

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

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STATISTICAL REVIEW(S)



U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Pharmacoepidemiology and Statistical Science
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION MEMORANDUM

NDA/Serial Number: BB 125164/0

Drug Name: Mircera® (Pegserepoetin alfa)

Indication(s): Anemia due to Chronic Kidney Disease

Applicant: Hoffman La-Roche Inc.

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During the first circle review of Mircera, it was recommended that the clinical studies, which were documented in the original BLA submission, provided with statistical supports for the efficacy claim in hemoglobin correction and maintenance. There are no additional statistical issues to review during the second cycle review.



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CLINICAL STUDIES

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1. EXECUTIVE SUMMARY

BLA 125164/0 is the original submission for new drug application in efficacy of pegserepoetin alfa (Mircera) in the treatment of patients with anemia due to chronic kidney disease. The sponsor proposed that Mircera administered intravenously or subcutaneously is effective in the correction of anemia in patients with chronic kidney disease on dialysis or not on dialysis that are not currently treated with an erythropoiesis stimulating agent (ESA). The results from two Phase III anemia correction studies were included in this submission for review. In addition, the sponsor also submitted the results from four Phase III pivotal trials to claim that Mircera can be effectively used with a less intensive dosing regimen in maintaining control of anemia in patients with chronic kidney disease who are currently treated with an ESA.

1.1 Conclusions and Recommendations

Based on the efficacy results presented by the sponsor and this reviewer's statistical evaluation, BLA Submission 125164/0 has presented the non-inferiority in efficacy of using Mircera both in correction and maintenance of hemoglobin level of anemic patients with chronic kidney disease (CKD) compared to reference. Two Phase III studies provided statistical support for the efficacy claim in hemoglobin correction and four Phase III studies provided statistical support for the efficacy claim in hemoglobin maintenance. However, the efficacy of this product has to be evaluated in the light of considerable safety concerns, and whether it is an appropriate usage will be a clinical decision.

1.2 Brief Overview of Clinical Studies

The BLA submission includes six of Phase III pivotal studies: Two studies for correction of anemia and four studies for maintaining control of anemia. All of the six studies were randomized, open-label, titrated trials. In this report, reviewing correction studies and reviewing maintenance studies are presented separately in all sections.

1.2.1 Brief overview of the two correction studies

Study BA16736 was an open-label, randomized, multicenter study with a non-comparative reference group (epoetin alfa/beta). A total of 181 subjects were recruited from 42 centers in Europe, Canada, USA, Brazil, Thailand, and South Africa. Among those 181 on-dialysis subjects, 135 and 46 (3:1 ratio) were randomized into Mircera and epoetin alfa/beta groups, respectively. The primary efficacy endpoint was hemoglobin response rate during the first 24 weeks. The hemoglobin response was defined as an increase in hemoglobin (Hb) ≥ 1.0 g/dL from baseline and a Hb concentration ≥ 11.0 g/dL without red blood transfusion (RBC). The study was conducted from March 29, 2004 to September 23, 2005.

Study BA16738 was an open-label, randomized, multicenter study with a comparative reference group (darbepoetin alfa). A total of 324 subjects were recruited from 82

centers in Europe, USA, Canada and Australia. Each of Mircera and darbepoetin alfa groups enrolled 162 non-dialysis subjects during the study time from June 23, 2004 to September 23, 2005. The two primary efficacy endpoints were hemoglobin response during the first 28 weeks and the change in hemoglobin concentration between baseline and evaluation periods. The hemoglobin response was defined as an increase in Hb \geq 1.0 g/dL from baseline and a Hb concentration \geq 11.0 g/dL without red blood transfusion (RBC).

1.2.2 Brief overview of the four maintenance studies

Study BA16739 was an open-label, randomized, multicenter, non-inferiority study (IV administration, 1x/2 weeks and 1x/4 weeks in dialysis patients, versus epoetin alfa/beta 1-3x/week). A total of 673 subjects were enrolled from 91 centers in USA, European and Canada. Subjects of the two Mircera arms were administered IV 1x2 weeks and 1x4 weeks, respectively. The study was conducted during February 25, 2004 to August 17, 2005. The primary efficacy endpoint was the change hemoglobin concentration between baseline and evaluation periods.

