible populations.

The dosing recommendation for Mircera in the correction setting is an IV or SC dose of 0.6 µg/kg once every 2 weeks in patients with anemia associated with CRF who are on dialysis or not on dialysis and who are not treated with an ESA.

The demographic characteristics of age, weight, gender, race (Caucasian and Black), and geographic location (US or non-US) did not affect the response rates in the reference or Mircera treatment groups of the Phase III correction studies. Subgroups of ethnicity (Hispanic) and race (Oriental, other, and Black [in study BA16736 only]) were too small to draw clinically meaningful conclusions.

Phase III Maintenance Studies

The sponsor provided 4 Phase III maintenance studies:

Study 3 (BA16739): IV administration, 1x/2 weeks and 1x/4 weeks in dialysis patients, vs epoetin alfa or beta

Study 4 (BA16740): SC administration, 1x/2 weeks and 1x/4 weeks in dialysis patients, vs epoetin alfa or beta

Study 5 (BA17283): IV administration, 1x/2 weeks in dialysis patients, vs darbepoetin alfa

Study 6 (BA17284): SC/IV administration with prefilled syringes, 1x/2 weeks in dialysis patients, vs epoetin alfa or beta

All were open-label, randomized, multicenter, non-inferiority studies. The studies had the same basic design: a 4-week screening/baseline period to ensure that patients maintained their previous ESA dose and regimen; a 28-week dose titration period used for Mircera dose titration and stabilization of Hb concentration; and an 8-week evaluation period. With the exception of study 6, the studies also included a 16-week long-term safety follow-up period. The primary efficacy parameter in each study was the mean change in Hb concentration (g/dL) between the baseline and evaluation periods in PP population. The Mircera group was regarded as non-inferior to the reference group when the lower limit of the two-sided confidence interval was greater than or equal to -0.75 g/dL. A non-inferiority limit of -0.75g/dL for the difference in mean Hb was chosen since a decline of 0.75g/dL over a 36 week period was considered small and acceptable. In two recently published studies it was shown that Hb levels decreased more than 2 g/dL within 7-9 weeks after treatment discontinuation in patients receiving sc darbepoetin alfa.

A total of 1894 patients were randomized into the studies, of which, 1509 completed.

The efficacy results, differences in adjusted group means for hemoglobin change between baseline and the evaluation period (PP Population) are summarized in Table 2 below.

Table 2: Summary of Differences in Adjusted Group Means for Hemoglobin Change between Baseline and the Evaluation Period - (PP Population)

Study	Treatment	Adj. Mean Hb Change	Difference Between Groups	p-value of NI Test (97.5% CI)
3	Mircera			
	1x /2 weeks	-0.071 (n=188)	0.004	< 0.0001 (-0.215; 0.223)
	1x /4 weeks	-0.025 (n=172)	0.050	< 0.0001 (-0.173; 0.275)
	Epoetin	-0.075 (n=180)		
4	Mircera			
	1x /2 weeks	0.032 (n=154)	0.141	< 0.0001 (-0.098; 0.380)
	1x /4 weeks	-0.131 (n=153)	-0.022	< 0.0001 (-0.262; 0.217)
	Epoetin	-0.109 (n=167)		
5	Mircera			
	1x /2 weeks	0.063 (n=123)	0.180	< 0.0001 (-0.049; 0.408)*
	Darbepoetin α	-0.116 (n=126)		
6	Mircera			
	1x /2 weeks	0.088 (n=123)	0.118	< 0.0001 (-0.116; 0.353)*
	Epoetin	-0.030 (n=133)		

*95%CI, Non-inferiority test for treatment differences with a non-inferiority limit of -0.75 g/dL

At the end of the 8-week evaluation period, the primary efficacy analysis using the ANCOVA model showed that treatment with Mircera both 1x/2 weeks and 1x/4 weeks, as specified by the protocol, was similar to treatment with epoetin alfa or beta and darbepoetin alfa. The largest changes from baseline occurred in the Mircera 1x/4 weeks group of Study 4 (-0.21 g/dL) and the Mircera 1x/2 weeks group of Study 6 (0.25 g/dL).

The majority (66% to 76%) of patients in each of the treatment groups (Mircera or reference) maintained average Hb concentrations during the evaluation period within ± 1 g/dL of their average baseline Hb concentrations; and mean and median monthly Hb concentrations in each of the treatment groups in each of the maintenance studies remained within the clinically acceptable range for the treatment of dialysis patients, 11 to 13 g/dL, throughout the study period.

During the titration and evaluation periods of the maintenance studies, 6% to 12% of patients in the Mircera groups required transfusions compared with 8% to 11% in the reference groups.

Dose adjustments were required in a comparable percentage of patients in each group of each study: 88% to 96% in the Mircera 1x/2 weeks treatment group, 87% to 88% in the 1x/4 weeks treatment group, and 86% to 91% in the reference groups.

The demographic characteristics of age, weight, gender, race (Caucasian and Black), or demographic location (US or non-US) did not affect the change in average Hb between baseline and the evaluation period in the reference or Mircera treatment groups of the Phase III maintenance studies. Subgroups of ethnicity (Hispanic) and race (Oriental and other) were too small to draw clinically meaningful conclusions.

The median change in average Hb between the baseline and evaluation periods was comparable between Mircera and reference treatment groups in analyses of CRF etiology and comorbid diabetes subgroups. Previous ESA, dialysis type, and route of drug administration had no effect on the change in average Hb in any treatment group.

In conclusion, Mircera was efficacious in correcting anemia associated with CRF in patients who were on dialysis or not on dialysis and who were not currently treated with an ESA, regardless of route of administration (IV or SC). Mircera was comparable to both epoetin and darbepoetin alfa reference groups in all study parameters tested with the exception of time to target Hb response in the correction studies, which was longer with Mircera. In addition, Mircera was efficacious in maintaining Hb concentrations in dialysis patients currently treated with an ESA regardless of route of administration (IV or SC), dosing regimen (1x/2 weeks or 1x/4 weeks), or previous ESA (epoetin alfa, epoetin beta, or darbepoetin alfa). For detail analysis, please see Dr. John Lee's clinical review.

Safety:

In total, 1789 patients received Mircera in the overall safety population. Of these patients, 1422 patients were receiving Mircera at 6 months; 1011 patients at 12 months; and 95 patients at 24 months. The total duration of exposure was 1532 patient exposure years (PEY) giving an average of 0.86 PEY/patient. The combined reference groups comprised a total of 948 patients with 778 PEY and a slightly shorter average of 0.82 PEY/patient for comparison. Approximately half of the patients received IV administration and half received SC administration of the study drug.

The overall AE profile was similar between Mircera and reference groups with a similar overall incidence of adverse events (AEs), severe AEs, serious AEs and deaths (Table 3).

Table 3: Overall Adverse Event Experience (Phase II/III Safety Population)

	RO0503821 (N = 1789)	Reference (N = 948)
Adverse Events		
Any AE	1589 (88.8%)	862 (90.9%)
Serious AEs	660 (36.9%)	383 (40.4%)
Severe AEs	563 (31.5%)	301 (31.8%)
AEs leading to withdrawal	45 (2.5%)	17 (1.8%)
AEs related to TT	108 (6.0%)	33 (3.5%)
Serious AEs related to TT	16 (0.9%)	8 (0.8%)
Severe AEs related to TT	21 (1.2%)	10 (1.1%)
Withdrawals and Patient Deaths		
Withdrawals incl. Deaths	399 (22.3%)	146 (15.4%)
Deaths	126 (7.0%)	58 (6.1%)

Multiple occurrences of the same adverse event in one individual counted only once.

TT = trial treatment

A difference in withdrawals was observed between the groups. A higher proportion of patients withdrew from Mircera group than reference group (22.3% vs 15.4%).

The difference is mainly attributable to withdrawals for “non-safety” reasons (242[14%] vs 88 [9%]), a proportion of which were withdrawals from the study in order to receive a kidney transplant (101 patients [6%] in the Mircera group and 34 patients [4%] in the reference group). Another imbalance in “non-safety” reasons for withdrawal was observed in the number of patients who ‘refused treatment’ (47 vs 13 patients). In 18 of these cases patients were experiencing an AE at the time of withdrawal (16 Mircera and 2 reference), although the AE was not reported as the reason for refusal of treatment. Other less frequent non-safety reasons for withdrawal were reported by a similar proportion of patients in each group and included withdrawal of dialysis care, patient transfer or relocation, and conflicts with holiday schedules.

Withdrawals for insufficient therapeutic response were rare in both groups (14 vs 3 patients in Phase III and Phase II, where low doses were administered by design in order to characterize dose response).

The majority of withdrawals for safety were deaths, the incidence of which was not markedly different across groups. The overall death rate (including deaths which occurred after withdrawal from the study) was similar across arms and is discussed in the next section. A higher proportion of patients experienced AEs which led to withdrawal from the study in Mircera group than reference groups (45 [2.5%] and 17 [1.8%], respectively). The difference in the proportion of patients withdrawing for AEs stems from the BA16739, IV study (15 vs 1 patient withdrew in the two Mircera arms and epoetin reference arm, respectively). In this study, the types of AEs that led to withdrawal were varied. The proportion of patients who experienced serious or severe events was similar in that study and does not suggest that there was a relevant difference in overall tolerability between the treatment arms. In these open-label studies, it is possible that investigators were more likely to withdraw patients for potential side effects with a new treatment than with the established treatments in the reference arms.

A higher proportion of patients had AEs that were judged related to study medication by the investigator in the Mircera group (6% vs 3.5%).

Many of the AEs reported are typically associated with CKD, ie, consistent with comorbidities known in the population or recognized complications of dialysis. The most common AEs in both groups included hypertension, diarrhea, headache, and upper respiratory tract infections. Most events were mild or moderate in intensity.

The overall incidence of AEs of special interest is comparable between the treatments and does not suggest an overall increased risk of these types of events with Mircera treatment (Table 4).

Table 4: Summary of Adverse Events of Special Interest

AE grouping ^a	RO0503821 N=1739 n (%)	Reference N=948 n (%)
Any AE	715 (40)	365 (39)
Hypertension	306 (17)	145 (15)
Vascular access thrombosis	170 (10)	98 (10)
Arrhythmia	154 (9)	73 (8)
CHF	88 (5)	49 (5)
Sepsis	61 (3)	35 (4)
MI	62 (3)	29 (3)
Cerebrovascular accident	49 (3)	24 (3)
Cardiac arrest	42 (2)	19 (2)
Seizures	15 (<1)	8 (<1)
Deep vein thrombosis	11 (<1)	9 (<1)
Other thromboembolic events	11 (<1)	2 (<1)
Pulmonary embolism	6 (<1)	0
Hypertensive encephalopathy	2 (<1)	1 (<1)

^a Pre-specified groupings of MedDRA preferred terms.

Death

According to the safety update on September 2006, the incidence of death was 10.2% (182/1789) in the Mircera group to yield an overall death rate of 7.6 per 100 PEY (compared with 10.9% and 7.8 per 100-PEY in the reference group). Kaplan-Meier analysis indicates a constant death rate over time after Mircera treatment.

The most common causes were cardiac arrest, myocardial infarction (MI), cardiorespiratory arrest, chronic renal failure, and sepsis/septic shock. A total of 14 fatal events which mapped to the MedDRA preferred term of 'sudden death' occurred in the Mircera group and 5 in the reference arm. However, based on the original submission when placed in the overall context of cardiac-related deaths and, more specifically, events grouped under the category of cardiac arrest (42 [2%] vs 19 [2%] Table 4), the overall incidence of events of this nature is similar between the treatment arms. Thus, the apparent imbalance may relate to definition (MedDRA preferred term) rather than the underlying cause.

Serious AEs

Overall incidence of serious (fatal and non-fatal) events was slightly lower in the Mircera group than in the comparator group (37% and 40%, respectively). The most common types of serious event were those expected in a CKD population and included pneumonia, sepsis, MI, congestive heart failure (CHF), arteriovenous fistula thrombosis, and fluid overload. The incidence of these most common SAEs was similar between groups. One type of serious adverse event that was identified as having a potentially increased incidence in Mircera compared with reference was gastrointestinal (GI) hemorrhage (1.2% (21/1789) vs 0.2% (2/948)).

Since GI hemorrhage was reported by a higher percentage of patients in the Mircera group than in the reference group, the overall incidence of serious bleeding events was also examined and showed an incidence of 5% in the in the Mircera group and 4% in the Reference group.

There was no relationship of serious hemorrhage to dose of Mircera. Co-medications affecting coagulation or mucosal integrity were received by a similar proportion of the overall study population in each arm at baseline and during the study.

Safety update for study in anemic patients with non-small cell lung cancer receiving first-line myelosuppressive chemotherapy

Per the FDA request of March 20, 2007, the sponsor provided a summary of interim results for phase 2 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."

This study was an open-label, parallel, randomized (1:1:1:1), multicenter dose-finding study. An entry criterion of Hb level was ≤ 11 g/dL. Patients were randomized to receive one of four treatments: darbepoetin (either 2.25 μ g/kg every week [q1w] or 6.75 μ g/kg

every three weeks [q3w]) or one of the following 3 doses of Mircera (RO0503821): 6.3, 9, or 12 µg/kg q3w. All doses were administered by SC injection over a 12-week period.

The study was terminated on March 26, 2007 as recommended by the data safety monitoring board (DSMB) based on interim mortality results. A total of 153 patients were randomized when enrollment was suspended (planned 200 patients).

Out of 153 patients randomized, there were 33 deaths, distributed among the treatment groups as follows:

- RO0503821 6.3 µg/kg: 7 out of total 38 (18.4%)
- RO0503821 9 µg/kg: 13 out of total 38 (34.2%)
- RO0503821 12 µg/kg: 9 out of total 38 (23.7%)
- Darbepoetin alfa: 4 out of total 39 (10.3%)

There were 4 death cases occurring on study with patients meeting one or both Hb criteria of >13 g/dL (ie, above the protocol-defined Hb target range of 11-13 g/dL) and/or rate of rise >1.5 g/dL in a 3-week interval, distributed as follows:

- One patient on the 6.3 µg/kg dose group (3 doses received): 73015/5444 (Pulmonary hemorrhage - led to death). This patient died within 28 days after meeting both Hb criteria. Last Hb was 10.2 g/dL.
- One patient on the 9 µg/kg dose group (4 doses received): 73009/6006 (NSCLC - led to death). This patient died within 28 days after meeting both Hb criteria. Last Hb was 15.2 g/dL.
- One patient on the 12 µg/kg dose group (1 dose received): 73021/5122 (Fall - led to death). This patient died within 28 days after meeting only the rate of rise (>1.5 g/dL) criteria. Last Hb was 11.3 g/dL.
- One patient on the 12 µg/kg dose group (3 doses received): 73015/5445 (NSCLC - led to death). This patient died outside the 28 days after meeting the rate of rise (>1.5 g/dL) criteria. Last Hb was 10.6 g/dL.

In conclusion, higher rates of all cause mortality were observed in the all 3 Mircera groups (18.4% to 34.2%) than darbepoetin group (10.3%) during the study (ie, within 28 days from the last dose of study medication), with the highest rate seen in the 9 µg/kg dose group. No dose-response relationship in all cause mortality was observed with the RO0503821 doses actually administered.

F. Pediatric Use:

In accordance with the pediatric research equity act of 2003, Roche submitted to BB-IND 10158, a pediatric development plan, a request for waiver and deferral of pediatric assessment for MIRCERA (S-198). The Division granted a waiver of pediatric assessment in neonates up to age of 5 as well as a deferral of pediatric assessment for ages 5 - 16 (February 2006) until the efficacy and safety data are available in adults. The

sponsor is required to submit a pediatric study plan to fulfill the requirement for this application within 120 days of the date of approval of the application.

III. Labeling Recommendations:

I concur with Dr. John Lee's labeling recommendations listed in his review. In addition, since higher percentages of GI hemorrhage (especially upper GI bleeding) in patients with CRF and all cause mortality during the cancer study were reported in the Mircera group than in the reference groups, these safety data should be included in the label.

**Appears This Way
On Original**

Date: May 14, 2006

From: John Lee, M.D., Medical Officer, DMIHP, OODP

SL 5/14/07

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KA 5/14/07
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see memo for [initials]

To: BLA File, STN 125164

Subject: Clinical Review of BLA, STN 125164: Pegzerepoetin alfa (Mircera) for the treatment of anemia associated with chronic renal failure

CLINICAL REVIEW

Application Type BLA
Submission Number STN 125164/0
Submission Code

Letter Date
Stamp Date
PDUFA Goal Date

Reviewer Name John Lee
Review Completion Date

Established Name Pegzerepoetin Beta
(Proposed) Trade Name Mircera
Therapeutic Class
Applicant Hoffman LaRoche, Inc.

Priority Designation S

Formulation
Dosing Regimen IV or SC injection Q2W or QM

Indication Treatment of Anemia Associated
with Chronic Renal Failure (CRF)

Intended Population Patients with CRF on Dialysis or
Not on Dialysis

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Abbreviations

AE	Adverse event
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
AST	Aspartate aminotransferase
AUC	Area under the curve
CAPD	Chronic ambulatory peritoneal dialysis
CI	Confidence interval
CRF	Chronic renal failure
CRP	C-reactive protein
DRAM	Data reporting and analysis manual
DSMB	Data and safety monitoring board
HD	Hemodialysis
ITT	Intent-to-treat (population)
IV	Intravenous
LOCF	Last observation carried forward
PD	Peritoneal dialysis
PP	Per-protocol (population)
RBC	Red blood cells
SAE	Serious adverse event
SC	Subcutaneous
TIBC	Total iron binding capacity
URR	Urea reduction ratio
USRDS	United States Renal Data System

1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

The sponsor claims that Mircera is effective in correcting anemia and in maintaining the hemoglobin in patients with chronic renal failure (CRF) on dialysis or not on dialysis. The sponsor also claims that Mircera is comparable to the reference erythropoietins (epoetin alfa, epoetin beta, and darbepoetin alfa) with respect to efficacy and safety. In evaluating the data submitted in support of these claims, the following major differences between Mircera and reference erythropoietins should be noted:

- As a result of chemical modification (introduction of methoxy polyethylene glycol moiety into the erythropoietin peptide backbone) and increased circulating half-life, Mircera should be dosed less frequently than dosing of the reference erythropoietins (epoetin alfa, epoetin beta, and darbepoetin alfa).
- The sponsor recommends dosing every two weeks (Q2W) or every four weeks (Q4W) based on clinical data, or every month (QM) based on extrapolation from the Q4W data. As might be expected from pharmacokinetic (PK) considerations (see Section 5), the time to reach the target hemoglobin is significantly longer with Mircera than with the reference agents.
- Unlike the reference erythropoietins, the safety and efficacy of Mircera appears to be less dependent on the administration route; intravenous (IV) or subcutaneous (SC) injection routes appears to be equivalent with respect to safety and efficacy.

The sponsor recommends the following specific dosing guidelines in using Mircera to treat anemia associated with CRF, either as de novo therapy in patients not previously treated with an erythropoietin product (anemia correction) or in converting from another erythropoietin in previously treated patients (hemoglobin maintenance).

- For anemia correction in patients not currently treated with an erythropoietin product, the recommended starting dose of Mircera is 0.6 ug/kg Q2W, IV or SC, irrespective of dialysis status (on or not on dialysis).
- For hemoglobin maintenance in patients currently treated with an erythropoietin product (epoetin alfa or darbepoetin alfa), the starting dose of Mircera should be determined using a dose conversion ratio specific to the total weekly dose of epoetin alfa or darbepoetin alfa. Mircera may be administered either IV or SC, and either QM or Q2W.

Major Safety Concerns

The review of this BLA supports the sponsor's claims about Mircera efficacy. The sponsor's claims about the safety of Mircera, although largely supported by the data submitted, need additional supportive data to resolve the following residual concerns:

1. Laboratory screening and systematic exclusion of subjects with elevated levels of C-reactive protein (CRP) from all phase 2 and phase 3 clinical studies

Patients with CRP levels above 30 mg/dL were not represented in the phase 3 studies. The safety and efficacy data may not apply to CRF patients with CRP levels above 30 mg/dL, and it may be necessary to recognize this limitation in the product label for Mircera.

2. A statistically significant greater incidence of sudden death with Mircera than with the reference agents in the phase 2 and phase 3 (safety) study population

The imbalance in sudden deaths was statistically significant ($p = 0.03$). Upon extended safety follow up, the degree of imbalance decreased to a statistically non-significant level ($p = 0.4$). Upon adjudication by a blinded cardiac panel, the incidence of sudden deaths was comparable between Mircera and the reference agents. Results obtained at extended follow up or cardiac adjudication, however, do not demonstrate that the initially observed imbalance in sudden deaths is spurious; the definition of "sudden death" may have changed from one that is specific but unstated (by the clinical investigators) to one that is rigorously defined (by the cardiac adjudication panel) but less specific.

3. A statistically significant difference between Mircera and the reference agents in the mean time to sudden death upon extended safety follow up of the phase 2 and phase 3 (safety) study population

Sudden deaths on Mircera were observed at all time points. Sudden deaths on a reference agent were observed only after the initial data lock. Although the difference between Mircera and the reference agents in the incidence of sudden death decreased to a statistically non-significant level upon continued follow up, the duration of survival after initiating Mircera therapy was shorter (statistically significant) than after initiating therapy using a reference agent.

4. Lack of an adequate determination of a QT effect regarding cardiac safety

Malignant cardiac arrhythmia is a possible mechanism of sudden death. Given the concern about sudden death, a cardiac toxicity assessment should include a complete evaluation of a potential QT effect.

5. A statistically significant greater overall mortality with Mircera than with epoetin (alfa or beta) at approximately treatment day 190.

In two of the three phase 3 hemoglobin maintenance studies in dialysis in which epoetin (alfa or beta) was used as the comparator agent (BA16739, BA16740), greater mortality was suggestive for Mircera, maximally at about treatment day 190. In the third study (BA17284) in which a statistically significant difference was not observed, the use of Mircera in pre-filled syringes may have resulted in hemoglobin titration to a level lower than the maximum level permitted in the study protocol. Greater mortality was not seen in BA17283, a phase 3 hemoglobin maintenance study in dialysis in which a long-acting agent was used as the reference agent (darbepoetin alfa).

6. A statistically non-significant trend to a greater overall mortality with Mircera than with the reference agents in the phase 2 and phase 3 (safety) study population

7. A statistically significant lower mean time to death with Mircera than with the reference agents in all four phase 3 hemoglobin maintenance studies in dialysis

Although overall mortality was not significantly different between Mircera and the reference agents, the duration of survival after initiating Mircera therapy was appreciably shorter than after initiating a reference agent.

- 8. A statistically significant greater proportion of patients experiencing a treatment-related adverse event (as assed by the clinical investigators) with Mircera than with epoetin (alfa or beta) at any given time in all four phase 3 hemoglobin maintenance studies in dialysis
- 9. A statistically significant lower mean time to first drug-related adverse event with Mircera than with the reference agents in all four phase 3 hemoglobin maintenance studies in dialysis
- 10. A statistically significant greater reduction in the mean platelet count with Mircera than with the reference agents after initiating treatment

This reduction in platelet count after initiating Mircera therapy may increase the risk for thrombosis (including acute coronary syndrome) and may be mechanistically related to the increased incidence of sudden deaths and the trend to increased overall mortality.

- 11. A statistically significant greater proportion of patients experiencing arterial-venous graft thrombosis with Mircera than with the reference agents

This observation is consistent with the reduction in platelet count after initiating Mircera therapy and the potential for increased risk for thrombosis.

The labeling for Mircera may be acceptable if:

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1.2 Recommendation on Postmarketing Actions

1.2.1 Risk Management Activity

No risk management activities are recommended at this time, other than the potential phase 4 studies as described below.

1.2.2 Required Phase 4 Commitments

Emerging data indicate that renal anemia should not be corrected to normal or near normal hemoglobin levels. Current erythropoietin product labels (as a drug class) state that a hemoglobin level of 12.0 g/dL should not be exceeded as the result of erythropoietin therapy. This labeling

statement has not been previously validated, and the emerging literature about the target hemoglobin level raises new questions about the maximum target hemoglobin level.

For each specific erythropoietin product, the sponsor (Roche and others) should be encouraged to perform a study as soon as feasible to validate current labeling statements about the target hemoglobin. Upon availability of validation data, each erythropoietin product label may be updated to indicate that the hemoglobin target as stated in the label has been validated in a clinical study for that particular erythropoietin product. As the mechanism that relates the hemoglobin level to serious adverse events associated with erythropoietin therapy is not well understood, sponsors should not be permitted to use results obtained with one erythropoietin product to update the label for a different erythropoietin product; for example, Amgen may not update the label for Aranesp or Eprex based on results that Roche obtained with Mircera.