Study BA16740 was an open-label, randomized, multicenter, non-inferiority study (SC administration, 1x/2 weeks and 1x/4 weeks in dialysis patients, versus epoetin alfa/beta 1-3x/week). A total of 572 subjects were enrolled from 89 centers in USA, European, Thailand, South Africa, Brazil, Taiwan, New Zealand and Panama. Subjects of the two Mircera arms were administered SC 1x2 weeks and 1x4 weeks, respectively. The study was conducted during March 3, 2004 to September 23, 2005. The primary efficacy endpoint was the change hemoglobin concentration between baseline and evaluation periods.

Study BA17283 was an open-label, randomized, multicenter, non-inferiority study (IV administration, 1x/2 weeks in dialysis patients, vs. darbepoetin alfa 1x/week or 1x/2 weeks). A total of 313 subjects were enrolled from 91 centers in USA, European and Canada. Subjects of Mircera arm were administered IV once every 2 weeks to compare with subjects of darbepoetin alfa arm. The study was conducted during March 10, 2004 to August 31, 2005. The primary efficacy endpoint was the change hemoglobin concentration between baseline and evaluation periods.

Study BA17284 was an open-label, randomized, multicenter, non-inferiority study (SC/IV administration with pre-filled syringed, 1x/2 weeks in dialysis patients, versus epoetin alfa/beta 1-3x/week). A total of 363 subjects were enrolled from 62 centers in USA, European, Canada, Thailand and Taiwan. Subjects of the two Mircera arms were administered IV 1x2 weeks and 1x4 weeks, respectively. The study was conducted during February 25, 2004 to August 17, 2005. The primary efficacy endpoint was the change hemoglobin concentration between baseline and evaluation periods.

Tables 1 and 2, which are adapted from sponsor's submission, present the summaries of key design features of the two Phase III correction studies and the four Phase III maintenance studies.

Table 1. Summary of Key Design Features of the Two Phase III Correction Studies

Study No. Status Trial Dates	Population	Study Design And Duration	No. of Centers and Locations	Primary Objectives	Treatment Regimen Dose / Route of Admin.	No. of Pts. per Treatment Group	Primary Parameters
Phase III Correction Studies							
BA16736 complete Mar 29, 2004 to Sept 23, 2005	Anemia associated with CKD / HD or PD / not treated with epoetin	Open-label, randomized, multicenter, with a non-comparative reference group 54 wks; 2-wk screen, 24-wk correct, 28-wk ext.	42 centers (Europe, Canada, USA, Brazil, Thailand, S. Africa, Brazil)	To demonstrate the efficacy of IV RO0503821 treatment for correction of anemia in patients with stage 5 CKD who were on dialysis and were not treated with epoetin.	RO0503821 0.4 µg/kg IV 1x/2 wks (correction period) RO0503821 IV 1x/2 wks or 1x/4 wks (extension period) Epoetin alfa or beta dose per label 3x/wk (correction and extension periods)	Planned: 168 126 RO0503821 42 Epoetin alfa / beta Actual: 181 135 RO0503821 46 Epoetin alfa / beta	Hb response rate* during the first 24 weeks
BA16738 complete Jun 23, 2004 to Sept 23, 2005	Anemia associated with CKD / not on dialysis/ not treated with epoetin	Open-label, randomized, parallel-group, multicenter, comparative active-controlled 54 wks; 2-wk screen, 18-wk correct, 10-wk eval, 24-wk ext.	82 centers (Europe, USA, Canada, Australia)	To demonstrate the efficacy of RO0503821 treatment administered SC 1x/2 weeks for correction of anemia in patients with stage 3 or 4 CKD who were not on dialysis and were not treated with epoetin	RO0503821 0.6 µg/kg SC 1x/2 weeks (correction and evaluation period) RO0503821 SC 1x/2 wks or 1x/4 wks (extension period) Darbepoetin alfa SC 1x/wk or 1x/2 wks per label (correction, evaluation, and extension periods)	Planned: 264 132 / arm Actual: 324 162 RO0503821 162 darbepoetin alfa	Hb response rate during the first 28 weeks, and the change in Hb concentration between the baseline and evaluation periods

* Response was defined as an increase in Hb \geq 1.0 g/dL from baseline and Hb \geq 11 g/dL without RBC transfusion