This BLA may be approved, provided that the sponsor responds successfully to the concerns identified at review of the QT study (see Attachment 1, QT Study Review). In follow up at approval, the sponsor should perform one or more clinical studies that support the following major objectives.

The CHOIR study shows that important safety differences can be demonstrated between hemoglobin targets that differ by 2.2 g/dL (13.5 g/dL minus 11.3 g/dL). Similar to the CHOIR study, it may be feasible to demonstrate important safety differences between other hemoglobin target pairs that differ by 2.2 g/dL (or more). A post-marketing study modeled after the CHOIR study but substituting 9.8 g/dL and 12.0 g/dL (in lieu of 13.3 g/dL and 13.5 g/dL) for the target hemoglobin levels may be a reasonable study for the sponsors to perform. The safety findings of such a study may be as surprising as the findings of the CHOIR study, and the "unexpected" findings of the two studies may be consistent with each other.

~~Similar to the CHOIR study, it may be feasible to demonstrate important safety differences between other hemoglobin target pairs that differ by 2.2 g/dL (or more). A post-marketing study modeled after the CHOIR study but substituting 9.8 g/dL and 12.0 g/dL (in lieu of 13.3 g/dL and 13.5 g/dL) for the target hemoglobin levels may be a reasonable study for the sponsors to perform. The safety findings of such a study may be as surprising as the findings of the CHOIR study, and the "unexpected" findings of the two studies may be consistent with each other.~~

1.2.3 Other Phase 4 Requests

The sponsor has requested a waiver to delay the pediatric development program until after the approval of Mircera for the adult renal anemia indication. The sponsor plans to perform one or more pediatric studies as post-marketing commitment(s), according to the sponsor's timeframe, to

1.3 Summary of Clinical Findings

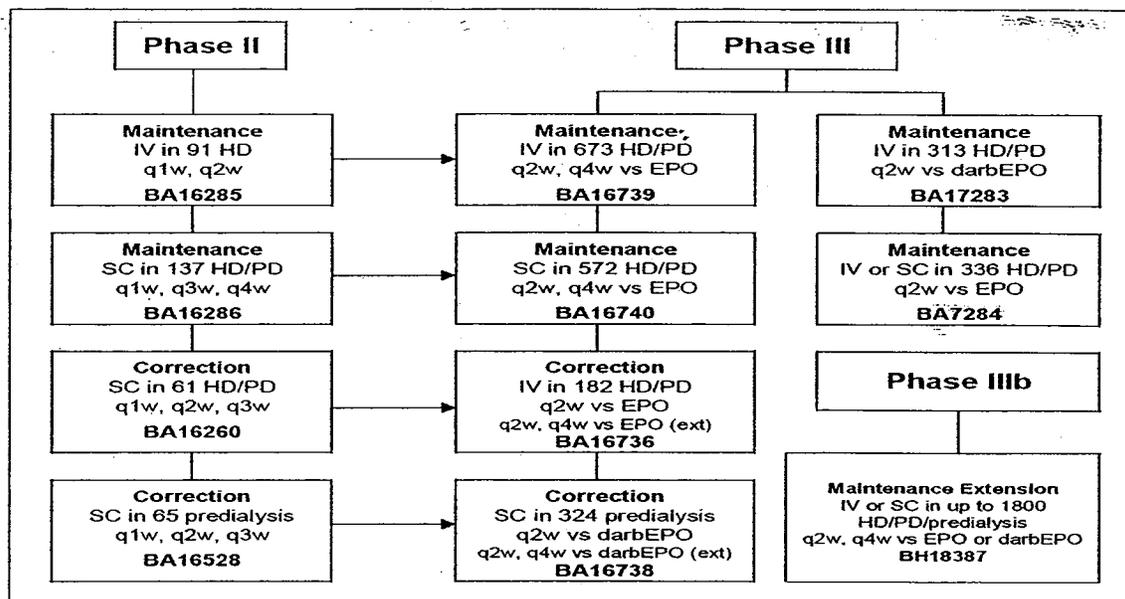
1.3.1 Overview of Clinical Program

Mircera (pegzerepoetin beta, Mircera) is a chemically synthesized erythropoietin developed by Hoffman La Roche, Inc. for the treatment of anemia associated with chronic renal failure (CRF). In comparison with the erythropoietins that are currently approved in the United States (US) (epoetin alfa, darbepoetin alfa), Mircera is expected to require less frequent administration as the result of prolonged circulating half-life, despite reduced affinity for the erythropoietin receptor. This submission is intended to support Q2W dosing for anemia correction, and Q2W or monthly dosing for hemoglobin maintenance, using either intravenous (IV) or subcutaneous (SC) routes of administration, irrespective of the dosing interval or dialysis status.

The clinical development program for Mircera for the treatment of anemia in patients with CRF consisted of 13 phase 1 studies, four phase 2 studies, and six phase 3 studies. The results of the phase 1 studies, including the pharmacokinetic and pharmacodynamic results, are presented in the Summary of Clinical Pharmacology Studies. The primary efficacy information in this summary comes from the six phase 3 studies. The phase 2 studies were designed primarily to establish starting doses of Mircera for phase 3, and, therefore, had no reference groups.

The phase 2 and phase 3 studies were of two basic types: one addressed the treatment of anemia associated with CRF in patients not treated with an erythropoietin (anemia correction studies) and the other addressed the treatment of anemia associated with CRF in patients converting from an erythropoietin to treatment with Mircera (hemoglobin maintenance studies). Four major studies were conducted for anemia correction and six major studies for hemoglobin maintenance (treatment conversion from another erythropoietin to Mircera). A phase 3b extension study (BH18387) was conducted to collect long-term safety data (2 years) for the phase 2 and phase 3 studies (study on-going at time of original BLA submission). The studies are listed below, and the relationship among these studies is shown in **Figure 1**.

- Two phase 2 studies (BA16260, BA16528): Both examined QW, Q2W, and Q3W SC injection for anemia correction (BA16260 in dialysis, BA16528 in non-dialysis).
- Two phase 3 studies (BA16736, BA16738): BA16736 examined Mircera Q2W IV in dialysis versus an epoetin reference group. BA16738 examined Mircera Q2W SC in non-dialysis, versus a darbepoetin alfa reference group.
- Two phase 2 studies (BA16285, BA16286): Both tested three conversion factors in dialysis. BA16285 examined IV injection of Mircera QW and Q2W, and BA16286 examined SC injection of Mircera QW, Q3W, and Q4W.
- Four phase 3 studies (BA16739, BA16740, BA17283, BA17284): BA16739 and BA16740 were in dialysis and examined Q2W and Q4W Mircera treatment intervals compared with epoetin. BA16739 studied IV injection and BA16740 studied in SC injection. BA17283 and BA17284 examined a Q2W dosing schedule in dialysis, for IV injection in BA17283 with darbepoetin alfa as the reference treatment, and for IV or SC injection in BA17284 using prefilled syringes with epoetin (alfa or beta) as the reference treatment.

Figure 1: Phase 2 and Phase 3 Studies

1.3.2 Efficacy

Phase 3 Studies for Anemia Correction

Two randomized, open-label, multicenter studies were conducted as pivotal studies for anemia correction in follow up of the phase 2 studies described above (one study in patients not on dialysis, and a second study in patients on dialysis). The study designs for the two studies were similar. Both studies included a core period for evaluation of safety and efficacy: BA 16736 included a 24-week anemia correction period, and BA16738 included an 18-week anemia correction period followed by a 10-week evaluation period. Both studies included an extension period to evaluate long term safety.

The primary objective in both studies was to demonstrate the efficacy of Mircera in anemia correction using the hemoglobin response rate as the primary efficacy endpoint, where hemoglobin response is defined as an increase in hemoglobin from baseline by at least 1.0 g/dL and an absolute hemoglobin of at least 11.0 g/dL without red blood cell (RBC) transfusion during the anemia correction period (BA16736) or anemia correction and evaluation periods (BA16738).

Secondary efficacy endpoints included: hemoglobin values and their changes from baseline over time, time to target hemoglobin response, and the incidence of RBC transfusions during the first 24 weeks (BA16736) or the first 28 weeks (BA16738). A total of 505 patients were randomized into the studies, of whom 462 completed study treatment. In BA16738, the median dose at time of response was the same as the starting dose (0.6 ug/kg SC Q2W). In BA16736, the median dose at the time of hemoglobin response was 0.6 ug/kg IV Q2W, which is higher than the starting dose of 0.4 ug/kg IV Q2W.

The demographic characteristics of age, weight, gender, race (Caucasian or African-American), and geographic location (US or non-US) appeared not to affect the response rates in either the reference or Mircera treatment groups. Responder analyses showed no evidence of an altered hemoglobin response in the subgroup of patients with CRF secondary to diabetes mellitus. For anemia correction in patients with CRF, the sponsor determined the appropriate starting dose to

be 0.6 ug/kg Q2W, either IV for patients on dialysis or SC for patients not on dialysis. The two anemia correction studies are described in more detail below:

- BA16736: 0.4 ug/kg IV Q2W in patients on dialysis (vs epoetin alfa or beta)

Study BA16736 was intended to demonstrate that the response rate was at least 60% in the Mircerca group and that the results observed with Mircerca were comparable to those seen with epoetin (alfa or beta). The response rate (end of correction period, ITT population) in the Mircerca group was 93% (95% CI = 88 - 97%). The response rate in the epoetin group was comparable (91%).

Anemia correction was slower with Mircerca than with epoetin: the median time to response was 57 days with Mircerca and 31 days with epoetin. The proportion of patients who required blood transfusions (during correction period) was 5% with Mircerca and 4% with epoetin. In both groups, most patients required dose adjustments (90% with Mircerca, 98% with epoetin).

- BA16738: 0.6 ug/kg SC Q2W in patients not on dialysis (vs darbepoetin alfa)

Study BA16738 was intended to demonstrate that the response rate was greater than 60% in the Mircerca group and that the results observed with Mircerca were clinically not inferior to those observed with darbepoetin alfa. Study BA16738 had a second primary efficacy parameter: the change in hemoglobin between baseline and evaluation periods. The response rate in the Mircerca group (anemia correction and evaluation periods, ITT population) was 98% (95% CI = 94 - 99%). The response rate with darbepoetin alfa was comparable (96%).

An ANCOVA indicated that the adjusted mean change in hemoglobin from baseline with Mircerca (2.12 g/dL) was not inferior to that with darbepoetin alfa (1.95 g/dL). The results were consistent in the PP, ITT, and eligible populations. Anemia correction was slower in the Mircerca group than in the darbepoetin alfa group: the median time to response was 43 days (approximately 6 weeks) with Mircerca and 29 days (approximately 4 weeks) with darbepoetin alfa. The proportion of patients who required blood transfusions (during anemia correction and evaluation periods) was 3% with Mircerca and 7% with darbepoetin alfa. In both groups, most patients required dose adjustments (96% Mircerca, 98% darbepoetin alfa).

Phase 3 Studies for Hemoglobin Maintenance (Dose Conversion)

The sponsor conducted four randomized, open-label, non-inferiority studies to confirm the efficacy of Mircerca in maintaining the hemoglobin (after converting from epoetin alfa, epoetin beta, or darbepoetin alfa to Mircerca), all in patients with CRF on dialysis:

- BA16739: Q2W and Q4W, IV (reference = epoetin, alfa or beta)
- BA16740: Q2W and Q4W, SC (reference = epoetin, alfa or beta)
- BA17283: Q2W, IV (reference = darbepoetin alfa)
- BA17284: Q2W, SC or IV (prefilled syringes) (reference = epoetin, alfa or beta)

The four studies followed the same basic design: 4-week screening period to confirm stable hemoglobin on the previous erythropoietin, 28-week dose titration period to determine a stable Mircerca dose to maintain the hemoglobin, and 8-week evaluation period. Three of the four studies (BA16739, BA16740, BA17283) also included 16 weeks of long-term safety follow-up following the evaluation period.

In each study, the primary efficacy endpoint was the mean change in hemoglobin from baseline to evaluation. Secondary endpoints were: the proportion of patients maintaining the hemoglobin

(during evaluation period) within 1.0 g/dL, and the incidence of red blood cell (RBC) transfusion during study treatment (dose titration and evaluation periods). A total of 1894 patients were randomized into the studies, of whom 1509 completed study treatment. The initial starting doses were 60, 100, or 180 ug for the Q2W regimens, or 120, 200, or 360 ug for the Q4W regimens.