Table 2 Summary of Key Design Features of the Four Phase III Maintenance Studies

Study No. Status Trial Dates	Population	Study Design And Duration	No. of Centers and Locations	Primary Objectives	Treatment Regimen / Dose / Route of Admin.	No. of Pts. per Treatment Group	Primary Parameters
Phase III Maintenance Studies							
BA16739 complete Feb 25, 2004 to Aug 17, 2005	Anemia associated with CKD / on dialysis / IV epoetin maintenance treatment	Open-label, randomized, controlled, multicenter, parallel-group, non-inferiority study	91 centers (USA, Europe, Canada)	Demonstrate that RO0503821 administered IV maintains Hb concentrations in dialysis patients on prior IV epoetin maintenance treatment for anemia associated with CKD	RO0503821 60-180 µg IV 1x/2 wks RO0503821 120- 360 µg IV 1x/4 wks Epoetin alfa or beta per label 1 to 3x/wk 52 weeks of treatment	Planned: 465 155 / grp Actual: 673 223 RO0503821 1x/2wk 224 RO0503821 1x/4wk 226 epoetin	The change in Hb, concentrations between baseline and evaluation periods
BA16740 complete Mar 03, 2004 to Sep 23, 2005	Anemia associated with CKD / on dialysis / SC epoetin maintenance treatment	Open-label, randomized, controlled, multicenter, parallel-group, non-inferiority study	89 centers (Europe, USA, Thailand, S. Africa, Brazil, Taiwan, Mexico, New Zealand, Panama)	Demonstrate that RO0503821 administered SC maintains Hb concentrations in dialysis patients on prior SC epoetin maintenance treatment for anemia associated with CKD	RO0503821 60-180 µg SC 1x/2 weeks RO0503821 120- 360 µg SC 1x/4 weeks Epoetin alfa or beta per label 1 to 3x/wk 52 weeks of treatment	Planned: 465 155 / grp Actual: 572 190 RO0503821 1x/2wk 191 RO0503821 1x/4wk 191 epoetin	The change in Hb concentrations between baseline and evaluation periods

Table 2 Summary of Key Design Features of the Four Phase III Maintenance Studies (continued)

Study No. Status Trial Dates	Population	Study Design And Duration	No. of Centers and Locations	Primary Objectives	Treatment Regimen / Dose / Route of Admin.	No. of Pts. per Treatment Group	Primary Parameters
Phase III Maintenance Studies (continued)							
BA17283 complete Mar 10, 2004 to Aug 31, 2005	Anemia associated with CKD / on dialysis / IV darbepoetin alfa maintenance treatment	Open-label, randomized, multicenter, parallel-group, non-inferiority study 57 Wks; 4-wk screen 28-wk titration 8-wk eval, 16-wk SFU	48 centers (Europe Australia, and Canada)	Demonstrate that RO0503821 administered IV maintains Hb concentrations in dialysis patients on prior IV darbepoetin α maintenance treatment for anemia associated with CKD	RO0503821 60 – 180 μ g IV 1x/2 wks Darbepoetin alfa per label 1x/wk or 1x/2 wks	Planned: 264 132 RO0503821 132 darbepoetin alfa Actual: 313 157 RO0503821 156 darbepoetin alfa	The change in Hb concentrations between baseline and evaluation periods
BA17284 complete Aug 4, 2004 to Sept 22, 2005	Anemia associated with CKD / on dialysis / SC or IV epoetin maintenance treatment	Open-label, randomized, multicenter, parallel-group, non-inferiority study 41 Wks; 4-wk screen 28-wk titration 8-wk eval, SFU visit	62 centers (USA, Europe, Canada, Thailand, Taiwan)	Demonstrate that RO0503821 administered with prefilled syringes maintains Hb concentrations in dialysis patients on prior IV or SC epoetin maintenance treatment for anemia associated with CKD	RO0503821 60 – 180 μ g IV or SC 1x/2 weeks in prefilled syringes Epoetin alfa or beta dose per label 1 to 3x/weeks	Planned: 264 132 RO0503821 132 epoetin alfa or beta Actual: 336 168 RO0503821 168 epoetin alfa or beta	The change in Hb concentrations between baseline and evaluation periods