Primary efficacy analysis using the ANCOVA model showed that Mircera treatment (Q2W or Q4W, as specified by the protocol) was not inferior to treatment with epoetin (alfa or beta) (BA16739, BA16740, BA17284) or darbepoetin alfa (BA17283). The median hemoglobin did not appreciably change from baseline to evaluation (ITT population). The largest changes were observed in BA16740 with Q4W (-0.21 g/dL) and in BA17284 with Mircera Q2W (+0.25 g/dL).

In all studies (Mircera and reference), the majority of patients (66% to 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 to 13 g/dL) throughout the study.

The proportions of patients requiring RBC transfusion (during study treatment) were not significantly different between Mircera (6% to 12%) and reference erythropoietins (8% to 11%). The proportions of patients requiring dose adjustments were also not significantly different: 88% to 96% of patients with Mircera Q2W, 87% to 88% with Mircera Q4W, and 86% to 91% with the reference erythropoietins.

1.3.3 Safety

The primary safety analysis was performed using data obtained from the safety population, which consisted of data pooled from four phase 2 and six phase 3 studies involving 2737 patients (1789 receiving Mircera and 948 receiving a reference agent (epoetin alfa, epoetin beta, or darbepoetin alfa). In addition to these 10 studies in patients, the sponsor provided safety data from 499 healthy subjects and 40 patients in phase 1 clinical pharmacology studies.

Patient Populations

The overall safety population consisted of CRF patients not previously treated with an erythropoietin product (anemia correction population) as well as those already being treated with an erythropoietin product (hemoglobin maintenance population). In the overall safety population, most patients were on dialysis and the majority of patients received hemodialysis (84% and 80% in the Mircera and reference groups, respectively). Among dialysis patients, the median time for which patients had been receiving dialysis in both groups was approximately 3 years. The percentage of patients receiving dialysis for 6 months, 1 year, 2 years, etc, was similar between treatment groups, suggesting that the patients in both groups were at a similar disease stage and treatment level. A total of 95 patients were treated with peritoneal dialysis.

Approximately one third of the patients were from the United States (US). The majority of patients were Caucasian (approximately 70%), and 20% were Black patients (including African Americans). Forty-four percent of the population was over 65 years of age and 20% over 75 years. There were no notable demographic imbalances across treatment groups.

Baseline co-morbidities reflected those expected in the CRF population. Differences in pre-specified risk factors for vascular events and hemorrhages were included in statistical models used to assess safety outcomes.

Patient Exposure

In total, 1789 patients received RO030581 in the overall safety population. Of these patients, 1422 patients were receiving Mircera at 6 months; 1011 patients at 12 months; and 95 patients at 24 months. The total duration of exposure was 1532 patient exposure years (PEY) giving a mean of 0.86 PEY per patient. The combined reference groups comprised a total of 948 patients with 778 PEY and a slightly shorter average of 0.82 PEY per patient for comparison. The shorter follow-up in the reference group reflects the lack of comparator arms in the long-term extension portions of the phase 2 studies. The proportions of patients receiving the study medication IV or SC were approximately equal (50%).

Safety Findings

The results of the primary analyses of AE for the pooled phase 2 and 3 studies showed comparable 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. 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. When clinically related AE preferred terms were collapsed into single project-defined terms for AE of special interest (e.g., thromboembolic events, cardiovascular system events, nervous system events, and infections), all pre-defined terms were reported with similar frequency in the Mircera and reference groups.
- Vascular access thrombosis was associated with Hb > 13 g/dL, as reported in the literature. An extensive analysis of potential associations between AE and Hb rate of rise did not produce any clinically relevant findings.
- There were no 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 a major review concern. An adjudicated evaluation of all deaths by a blinded cardiac panel, however, indicate that the apparent imbalance in the incidence of sudden deaths resulted from a chance imbalance in the selection of "sudden death" as the reported term by the clinical investigators; the apparent imbalance appears to be spurious. 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 will be important component in evaluating sudden deaths.

Administration of Mircera for the treatment of anemia associated with CRF was generally well tolerated with no difference in the safety profile in comparison to reference erythropoietin products.

1.3.4 Dosing Regimen and Administration

Anemia Correction

These results suggested that a dose of 0.6 ug/kg Q2W is appropriate for both IV and SC routes of administration, and that a reduction in dose was not necessary in using SC phase 2 data to design an IV phase 3 study. In both studies, a much lower proportion of patients treated with Mircera

had hemoglobins above 13.0 g/dL during the first 8 weeks of the anemia correction period, in comparison with patients treated with the reference medication.

Hemoglobin Maintenance

The results of the studies indicate that the hemoglobin can be effectively maintained (starting doses of 60, 100, and 180 ug for the Q2W regimens and 120, 200, and 360 ug for the Q4W regimens, in combination with protocol-specified dose adjustments guidelines) with Mircera in patients with CRF on dialysis after converting from a previous erythropoietin, irrespective of the administration route (IV or SC), drug presentation (vials or prefilled syringes), dosing interval (Q2W or Q4W), or previous erythropoietin (epoetin alfa, epoetin beta, or darbepoetin alfa). Subgroup analyses based on baseline patient characteristics (age, weight, gender, race, geographic region, etiology of CRF) showed no appreciable differences from the overall efficacy findings.

1.3.5 Drug-Drug Interactions

In the hemoglobin maintenance studies, the hemoglobin levels decreased with study treatment in iron deficient patients but not in iron replete patients, for both Mircera and reference erythropoietins. This observation underscores the expected relationship between erythropoietin and iron therapies in treating anemia. The observation also raises questions about the quantitative relationship between iron therapy and erythropoietin therapy in treating renal anemia (independent vs dependent effects, additive vs synergistic effects). No other drug-drug interactions were expected or observed.

1.3.6 Special Populations

The current submission does not address the safety and efficacy of Mircera in treating children with renal anemia. The sponsor may perform a pediatric study, according to the sponsor's timeframe,

2 INTRODUCTION AND BACKGROUND

2.1 Product Information

Erythropoietin, a hormone produced primarily in the kidneys, stimulates the production of red blood cells (RBC) in bone marrow and is essential for the hemoglobin maintenance of normal RBC count. Anemia, caused by erythropoietin deficiency, is a hallmark of chronic renal failure (CRF). Although the pathogenesis of anemia associated with CRF is multifactorial, decreased production of erythropoietin is considered the main etiologic factor. Exogenous replacement of erythropoietin by the recombinant hormone, epoetin, is a well-accepted therapy for treatment of anemia associated with CRF. The current treatment options (epoetin (alfa or beta), darbepoetin alfa) require administration from 3 - 7 times per week to once every 2 weeks (Q2W).

Mircera (methoxy polyethylene glycol-epoetin beta) is a chemically synthesized continuous erythropoietin receptor activator. It differs from erythropoietin through integration of an amide bond between an amino group and methoxy polyethylene glycol-succinimidyl butanoic acid. In contrast with erythropoietin, Mircera shows a different activity at the receptor level characterized by a slower association to and faster dissociation from the receptor, a reduced specific activity in vitro with an increased activity in vivo, as well as an increased half-life. These differential pharmacological properties are relevant in order to achieve a once monthly dosing regimen with Mircera in patients.

2.2 Currently Available Treatment for Indications

In treating anemia associated with CRF, epoetin alfa (Procrit and Epogen) and darbepoetin alfa (Aranesp) are currently available in the US and elsewhere, to treat adults and children to increase or maintain the hemoglobin concentration. Procrit and Epogen are identical molecules of epoetin alfa (human recombinant erythropoietin), and Aranesp differs from these in that increased glycosylation and molecular weight permits less frequent dosing as the result of prolonged circulating half-life.

Mircera differs from epoetin alfa in the cell culture system used in product manufacturing (resulting in epoetin beta rather than alfa), and differs from darbepoetin alfa in that increased molecular weight and circulating half-life are achieved by the introduction of a methoxy-polyethylene glycol moiety into the peptide backbone in lieu of hyperglycosylation. In comparison with darbepoetin alfa, greater molecular weight and circulating half-life presumably permits an even greater dosing interval. Epoetin beta (Recormon and Neorecormon) is available in Europe. Mircera is currently under evaluation for approval in US, Europe, and Japan.

2.3 Availability of Proposed Active Ingredient in the United States

The drug substances (PEG and epoetin beta) will be manufactured in Europe and US. The PEG reagent will be manufactured in US by ~~_____~~ and epoetin-beta will be manufactured in Germany by Roche (Penzberg). The drug product (pegzerepoetin beta) will be manufactured in Germany by Roche.

2.4 Important Issues with Pharmacologically Related Products

Many erythropoiesis stimulating proteins are available in US and elsewhere to treat anemia associated with various clinical conditions, and additional products continue to be developed. For currently available products and for new products under development, the ability to provide effective therapy for anemia with less frequent dosing has been a major goal in product development. This goal appears to be most urgent for CRF, a prevalent and typically irreversible condition affecting over 8 million patients in the US (about 3% of US population). This product development goal in CRF reflects the growing trend in clinical practice to use “off-label” infrequent dosing regimens. Product labeling that recognizes less frequent dosing may increase treatment compliance and decrease “under-treatment” of anemia associated with CRF.

Anemia Correction in CRF

The concept of “under-treatment” of CRF-associated anemia, however, has not been clearly defined. In CRF, it remains plausible that the disease-associated anemia protects against serious morbidity to increase survival. Limited data in the current literature suggest that anemia correction in CRF may be less beneficial than expected. In fact, correcting CRF-associated anemia to hemoglobin levels above 13.5 g/dL is ill-advised:

- In a randomized study involving over 1200 patients with anemia, cardiovascular disease, and CRF on hemodialysis, epoetin alfa therapy that sustains a 42% hematocrit was associated with a higher rate of deaths and non-fatal myocardial infarctions (myocardial infarctions) than epoetin alfa therapy that sustains a 30% hematocrit (183 deaths and 19 myocardial infarctions vs 150 deaths and 14 myocardial infarctions). Although the results were not statistically significant (risk ratio = 1.3, 95% confidence interval 0.9 to 1.9), the study was halted at 29 months of the planned 3 years after last patient enrollment (1).

- In a randomized study involving over 1400 patients with anemia, cardiovascular disease, and CRF non on dialysis, epoetin alfa therapy that sustains a hemoglobin of 13 g/dL (13.5 g/dL) was associated with a higher rate of deaths, myocardial infarctions, strokes, and hospitalizations related to congestive heart failure than epoetin alfa therapy that sustains a hemoglobin of 11 g/dL (11.3 g/dL) (125 vs 97 events). The study was terminated early based on the statistically significant result (2).

In the patient populations studied, these two studies described above indicate that erythropoietin therapy to sustain a normal or near-normal hemoglobin (13.5 to 14.0 g/dL) increases long-term mortality and morbidity, in comparison with treatment to sustain a lower hemoglobin (10.0 to 11.3 g/dL). Within each treatment group, however, higher hemoglobin levels were associated with lower adverse event rates.

In treating anemia of CRF using erythropoietins, studies that prospectively compare target hemoglobin levels lower than 13.5 g/dL have not been performed. The following hypotheses remain untested to explain these observations:

- In CRF, anemia may be an “adaptive response” to limit disease-associated morbidity, rather than a contributor to morbidity, and eliminating this “adaptive response” through erythropoietin therapy may increase morbidity.
- The lower event rates seen at higher hemoglobin levels (two studies described above) reflect lower rates expected in less severe disease. The lower observed rates may also reflect selection bias induced by exogenous erythropoietin therapy – i.e., patients with less severe disease respond more readily to achieve higher hemoglobin levels.

Erythropoietin Product Labeling

The results of these studies are consistent with the current product labeling (all erythropoietins), which recommends a target dose “not to exceed 12 g/dL” in treating CRF-associated anemia.

- The upper limit of 12 g/dL, however, is not based on data obtained from studies similar to the two described above.
- The choice of 12 g/dL was based on an observation at review of the original BLA for darbepoetin alfa, which suggested that rates of “adverse events of special interest” were lowest for the 11 to 12 g/dL range, in comparison with higher or lower hemoglobin levels.
 - The term “adverse events of special interest” was defined as those considered to be “more possible to be related to the hemoglobin level or changes in the hemoglobin level” (signs and symptoms consistent with fluid overload, cardiac and cerebrovascular disorders, and thromboembolic events).
 - This review finding (original darbepoetin alfa BLA) was not statistically significant, and analyses of previous and new data at review of the current BLA do not support this earlier review observation.
 - Prospectively raising the hemoglobin level in patients with CRF may increase the incidence of adverse events. At FDA analysis of data submitted in support of the original BLA, the decreasing rate of adverse events up to a hemoglobin range of 11 – 12 g/dL may primarily reflect underlying disease, whereas the increasing incidence of adverse events above a hemoglobin level of 12 g/dL may primarily reflect therapeutic intervention.

- In the two studies described above (1,2), a higher incidence of adverse events (safety endpoints) were observed with higher target hemoglobin levels (reflecting therapeutic intervention), but decreasing incidence of adverse events were observed with decreasing hemoglobin levels when hemoglobin levels were retrospectively analyzed (reflecting underlying disease). In both studies, this opposite association between the hemoglobin level and the incidence of adverse events were observed for both treatment arms (higher vs lower target hemoglobin).

These considerations indicate that the optimal target hemoglobin range has not been defined in using erythropoietins to treat anemia of CRF. Additional prospective randomized studies (preferably stratified by baseline hemoglobin) are needed to define the relationship between long-term clinical outcome and correcting anemia to various hemoglobin levels, particular to levels below 12 g/dL.

2.5 Pre-Submission Regulatory Activity

The clinical development program for Mircera was conducted under FDA guidance, under IND 10158. In particular, the conduct of the phase 3 program and the construction of the BLA submission were discussed in some detail at an "end of phase 2" meeting in October 2003, about 30 months prior to the BLA submission in April 2006. Highlights of prior regulatory guidance (emphasized or permitted by FDA) regarding phase 3 development are listed below:

- No formal drug-drug interaction studies will be performed. Exploratory studies using a population approach may substitute for formal studies. If the exploratory studies suggest potential drug-drug interactions, the need for formal drug-drug interaction studies will be determined at BLA review.
- The primary focus of FDA review will be on product safety. Mircera is expected to be effective in raising or maintaining the hemoglobin as long as an adequate amount of the drug is given (titration to effect). In evaluating product safety, the sponsor should closely examine the hemoglobin response and immunogenicity:
 - In treating patients, the hemoglobin level should be increased cautiously; FDA considers rapid hemoglobin ROR as a significant risk for cardiovascular adverse events. In analyzing data, clinical adverse events should be correlated with the hemoglobin levels leading up to the events. In addition to clinical adverse events, safety evaluation should include an assessment of dose adjustments, hemoglobin excursions, and excessive hemoglobin ROR as surrogate safety measures, whether or not these parameters were associated with clinical events.
 - In evaluating immunogenicity, the time point for collecting blood samples for testing will be important, in addition to assay sensitivity. Inappropriately early sampling may result in interference (masking of existing antibodies) by residual product.
- Subject selection for the phase 3 program should be as inclusive as possible. The phase 3 program should include an adequate number of patients of minority background. In particular, the sponsor should make an effort to enroll African-Americans, who comprise a greater proportion in the treatment population and in the general US population.
- The sponsor may submit a safety update four months after the BLA submission, provided that the BLA already includes substantial evidence of safety. The update should not require new analyses and should be consistent with the existing BLA findings.

2.6 Other Relevant Background Information

As of 20 December 2006, the sponsor had amended the BLA fifteen times since its original submission in 18 April 2006. Clinical amendments are shown **highlighted**.

- **Amendment 1**, 7 Jul 2006: An outline of steps undertaken to address FDA concern regarding an imbalance in sudden deaths (74-day letter), including developing a plan for additional retrospective statistical analyses.
- **Amendment 2**, 18 Jul 2006: Information to assist FDA in inspecting manufacturing sites. Revised Letter of Authorization to cross-reference the ~~_____~~ Drug Master File for the PEG reagent used in the manufacture of the drug substance.
- **Amendment 3**, 11 Aug 2006: Clarification as requested by FDA (74-day letter) regarding preclinical data.
- **Amendment 4**, 14 Aug 2006: Four-month safety update, consisting of Safety Update, Case Report Forms, and Labeling Update.
 - Safety Update, consisting of Core Report and Cardiac Safety Report.
 - Core Report provided updated safety information from studies on-going at time of initial BLA submission using a cutoff of 15 March 2006 (extension periods in phase 3 studies BA16376 and BA16738). The Core Report also included safety data from roll-over studies BH18387 and ML19382, and from studies completed or on-going in Japan.
 - Cardiac Safety Report shown the findings of a comprehensive evaluation of all deaths, with a special focus on cardiac events (including sudden death and other cardiac deaths) in completed phase 2 and phase 3 studies and in on-going roll-over studies, through a clinical cutoff of 15 March 2006.
 - Case Report Forms were provided from BA16736 and BA16738 for patients who had not completed the extension period at time of filing and who died, withdrew, had a serious adverse event or received transfusion. CRF were provided also from the on-going roll-over studies for patients who died or withdrew.
 - Labeling Update consisted of revisions to labeling on packaging and package inserts. The revisions reflected: (1) the a change in the non-proprietary name to pegzerepoetin alfa, (2) an updated hemoglobin target of 12 g/dL and maximum hemoglobin ROR of 1 g/dL in 2 weeks per FDA comments (74-day letter), and (3) updates to numbers and percentages of adverse reactions per four-month Safety Update.
- **Amendment 5**, 13 Oct 2006: Revised safety analyses that correlate adverse events of interest to hemoglobin levels and hemoglobin ROR, per FDA request (15 September 2006).
- **Amendment 6**, 23 Oct 2006: Pharmacokinetic datasets from the QT study BP17278, per FDA request (13 October 13 2006).
- **Amendment 7**, 27 Oct 2006: Additional Chemistry, Manufacturing and Controls information regarding drug product vials and pre-filled syringes. Revised Establishment Information.
- **Amendment 8**, 03 Nov 2006: A plan for submitting additional safety information as a major amendment to the BLA.

- **Amendment 9**, 10 Nov 2006: Source documentation from clinical trial sites for the sudden death cases as reported in the four-month Safety Update (Amendment 4).
- Amendment 10, 13 Nov 2006: Additional data from pre-clinical toxicology studies.
- Amendment 11, 15 Nov 2006: Clinical study site information to assist FDA with planning for pre-approval inspections.
- **Amendment 12**, 28 Nov 2006: Clarification of subject exclusion based on screening for elevated C-reactive protein, in phase 2 and in phase 3 studies.
- Amendment 13, 30 Nov 2006: Additional Chemistry, Manufacturing and Controls information regarding drug substance.
- Amendment 14, 01 Dec 2006: Notification that ECG data from study BP17278 have been uploaded to the ECG Warehouse (an annotated electrocardiogram waveform data storage and review system) at www.ecgwarehouse.com, per FDA request (3 November 2006).
- **Amendment 15**, 04 Dec 2006: September Safety Update Report, Cardiac Adjudication Report, Labeling Update, Datasets, and Case Report Forms. This major amendment extended the review clock by 3 months to PDUFA goal date in May 2006.
- Amendment 16, 19 Dec 2006: CMC information for drug substance in response to FDA request for information.
- Amendment 17, 18 Dec 2006: Clinical site information in response to FDA request for information to assist with inspection planning.
- Amendment 18, 21 Dec 2006: Comments on pre-clinical toxicology study in response to FDA request for clarification.
- Amendment 19, 3 Jan 2007: Sponsor request for a meeting with the FDA.
- Amendment 20, 4 Jan 2007: Clinical site information in response to FDA request for information to assist with inspection planning, addendum to Amendment 17.

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC (and Product Microbiology, if Applicable)

See Appendix (CMC).

3.2 Animal Pharmacology/Toxicology

See Appendix (Toxicology).

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

The phase 3 clinical data provided by the sponsor in this submission served as the primary source of data for clinical review. Secondary sources included phase 1 and phase 2 data (contained in this submission), data submitted by Amgen in support of previous BLA for darbepoetin alfa, and the clinical literature about the use of erythropoietins in managing renal anemia.

4.2 Tables of Clinical Studies

The study objectives and major design features of the phase 2 and phase 3 studies are presented below in **Tables 1 and 2**. **Figure 1** above provides an overview of the relationship among the ten phase 2 and phase 3 studies.

Table 1: Phase 2 Studies

Study & Objective	Patients & Sites	Study Design	Treatment Groups	Endpoint
BA16260, phase 2 correction, determine dosing regimen	61 pts on HD or PD at 17 sites in Europe, Taiwan	open-label, randomized (1:1), dose escalation	Mircera SC: 0.9, 1.8, 2.7 ug/kg/6-wk QW, Q2W, Q3W for 12 wks	Hemoglobin response curves for initial 6 wks
BA 16528, phase 2 correction, determine dosing regimen	65 pts not on dialysis at 22 sites in North America, Europe	open-label, randomized (1:1), dose escalation	Mircera SC: 0.9, 1.8, 3.6 ug/kg/6-wk QW, Q2W, Q3W for 19 wks	Hemoglobin response curves for initial 6 wks
BA16285, phase 2 maintenance, determine IV dose conversion factor	91 pts on HD and IV epoetin alfa at 14 US sites	open-label, randomized (1:1), dose escalation	Mircera IV: 0.25, 0.4, 0.6 ug/150 IU QW or Q2W for 19 wks	Hemoglobin response curves for initial 6 wks
BA16286, phase 2 maintenance, determine SC dose conversion factor	137 pts on dialysis & SC epoetin at 22 sites in US, Europe	open-label, randomized (1:1), dose escalation	Mircera SC: 0.4, 0.8, 1.2 ug/150 IU QW or Q3W for 19 wks QW or Q4W for 21 wks	Hemoglobin response curves for initial 6 wks

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Table 2: Phase 3 Studies

Study & Objective	Patients & Sites	Study Design	Treatment Groups	Endpoint
BA 16736, phase 3 correction, demonstrate efficacy IV in dialysis	181 untreated pts on dialysis at 42 sites worldwide	open-label, randomized (3:1), controlled	Mircera IV: 0.4 ug/kg Q2W (Q2W or Q4W extension) for 54 wks Epoetin (alfa or beta) TIW per labeling for 54 wks	Hemoglobin response rate for initial 24 wks
BA 16738, phase 3 correction, demonstrate efficacy SC in non-dialysis	324 untreated pts not on dialysis at 82 sites worldwide	open-label, randomized (1:1), parallel controlled	Mircera SC: 0.6 ug/kg Q2W (Q2W or Q4W extension) for 54 wks Darbepoetin alfa SC QW or Q2W per labeling for 54 wks	Hemoglobin response rate for initial 28 wks
BA 16739, phase 3 maintenance, demonstrate efficacy IV in dialysis	673 pts on dialysis & IV epoetin at 91 sites in US, Canada, Europe	open-label, randomized (1:1:1), parallel controlled	Mircera IV: 60-180 ug Q2W or 120-360 ug Q4W for 52 wks Epoetin (alfa or beta) TIW - QW for 52 wks	Change in hemoglobin from baseline
BA 16740, phase 3 maintenance, demonstrate efficacy SC in dialysis	572 pts on dialysis & SC epoetin at 89 sites worldwide	open-label, randomized (1:1:1), parallel controlled	Mircera SC: 60-180 ug Q2W or 120-360 ug Q4W for 52 wks Epoetin (alfa or beta) TIW - QW for 52 wks	Change in hemoglobin from baseline
BA 17283, phase 3 maintenance, demonstrate efficacy IV in dialysis	313 pts on dialysis & IV darbepoetin at 48 sites in Europe, Canada, Australia	open-label, randomized (1:1), parallel controlled	Mircera IV: 60-180 ug Q2W for 52 wks Darbepoetin alfa QW or Q2W for 52 wks	Change in hemoglobin from baseline
BA 17284, phase 3 maintenance, demonstrate efficacy of PFS in dialysis	336 pts on dialysis & IV or SC epoetin (alfa or beta) at 62 sites worldwide	open-label, randomized (1:1), parallel controlled	Mircera IV or SC in PFS: 60-180 ug Q2W for 52 wks Epoetin alfa or beta TIW - QW for 52 wks	Determine change in hemoglobin from baseline

4.3 Review Strategy

The clinical review focused on product safety. Efficacy data were regarded as "validation data" that confirm that Mircera is effective, as expected, in raising or maintaining the hemoglobin when an adequate amount of the drug is given based on hemoglobin response (titration to effect).