1.3 Statistical Issues and Findings

1. In BA16736 and BA16738, the hemoglobin response was the primary efficacy endpoint, which was defined as an increase in Hb ≥ 1.0 g/dL from baseline and ever reached a Hb measure ≥ 11.0 g/dL during the correction and evaluation periods. The alternative hypothesis for testing was H_1 : Hb response rate (r) $> 60\%$. Regardless of whether $r > 60\%$ was clinically meaningful or not, the efficacy results of Hb response rates for all Mircera and reference groups in the two studies were at least 93% (see Table 5). In Per-Protocol and eligible analysis populations, hemoglobin response rates were also retained above 93%, which were consistent with the results based on the ITT population.
2. Sustaining hemoglobin level during the correction and evaluation periods can be problematic after Hb measure reached 11.0 g/dL, one of the Hb response criteria. Figure 1 shows that the median hemoglobin over time in BA16736 were consistently higher than 11.0 g/dL after Week 10. Also, Figure 2 shows that the median Hb levels in BA16378 were higher than 11.0 g/dL during the evaluation period. The two figures suggest the sustaining hemoglobin level during the correction/evaluation periods.
3. The primary efficacy analyses for the four maintenance studies were based on the per-protocol population. Additional analyses were performed for the primary efficacy endpoint using the intent-to-treat, eligible and observation complete populations in order to assess the robustness of the results from per-protocol analysis. The primary efficacy results for all the four maintenance studies using different analysis populations were consistent and similar (see Table 12).

However, more attentions should be paid to the study design of the four maintenance studies. As mentioned, those four studies were open-label, non-inferiority trials. The 24-week titration period was followed by the 8-week evaluation period. It was assumed that Hb would become stabilized after 24-week dose titration. The primary efficacy measure was Hb change from baseline to the evaluation period. In fact, the dose titration still occurred during the evaluation period, which might allow the non-inferiority of treatment efficacy to be easily achieved under an open-label condition.

Many published articles have concluded that a higher hemoglobin level may increase the risk of death and hospitalization for congestive heart failure (Singh et al, 2006) and treating with EPO products decreases the overall survival (e.g., Wright et al, 2006; Henke et al, 2003). The safety of treating CKD patients with an approved ESA has a high profile currently. The non-inferiority, open-label study design with a primary efficacy endpoint without taking safety considerations into account may not be an ideal study design for a pivotal trial.

4. A significantly greater incidence of sudden deaths with Mircera than with reference was initially a major review concern when the extension data had not been submitted to the Agency. There were 9 cases of sudden death in Mircera patients and none in reference ($p= 0.0287$). All studies terminated at 52 weeks and after 52 weeks,

subjects were allowed to enroll in a long-term extension. Approximately half of all the patients enrolled in the long-term extension. When all long-term extension data included, sudden deaths incidence were 14 and 5 cases in Mircera and reference patients, respectively (p= 0.4431). However, the sudden death was not clearly defined and all studies were open-label trials. Table 3 shows the incidence of sudden death based on pooled data of all Phase II and III studies.

Table 3. Sudden Deaths in Mircera Phase II/III Studies

	Pooled Phase 2/3 Studies		With Extension of Follow-up	
	Mircera n = 1789	Reference n = 948	Mircera n = 1789	Reference n = 948
Sudden deaths	9 (0.5%)	0 (0.0%)	14 (0.8%)	5 (0.5%)

- An increased C-Reactive Protein (CRP) level has been importantly correlated with increased risk for cardiovascular events. The Agency requested the sponsor to perform CRP-related analyses that may help assess the extent to which CRP screening may have importantly limited the enrollment of patients into the clinical studies. Those analyses included (a) a logistic regression analysis to compare the treatment groups for a composite adverse event outcome, (b) the analysis described above repeated using each of the 5 components of the composite endpoint as 5 separate endpoints: hospitalization due to any SAEs, death, CHF hospitalization, non-fatal MI and non-fatal stroke, (3) the logistic analyses described above repeated with the input variable of baseline CRP changed to maximal CRP during the study and to AUC0CRP, respectively, (4) a survival analysis with time to event as the outcome variable for the composite events and the five component events separately, and (5) linear regression analysis, explore the potential relationship between the change in CRP and treatment.

Those analysis results suggested (1) Baseline CRP showed a significant effect on multiple composite cardiovascular toxicity endpoints as well as the components of the composites, including death, (2) no significant treatment by CRP interaction, and (3) Kaplan-Meier survival analyses generally confirmed the impact of baseline CRP > 10 mg/L on composite endpoints and on individual endpoints.

2. INTRODUCTION

2.1 Overview

Pegserepoetin alfa (Mircera) is a clinically synthesized continuous erythropoietin receptor activator, for the treatment of anemia in patients with chronic kidney disease. The current treatment options for anemic patients include epoetin alfa/beta and darbepoetin alfa. Either epoetin alfa/beta or darbepoetin alfa require frequent administration, from three times per week to once every 2 weeks.

Mircera shows a different activity at the receptor level characterized by a slower association to and faster activity from the receptor in correcting anemia and in maintenance the hemoglobin in patients with CKD on dialysis or not on dialysis.