The safety review focused on the controlled phase 3 studies, which permit a comparison of the safety of Mircera to currently marketed erythropoietin products (epoetin alfa or beta, darbepoetin alfa) when the products are used to achieve comparable levels of efficacy in raising or maintaining the hemoglobin. Uncontrolled phase 1 and phase 2 data were reviewed to confirm safety findings in phase 3 studies or when phase 3 findings were unclear.

The data submitted in the initial submission (data cutoff as of March 2006) were reviewed first, followed by updated data (four-month update and September update). The review of phase 3 safety data focused on the following comparisons between Mircera and the reference agents:

- Comparability of the baseline patient characteristics, between patients randomized to the Mircera arm and patients randomized to the reference agents.
- Incidence of adverse clinical events:
 - Based on previous erythropoietin review experience: All adverse events, adverse events occurring in over 5% of patients, serious adverse events, adverse events of special interest (considered to be potentially treatment-related, including deaths, thromboses, cardiac events, strokes, seizures, fluid overload including hypertension).
 - Based on initial 74-day review: Special emphasis on deaths, cardiac deaths, and sudden deaths. An initial review suggested a potential imbalance in sudden deaths.
 - Low numbers of deaths may preclude a statistically significant conclusion; however, a trend towards a relative increase in deaths (or any subset of deaths) for Mircera was to be regarded as an important safety concern, even if statistically non-significant.
 - Given that the efficacy of Mircera does not offer a medically significant advantage over the efficacy of currently marketed erythropoietin products, additional studies may be necessary to "disrupt" a seemingly consistent trend in an any potentially important safety finding
 - Based on literature reports: A composite endpoint consisting of death, stroke, myocardial infarction, congestive heart failure requiring hospitalization. In the recent CHOIR study, a statistically significant difference ($p = 0.03$) in this composite endpoint was observed between a hemoglobin target of 11.3 g/dL (13.5% incidence) vs 13.5 g/dL (17.5% incidence) when epoetin alfa was used to treat renal anemia in patients not on dialysis.
- Hemoglobin response and correlation with clinical events: An assessment of hemoglobin response and a correlation of the hemoglobin response with clinical events. In addition to clinical adverse events, safety evaluation will include an assessment of dose adjustments, hemoglobin excursions, and excessive hemoglobin ROR as surrogate safety measures, whether or not these parameters were associated with clinical events.
- Immunogenicity, with attention to assay sensitivity and blood sampling: Inappropriately early sampling may result in interference (masking of existing antibodies) by residual product.

Finally, the subject selection criteria were reviewed to identify potential mismatch between study findings and the intended treatment population as proposed in product labeling. A mismatch in baseline characteristics between the study population and the intended populations may limit the generalizability of the study findings to the patient population as intended per product labeling.

4.4 Data Quality and Integrity

4.5 Compliance with Good Clinical Practices

The studies were conducted in compliance with Declaration of Helsinki (as last amended as of April 2006) and with the local laws and regulations of the country in which the study was

conducted. Good clinical practice (GCP) guidelines were also followed in countries with established GCP guidelines.

4.6 Financial Disclosures

The sponsor adequately discloses the financial arrangements with the clinical investigators in this submission, as recommended in the FDA guidance document entitled "Financial Disclosure by Clinical Investigators." The disclosed financial arrangements do not raise significant or unusual concerns about the integrity of the data collected from the open-label studies that support this submission.

5 CLINICAL PHARMACOLOGY

See Appendix (Clinical Pharmacology).

6 INTEGRATED REVIEW OF EFFICACY

6.1 Indication

The sponsor seeks to market Mircera for the treatment of anemia associated with CRF in patients on dialysis or not on dialysis. The treatment indication includes both de novo anemia correction (in patients not treated previously with an erythropoietin) and hemoglobin maintenance (in patients converting to Mircera from a previous erythropoietin). Mircera is to be given Q2W for anemia correction, or Q2W or monthly for hemoglobin maintenance. Mircera is to be given by either intravenous (IV) or subcutaneous (SC) injection, irrespective of the dosing interval or dialysis status.

6.1.1 Methods

Efficacy data obtained from the six phase 3 studies provided the major portion of the overall evidence of effectiveness. The efficacy review focused on the phase 3 studies; phase 1 and phase 2 studies are discussed to the extent necessary to describe the design, conduct, and results of the phase 3 studies.

6.1.2 General Discussion of Endpoints

Anemia Correction Studies

The primary efficacy parameter in BA16736 and BA16738 was the hemoglobin response rate. This was defined as an increase in hemoglobin of at least 1.0 g/dL from baseline and a hemoglobin of at least 11.0 g/dL without RBC transfusion during the anemia correction period (first 24 weeks after first dose through week 25) in BA16736, and during the anemia correction and evaluation periods (first 28 weeks after first dose through week 29) in BA16738.

The average baseline hemoglobin value was to be calculated using all values recorded between the day of first study dose and the previous 20 days. The value on the day of the first dose was to be included in the baseline calculation (assessment performed before giving the first dose). Blood for hemoglobin assessments was collected QW in BA16736, and Q2W in BA16738, on the same day of the week, and prior to injection of the study drug.

Study BA16738 had a second primary efficacy parameter: the change in hemoglobin between the baseline and evaluation periods. The comparison of change in hemoglobin was to reflect all scheduled Q2W hemoglobin measurements and unscheduled hemoglobin measurements during

the evaluation period between weeks 21 and 29. The change in hemoglobin (g/dL) was to be calculated by subtracting the average baseline value from the average evaluation period value.

Secondary efficacy endpoints in BA16736 and BA16738 were: (1) hemoglobin values and their changes from baseline over time, (2) time to target hemoglobin response, and (3) RBC transfusions during first 24 weeks (BA16736) or first 28 weeks (BA16738).

Hemoglobin Maintenance Studies

The primary efficacy parameter for BA16739, BA16740, BA17283, and BA17284 was the change in hemoglobin (g/dL) between the baseline and evaluation periods.

The baseline period was defined as all assessments between the day of first study dose and the previous 30 days (including hemoglobin assessments on the day of first dose). During the baseline period when more than one hemoglobin measurement was taken, a time-adjusted average baseline hemoglobin value was calculated. The average hemoglobin for each individual during the evaluation period was estimated using the same method as for baseline. Subtracting the baseline value from the evaluation period value gave the final endpoint.

The secondary efficacy endpoints for BA16739, BA16740, BA17283, and BA17284 were: (1) number of patients maintaining average hemoglobin during the evaluation period within 1.0 g/dL of their average baseline hemoglobin, and (2) incidence of RBC transfusions during the dose titration and evaluation periods.

6.1.3 Study Design

Tables 1 and 2 provide an overview of the design for the phase 2 and phase 3 studies, respectively. The phase 3 studies were randomized using a concurrent active control. None of the studies (phase 2 or phase 3) were blinded.

Anemia Correction Studies

The phase 3 anemia correction studies (BA16736 and BA16738) were randomized, open-label, multicenter studies, and each had a reference group. Study BA16736 examined the anemia correction of anemia in patients with CRF receiving dialysis treatment, and BA16738 examined the anemia correction of anemia in patients with CRF who did not require dialysis treatment. Both studies included a Mircera group run in parallel with an approved erythropoietin: IV epoetin (alfa or beta) (BA16736) or SC darbepoetin alfa (BA16738).

The primary objective of the phase 3 anemia correction studies was to demonstrate the efficacy of Mircera treatment administered IV or SC in the anemia correction of anemia based on the hemoglobin response rate, defined as an increase in hemoglobin of at least 1.0 g/dL from baseline and a hemoglobin of at least 11.0 g/dL without RBC transfusion during the anemia correction period (first 24 weeks after first dose, BA16736) or during the anemia correction and evaluation periods (first 28 weeks after first dose, BA16738). The study designs for BA16736 and BA16738 are shown in **Figures 2 and 3**.

Figure 2: Design of BA16736

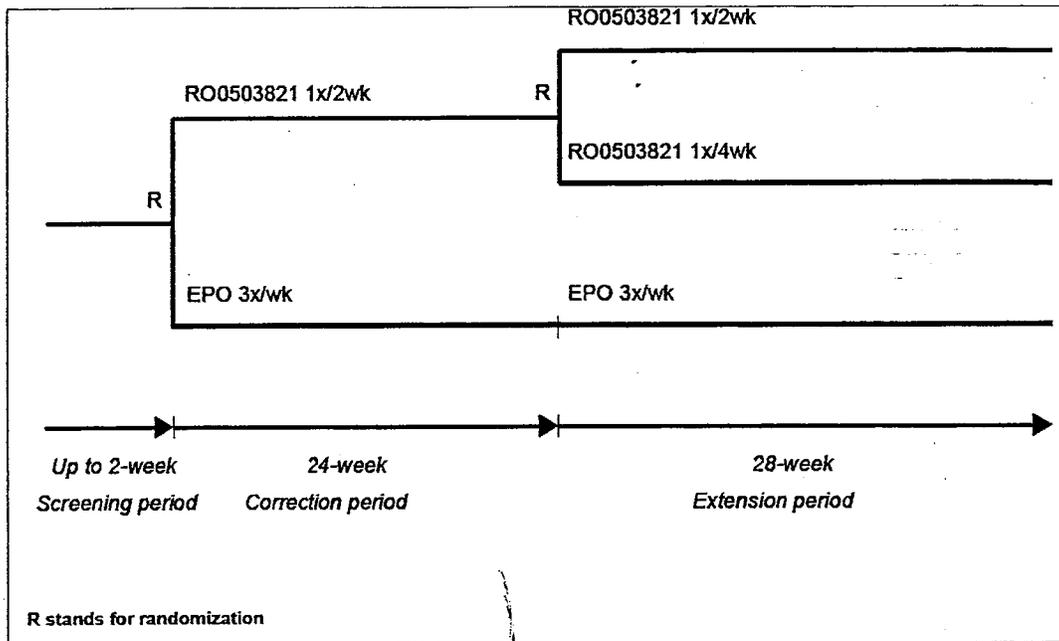
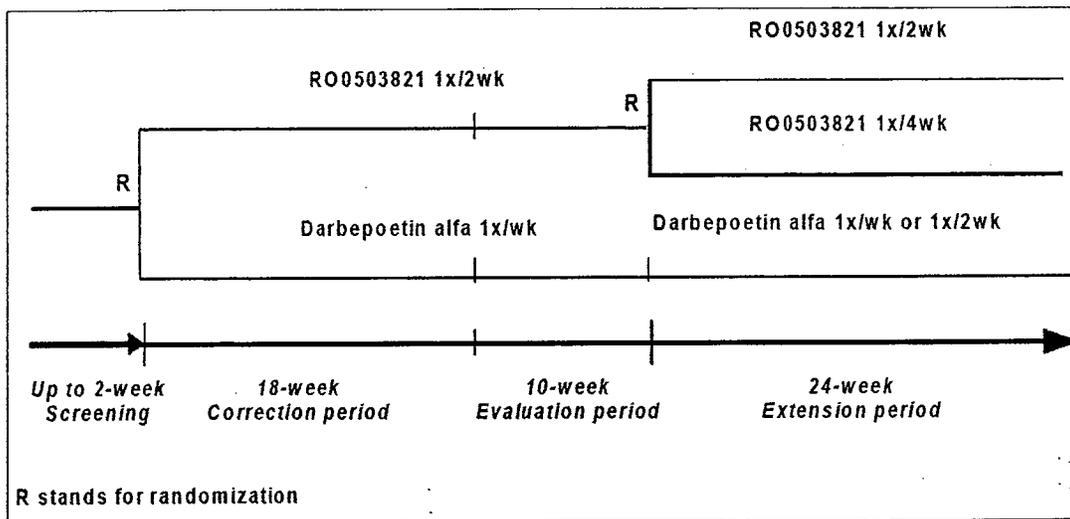


Figure 3: Design of BA16736



The anemia correction period (in BA16736) or anemia correction and evaluation periods (BA16738) were the core periods for evaluation of safety and efficacy. The extension periods were included for long term safety evaluation. The screening period performed the same function as the "run-in" period in the phase 2 studies, namely to ensure that only patients with stable hemoglobins and adequate iron status entered the study. In BA16736, this period also served to verify adequacy of dialysis therapy. Adequate dialysis was defined as Kt/V (urea clearance x dialysis duration / volume) > 1.2 or URR (urea reduction ratio) > 65% for hemodialysis patients, and weekly Kt/V > 1.8 for peritoneal dialysis patients.

Starting Mircerca doses were 0.4 ug/kg/2-wk IV in BA16736, and 0.6 ug/kg/2-wk SC in BA16738. Reference medications (epoetin alfa or beta in BA16736; darbepoetin alfa in BA16738) were administered according to approved labeling.

At the end of the anemia correction period (BA16736) or evaluation period (BA16738), after 24 to 28 weeks of treatment, patients were categorized as responders or non-responders. Responders in the Mircerca groups were re-randomized to receive Mircerca either Q2W or Q4W for the extension period. Responders in the reference group remained on their reference drug for the extension period. Non-responders in the Mircerca groups had to be withdrawn. Non-responders in the reference group were withdrawn in BA16738.

Hemoglobin Maintenance Studies

Four open-label, randomized, multicenter, non-inferiority phase 3 studies (BA16739, BA16740, BA17283, and BA17284) were conducted with the primary objective of showing that Mircerca, administered via IV or SC routes once every 2 or 4 weeks, maintains hemoglobins in patients on dialysis who have been using erythropoietins (epoetin alfa or beta; darbepoetin alfa). In addition, the hemoglobin maintenance BA17284 was conducted to support the registration of prefilled syringes as an alternative dosage form to the vials used in BA16739, BA16740, and BA17283.

All four studies had the same basic design: a 4-week screening/baseline period to ensure that patients maintained their previous dose and regimen of erythropoietins; a 28-week dose titration period used for Mircerca dose titration and stabilization of hemoglobin; and an 8-week evaluation period. With the exception of BA17284 (prefilled syringes), the studies also included a 16-week long-term safety follow-up period. The reference drugs included epoetin alfa, epoetin beta, and darbepoetin alfa. The study designs are depicted in Figures 4 - 6.

Figure 4: BA16739 (IV) and BA16740 (SC)

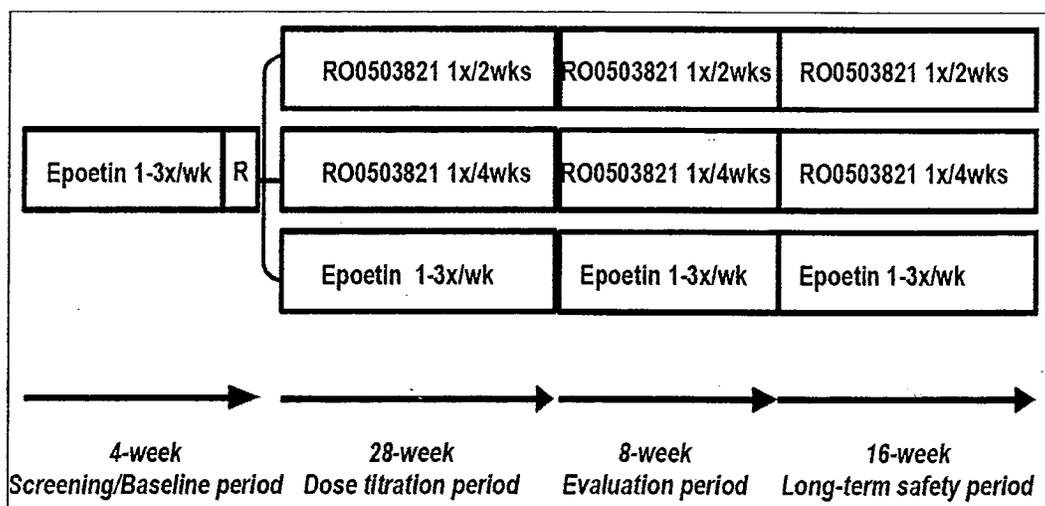


Figure 5: BA17283 (IV)

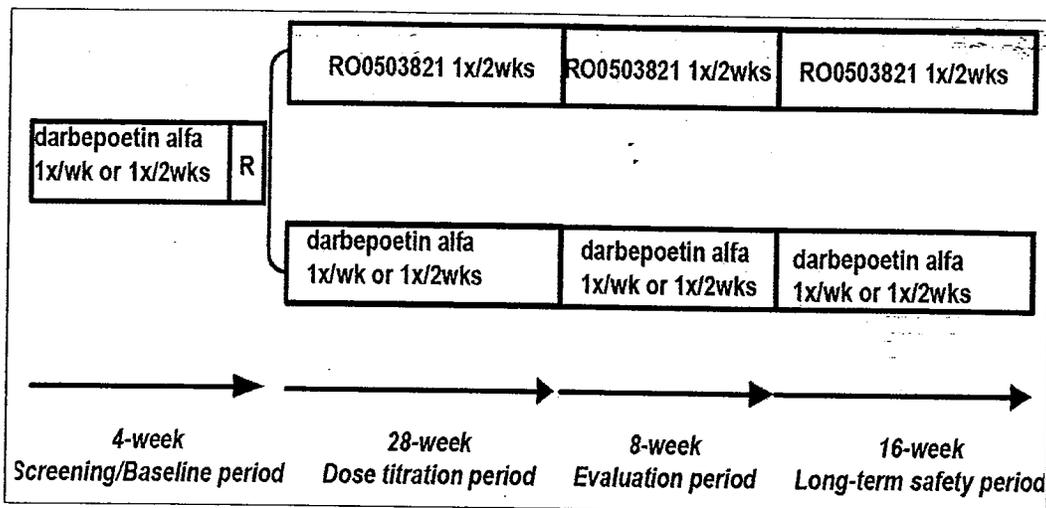
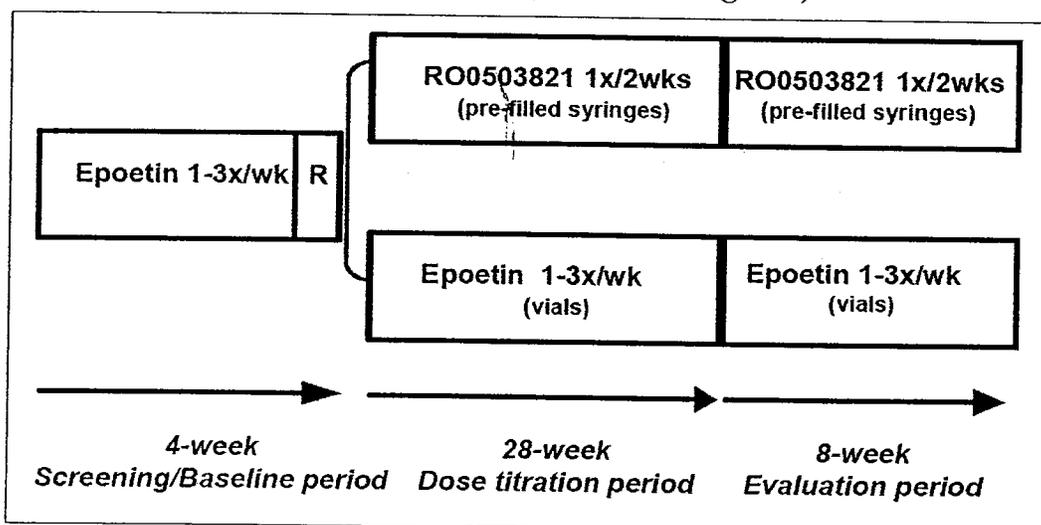


Figure 6: BA17284 (IV or SC using PFS)



Dialysis Studies

BA16736, BA16739, BA16740, BA16283, and BA16284 were conducted in dialysis patients. Dialysis modality changes were allowed during the randomized treatment period in case of medical need. In case of a switch between peritoneal dialysis and hemodialysis, the dialysis adequacy (Kt/V or urea reduction ratio [URR] for patients who switched to hemodialysis or the QW Kt/V for patients who switched to peritoneal dialysis) was reassessed.

Study BA16738 was in patients not on dialysis. Patients with an expected need for dialysis within 6 months were excluded from the study. If the patient required emergent or regular dialysis (peritoneal dialysis or hemodialysis) due to worsening of renal function, the patient was to be kept in the study, whenever possible, until the final study visit.

Randomization into Treatment Groups

Anemia Correction Studies

In BA16736 and BA16738, randomization numbers were allocated sequentially in the order in which the patients were enrolled. In BA16736, patients were randomized 3:1 (Mircera vs reference agent). In BA16738, the patients were randomized in equal ratio (Mircera vs reference agent). Randomization was stratified geographical region.

At week 25 in BA16736 or at week 29 in BA16738, the responders in the Mircera group (patients who reach the target hemoglobin at least once during the anemia correction period) were randomly assigned again (central randomization center) into a long-term safety follow-up regimen (Mircera Q2W or Mircera Q4W). Non-responders in the Mircera group were withdrawn from the study. Non-responders in the reference group were withdrawn in BA16738.

Hemoglobin Maintenance Studies

In BA16739, BA16740, BA17283 and BA17284, patients were randomized concurrently into their treatment groups. In BA16739 and BA16740, patients were randomized 1:1:1 (Mircera Q4W, Mircera Q2W, and reference treatment). In BA17283 and BA17284, patients were randomized in equal ratio (Mircera vs reference agent). Randomization was stratified by geographical region (US vs non-US) and injection route (IV vs SC) when appropriate.

Study Medication

Results of the phase 2 anemia correction studies (BA16260 and BA16528) determined that a starting dose of 0.3 ug/kg/wk SC provided an adequate clinical response without identifiable safety concerns. Since no schedule effect (QW, Q2W, or Q3W) was observed in the phase 2 studies, a starting dose of 0.3 ug/kg/wk was selected for BA16738, to be administered as 0.6 ug/kg/2-wk SC. The higher exposure expected with IV injection (than with SC injection) suggested that a lower IV dose (than SC dose) may be appropriate. A conservative approach was taken for BA16736 with a starting dose of 0.2 ug/kg/wk, administered as 0.4 ug/kg/2-wk IV.

Dosing regimens in the phase 3 hemoglobin maintenance studies (BA16739, BA16740, BA17283, and BA17284) were based on the results from the phase 2 hemoglobin maintenance studies (BA16285, IV injection; BA16286, SC injection). An analysis comparing epoetin treatment at study entry to the Mircera dose administered at week 28 (or the last available dose before this time) was performed to develop a simplified dosing regimen for initiating Mircera treatment when converting from a previous erythropoietin. Dose conversion ratios for the phase 3 studies in hemoglobin maintenance are shown in **Table 3**.

Table 3: Dose Conversion for Hemoglobin Maintenance

Previous weekly epoetin dose	RO0503821 1x/2 weeks dose	RO0503821 1x/4 weeks dose
< 8000 IU/week	60 µg	120 µg
8000-16000 IU/week	100 µg	200 µg
> 16000 IU/week	180 µg	360 µg
Previous weekly darbepoetin alfa dose	RO0503821 1x/2 weeks dose	
< 40 µg/week	60 µg	
40-80 µg/week	100 µg	
> 80 µg/week	180 µg	

Drug Administration

The clinical development program included studies comparing Mircera with darbepoetin alfa, epoetin alfa, and epoetin beta. The studies examined both IV and SC routes of administration, treatment intervals ranging from QW to Q4W, and the safety and effectiveness of using prefilled syringes to deliver Mircera.

SC injections were administered in the arm, thigh or abdomen; once an injection site was chosen, the same site had to be used throughout treatment unless two injections were necessary for the total dose to be administered. In this case, the second injection was given at a site opposite to the first injection site. The reference medications were administered according to label specifications.

Dose Adjustment

Dose adjustment guidelines differed slightly between studies due primarily to differences in study populations, doses, and dosing regimens. However, the purpose of the adjustments was similar in all studies: preventing an excessive ROR in hemoglobin, and maintaining stable and safe hemoglobins. This section provides general information on the dose adjustment guidelines for Mircera that were followed during the studies in this program.