The sponsor claims the efficacy and safety of Mircera administered intravenously or subcutaneously in the correction of anemia in patients with CKD who are on dialysis or not on dialysis and who are not on erythropoiesis stimulating agent (ESA) via the results from two Phase III trials. The sponsor also claims the efficacy and safety of Mircera administered to anemic patients who are currently treated with an ESA to maintain hemoglobin with a much less intensive dosing regimen via the results from four Phase III trials.

2.2 Data Sources

The data submitted by the sponsor can be found in CBER EDR under STN# 125164/0 through the link of <[\\cbsap58\M\EDR Submissions\2006 BLA\DCC60002806](#)>. The data files were well organized by study and variables of each file were clearly defined within each study. Data files can be found in the folder with the path of [\\cbsap58\M\EDR Submission\2006 BLA \DCC60002806\blamain\clinstat](#) and SAS programs can be found in the folder of [\DCC60002806\blamain\stats](#). Study reports of all Phase III studies are located in the folder of [\DCC60002806\blamain\clinstat\renalanmemia](#).

3. STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

This section includes two parts: Evaluation of efficacy for correction studies (3.1.1) and evaluation of efficacy for maintenance studies (3.1.2). Each part consists of study design, definition of efficacy endpoints, analysis populations, sample size estimation, patient population, statistical methodology and results. The part for correction studies covers BA16373 and BA16378, and the part for maintenance studies covers BA16379, BA16740, 17283 and 17284.

3.1.1 Correction studies: BA16736 and BA16738

3.1.1.1 Study Design and Efficacy Endpoints: BA16736 and BA16738

BA16736 was a randomized, open-label, multi-center, parallel-group study that consisted of a correction period of 24-weeks, followed by an extension period of up to 28 weeks. The patients were screened for eligibility during a 2-week period. Eligible patients were randomized in a 3:1 ratio either to receive IV Mircera 0.4 µg/kg every 2 weeks or to receive IV epoetin 3 times every week.

The primary efficacy endpoint in this study was the hemoglobin (Hb) response. The assessment of response was based on the weekly Hb measurements and defined as an increase in Hb ≥ 1.0 g/dL from baseline and a single Hb concentration ≥ 11 g/dL, without RBC transfusion before response, during the 24 weeks after first dose. The hypotheses to be tested for the primary efficacy analysis was H_0 : Hb response rate (r) $\leq 60\%$ versus H_1 : $r > 60\%$.

The secondary efficacy endpoints included (1) the Hb values and their changes from baseline over time, (2) the time to Hb response assessed via Kaplan-Meier methods, and (3) the incidence of RBC transfusions during the first 24 weeks post baseline.

BA16738 was a randomized, open-label, multi-center, darbepoetin alfa-controlled, parallel-group study. Patients were screened for eligibility during a 2-week period. After the screening period, eligible patients were randomized in a 1:1 ratio to either receiving Mircera SC once every 2 weeks at a starting dose of 0.6 µg/kg or receiving darbepoetin alfa SC once a week at a starting dose of 0.45 µg/kg. The study consisted of a correction period of 18 weeks and an evaluation period of 10 weeks, followed by an extension period of up to 24 weeks for safety.

The two co-primary efficacy endpoints in BA16738 were (1) the Hb response rate until the end of the evaluation period and (2) the change in Hb concentration (g/dL) between the baseline and evaluation periods.

The hypotheses to be tested for the first primary efficacy analysis, which was the same as those in BA16736, were H_0 : Hb response rate (r) $\leq 60\%$ versus H_1 : $r > 60\%$.

If H_0 for the first primary efficacy analysis was rejected, the second primary endpoint efficacy was tested. The hypotheses to be tested for the secondary primary efficacy endpoint were: H_0 : The mean difference in the second primary endpoint between the Mircera and the reference group is less than -0.75 g/dL versus H_1 : The mean difference in the second primary endpoint between the groups is greater than or equal to -0.75 g/dL

Similar to BA16736, the secondary efficacy endpoints of BA16738 were (1) the Hb values and their changes from baseline over time, (2) the time to Hb response assessed via Kaplan-Meier methods, and (3) the incidence of RBC transfusions during the first 28 weeks.

3.1.1.2 Analysis Populations: BA16736 and BA16738

Several analysis populations were defined in the protocol. The primary efficacy endpoint of hemoglobin response in both studies was analyzed based on the ITT population. In BA16738, the second primary efficacy endpoint of hemoglobin change from baseline to the evaluation period was analyzed based on the Per-Protocol population.