Dose Adjustments in Anemia Correction

In BA16260 and BA16528 (phase 2), investigators were encouraged to maintain patients on the assigned dose of Mircera for as long as possible to allow a determination of the effect of that dose level of Mircera on hemoglobins. After week 6, the changes in hemoglobins relative to baseline were calculated for each patient, and the dose of Mircera could be adjusted based on the following criteria: changes in mean hemoglobin < 0.7 g/dL/6-wk required a dose increase of 25% to 50% (BA16528) or 200% (BA16260), and changes in mean hemoglobin of > 2.0 g/dL/6-wk required a dose decrease of 50% (unless safety limits applied). Dose adjustments for safety reasons were allowed at any time during the studies. The dose of Mircera was to be:

- Decreased by 50%, if hemoglobins exceeded 13 g/dL
- Held, if hemoglobins exceeded 14.0 g/dL until hemoglobin < 13 g/dL was reached
- Doubled, if hemoglobins fell below the initial value and below 9.0 g/dL
- Decreased by 50%, if hemoglobins increased by > 0.5 g/dL (BA16528)
- Decreased by 50%, if the hemoglobin increased by > 2.5 g/dL (BA16260) over 4 weeks

In the phase 3 BA16736 and BA16738, a dose adjustment could be made Q4W in case of inadequate hemoglobin response to Mircera during the anemia correction period (BA16736) or anemia correction/evaluation period (BA16738). Target hemoglobin during these periods was defined as a hemoglobin > 11.0 g/dL and an increase in hemoglobin from baseline > 1.0 g/dL. The following dose adjustments for Mircera were to be performed during the anemia correction period of BA16736 and until response in BA16738. If the hemoglobin:

- Increased < 1 g/dL in 4 weeks, the dose was to be increased by 50%
- Increased above 13.0 g/dL, the dose was to be decreased by 50%
- Increased by > 2.0 g/dL in a 4-week period, the dose was to be decreased by 50%
- Exceeded 14.0 g/dL, interrupt treatment until hemoglobin fell below 13.0 g/dL
- Decreased below the initial value and below 9.0 g/dL, the dose was to be doubled

Hemoglobin determinations had to be confirmed before dosing adjustments were made (i.e., values had to be seen in 2 consecutive assessments). After achievement of response (in BA16736) and during the extension period (both studies), hemoglobins were to be maintained within a range of 11.0 g/dL to 13 g/dL. Dose adjustments for safety reasons were allowed at any time during the studies.

Dose Adjustments in Hemoglobin Maintenance

In BA16285 and BA16286 (phase 2), investigators were encouraged to maintain patients on the assigned dose of Mircera for as long as possible to allow a determination of the effect of Mircera on hemoglobins. After week 6, the change in hemoglobin relative to baseline was determined, and the dose of Mircera could be adjusted based on the individual study criteria. If a patient's hemoglobins decreased by > 1.5 g/dL over baseline, the dose was to be increased by 25%. If a patient's hemoglobins increased by > 1.5 g/dL over baseline, the dose was to be decreased by 50%. Dose adjustments for safety reasons were allowed at any time during the studies. The dose of Mircera was to be:

- Doubled, if hemoglobin < 9.0 g/dL or decrease > 2.5 g/dL over baseline
- Held for hemoglobin > 14.0 g/dL (resume at half previous dose when hemoglobin < 13 g/dL)
- Held for increase > 2.5 g/dL above baseline (resume at half previous dose when < 1.5 g/dL)

In BA16739, BA16740, BA17283, and BA17284 (phase 3), the dose of Mircera was adjusted to maintain the individual patient's hemoglobin within a target range of ± 1.0 g/dL of their baseline hemoglobin and between 10 and 13.5 g/dL throughout the dose titration/evaluation period. Dose adjustments were not to be performed more frequently than Q4W. Hemoglobin determinations had to be confirmed before dosing adjustments were made (two consecutive values).

- Mircera dose was to be reduced:
 - 25% if hemoglobin increased by > 1 g/dL over baseline, or was > 13.5 g/dL and = 14g/dL
 - 50% if hemoglobin increased by > 2.0 g/dL over baseline
- Mircera dose was to be increased:
 - 25% for hemoglobin decrease > 1.0 g/dL from baseline, or if between > 9.0 and < 10.0 g/dL
 - 50% if hemoglobin decreased by > 2.0 g/dL over baseline, or if hemoglobin is < 9.0 g/dL
- Mircera dose was to be held for hemoglobin > 14.0 g/dL (until < 13.0 g/dL).

During the long-term safety observation period in BA16739, BA16740, and BA17283, the dose of Mircera was adjusted to maintain the hemoglobin within a range of 11.0 to 13.0 g/dL. Hemoglobins above 14.0 g/dL, below 9.0 g/dL or changes of more than 2.0 g/dL compared to baseline were avoided for safety reasons. Dose adjustments for safety reasons were allowed at any time during all the studies.

Previous and Concomitant Medications

Allowed and disallowed concomitant therapies were similar among the 10 studies discussed in this summary.

- All medications and treatments for anemia associated with CRF and any concomitant diseases were permitted during the studies, with the exception of erythropoietin-related compounds (other than the reference groups specified in the phase 3 studies).

- Use of investigational drugs was not permitted during any of the studies. The phase 3 studies (BA16736, BA16738, BA16739, BA16740, BA17283, and BA17284) also required that participation in studies testing devices was reported to the investigator and approved.
- The studies either disallowed treatment (BA16260 and BA16528) or suggested avoiding intermittent treatment (all other studies) with androgens, immunosuppressants, angiotensin-converting-enzyme inhibitors, and angiotensin II receptor antagonists due to the possible effect of these medications on anemia. Intermittent treatment with one or more of these drugs could have resulted in increased variability in hemoglobin response, making the study results difficult to interpret. However, if in the phase 3 studies (BA16736, BA16738, BA16739, BA16740, BA17283, and BA17284), drugs that are highly bound to RBC were given, blood levels of drugs were to be monitored during the studies and their dosage adjusted as hemoglobins increased. Study BA16738 differed from the other studies in that the use of corticosteroids for chronic conditions as well as cyclosporine and monoclonal/polyclonal antibodies were permitted.

Iron Supplementation

Iron deficiency may cause a reduced response to erythropoietin. Moreover, erythropoiesis induced by treatment with Mircera may lead to a depletion of iron stores. Therefore, most patients received iron supplementation, in accordance with their individual study protocols:

- In BA16260, BA16285, and BA16286, all patients were to receive supplemental iron during the "run-in" and treatment periods. Patients with ferritin concentrations or TSAT values that did not meet the inclusion criteria at the end of the first "run-in" period were given iron according to center practice prior to the second "run-in" period (one week after last iron dose).
- In BA16528, patients with ferritin concentrations or TSAT values that did not meet the inclusion criteria at the end of the first "run-in" period were given iron according to center practice before entering the second "run-in" period. Supplemental iron was to be given during the entire treatment period according to center practice. If on-going at the start of the study, iron therapy was not interrupted during the "run-in" and treatment periods, unless serum ferritin > 800 µg/L or TSAT > 50% (hypochromic red cells < 2.5%). IV iron was not given if serum ferritin > 800 µg/L or TSAT > 50% (or hypochromic red cells < 2.5%).
- In BA16736, IV iron was given during the entire study period (screening, anemia correction, extension periods) according to center practice. If iron treatment was on-going at the start of the study, it was not to be interrupted.
- In BA16738, supplemental iron was given according to center practice, to correct iron deficiency during the screening period and during all treatment periods, whenever serum ferritin was < 100 µg/L or TSAT < 20% (or hypochromic RBC > 10%).
- In BA16739, BA16740, BA16283, and BA16284, iron supplementation was initiated or intensified in case of iron deficiency during the study. Iron supplementation was performed according to individual center practice.
- In all six phase 3 studies (BA16736, BA16738, BA16739, BA16740, BA16283, BA16284), in order to avoid iron toxicity, iron supplementation was temporarily held in patients with serum ferritin > 800 µg/L or TSAT > 50% until serum ferritin > 800 µg/L and TSAT > 50%.

Red Blood Cell Transfusion

Red blood cell transfusions were allowed in case of medical need, i.e., marked anemic symptoms (e.g., angina pectoris) or a hemoglobin below 8.0 g/dL. Every reasonable effort was made to avoid blood transfusions in patients with hemoglobins above 8.0 g/dL.

All RBC transfusions administered during the studies were documented (i.e., specified by type, number of units transfused, and total volume transfused). The pretransfusion hemoglobin was measured before each RBC transfusion and recorded.

Subject Selection

The phase 2 and 3 studies enrolled a combined total of 2748 patients at 369 centers world-wide. The subject selection criteria were generally similar among the studies; small differences were due primarily to the differences in clinical setting (anemia correction vs hemoglobin maintenance), development phase and study objective (phase 2 vs phase 3), and stage of CRF (dialysis vs non-dialysis).

Inclusion Criteria

The major inclusion criteria were similar for the phase 2 and phase 3 studies. All studies involved adults 18 years of age or older with anemia associated with CRF. Of primary interest was the baseline hemoglobin and iron status at study entry. These baseline criteria were based on recommendations in National Kidney Foundation Kidney Disease Outcomes Quality Initiative (NKF-KDOQI). The phase 3 criteria were defined to reflect the overall treatment population.

- Hemoglobin:

- BA16736, BA16738: These anemia correction studies required a mean screening (baseline) hemoglobin between 8 and 11 g/dL.
- BA16739, BA16740, BA17283, BA17284: These hemoglobin maintenance studies required a mean baseline hemoglobin between 10.5 to 13 g/dL. The hemoglobin had to be stable, defined as an absolute difference within 1.0 g/dL from weeks -4 and -3 to weeks -2 and -1.

- Iron status:

- The anemia correction studies (BA16736 and BA16738) required mean screening/baseline serum ferritin levels = 100 µg/L or TSAT = 20% (or hypochromic red cells < 10%).
- The hemoglobin maintenance studies (BA16739, BA16740, BA17283, and BA17284) required mean screening/baseline serum ferritin levels = 100 µg/L or TSAT = 20% (or hypochromic red cells < 10%), assessed at week -3.

Exclusion Criteria

- The following exclusion criteria were common to the phase 3 studies:
 - Overt gastrointestinal bleeding or any other bleeding episode necessitating transfusion within 8 weeks (phase 3 studies) before screening
 - RBC transfusions within 3 months before screening or anticipated need for RBC transfusions within 8 weeks before screening or during the screening baseline period; hemoglobinopathies (e.g., homozygous sickle-cell disease, thalassemia of all types); hemolysis

- Active malignant disease (except non-melanoma skin cancer); life expectancy less than 12 months; chronic, uncontrolled or symptomatic inflammatory disease, e.g., rheumatoid arthritis, systemic lupus erythematosus; acute infection
- High likelihood of early withdrawal or interruption of the study (e.g., myocardial infarction, severe or unstable coronary artery disease, stroke, severe liver disease) within 12 weeks (phase 3 studies) before screening
- Planned elective surgery during the study period. BA16736 allowed fistula surgery, and BA16738 specified exclusion for surgery planned over the next 7 months
- Pregnancy or breast-feeding; women of childbearing potential without effective contraception; administration of another investigational drug within 4 weeks before screening or planned during the study period
- Known hypersensitivity to recombinant human erythropoietin, polyethylene glycol or to any constituent of the study or reference drug formulations
- B₁₂ or folate deficiency; uncontrolled symptomatic secondary hyperparathyroidism; platelets > 500 x 10⁹/L; poorly controlled hypertension
- Additional study-specific exclusion criteria related to the study design (anemia correction or hemoglobin maintenance):
 - Previous treatment with erythropoietin within 12 weeks (anemia correction studies, BA16736 and BA16738)
 - Failing renal graft (anemia correction, BA16736 and BA16738); advanced stage CRF, dialysis, and rapid progression of CRF (BA16738, patients not on dialysis)
 - CRP > 15 (anemia correction, patients not on dialysis, BA16738); CRP > 30 mg/L (dialysis patients, BA16736, BA16739, BA16740, BA17283, and BA17284)
 - Temporary dialysis access catheter (dialysis patients, BA16736, BA16739, BA16740, BA17283, and BA17284)
 - Noncompliance with dialysis; need for dialysis within the next 6 months (patients not on dialysis, BA16738)
 - Pure red cell aplasia; chronic congestive heart failure, New York Heart Association Class IV; previous treatment with Mircera; immunosuppressive therapy in the 12 weeks before screening (BA16738)

Criteria for Withdrawal and Replacement of Patients

In case of a patient withdrawing from treatment, a complete final evaluation was to be made with an explanation of why the patient was withdrawing from the study. If the reason for withdrawal was an AE or an abnormal laboratory test result, the specific event or laboratory test was to be recorded.

Patients prematurely discontinued from the studies for any reason were not replaced in phase 3 studies. In these studies, it was necessary to have a sufficient number of patients with data at week 6 so that the optimal starting dose of Mircera could be determined for groups 2 and 3; therefore, a provision was made to replace patients who withdrew from treatment during the first 6 weeks for reasons that were not study-related.