The **Intent-to-Treat (ITT) Population** was defined as all randomized patients. The ITT population was used for all baseline outputs, the primary efficacy analysis for response rate, and the secondary efficacy analyses.

The **Eligible Population** was defined for additional confirmatory analysis of the primary efficacy parameter. The eligible population included all patients randomized who had received at least one dose of trial medication (safety population) with the exception of: (1) Patients who did not fulfill the criterion of stable baseline Hb concentration; (2) Patients with inadequate iron status defined as mean serum ferritin <100 ng/mL and mean TSAT <20% (or mean hypochromic RBCs \geq 10%) during baseline; (3) Patients who do fulfill the exclusion criterion of emoglobinopathies or hemolysis; (4) Patients with RBC transfusions or blood loss during baseline.

The **Per-Protocol (PP) Population** was a subset of the eligible population and consisted of all patients randomized with the exception of: (1) Patients who did not have a stable baseline Hb concentration; (2) Patients with inadequate iron status at baseline or at evaluation; (3) Patients who fulfilled the exclusion criterion of hemoglobinopathies or hemolysis; (4) Patients with RBC transfusions or blood loss during baseline or within weeks 21 to 33; (5) Patients with less than five recorded Hb values during the evaluation period; and (6) Patients with missing administrations of the study drug or reference drug in weeks 26 to 35.

The **Observation Complete Population**: An additional subset of the data was defined. No imputation for missing values was performed and the analyses only included Hb values for those patients with a complete set of observations during the evaluation period.

The **Safety Population** was defined as all patients who had received at least one dose of study medication and a safety follow-up. This population was used for the analysis of all safety parameters.

3.1.1.3 Sample Size Estimation for correction studies

Study BA16736: The sample size estimation was based on the Clopper-Pearson confidence limits. Based on a two-sided 95% Clopper-Pearson confidence interval (CI), at least 126 patients were needed in the Mircera treatment group to demonstrate with > 90% power that the lower limit of the response rate was \geq 60%, assuming the true response rate was \geq 75%. In total, 168 patients were to be randomized into the study in a 3:1 ratio (126 patients in the Mircera group and 42 patients in the epoetin reference group).

Study BA16738: Using the Clopper-Pearson confidence limits for the analysis of response, at least 126 subjects were required in the PO0503821 group to demonstrate with a power of greater than 90% that the response rate is $\geq 60\%$, assuming the true response rate was $\geq 75\%$. For the test of non-inferiority of Mircera versus the darbepoetin alfa group, 132 subjects per group were required. This assumed that a non-inferiority margin of -0.75 g/dL, a power of 90%, $\alpha = 0.05$, a true difference of not more than 0.3 g/dL between two groups, and a rate of 20% of subjects ineligible for the inclusion in the per-protocol population. Therefore, for the analysis of both endpoints, 264 subjects in total were planned to recruit.

3.1.1.4 Patient Population and Demographics: BA16736 and BA16738

BA16736: Patients were recruited at 42 centers in 10 countries. The percentage of patients enrolled in each country was Poland 35.9%, Russia 11.0%, South Africa 11.0%, Brazil 8.8%, Canada 8.8%, Thailand 6.1%, Greece 6.1%, Czech Republic 5.0%, Spain 3.9% and USA 3.3%.

In total, 164 randomized patients who completed the correction period: 124 patients (92%) in the Mircera group and 40 patients (87%) in the epoetin group. During the correction period, 11 patients (8.1%) in the Mircera group and six patients (13.0%) in the epoetin group withdrew from the study prematurely.

The gender, race, age and baseline body weight distributions were similar between Mircera and reference group in each of the two correction studies, respectively (see Table 4). Only 3.3% of subjects in BA16736 were recruited from the only site in the US. The mode of current dialysis for the majority of subjects (98.3%) in BA16736 was hemodialysis. Only 3 subjects (1.7%) of Mircera group were on peritoneal dialysis.

Of the 181 patients randomized, the majority was males (63.0%) and Caucasians (76.8%). Mean age \pm SD were 54.7 ± 14.4 years and 53.4 ± 15.2 years in Mircera and epoetin groups, respectively. Mean body weight was 67.9 ± 14.1 kg and 73.9 ± 15.6 kg in the Mircera and epoetin groups, respectively.

Table 4 provides baseline hemoglobin and ferritin levels for each group. The mean baseline Hb values were 9.39 ± 0.876 g/dL in the Mircera group and 9.40 ± 0.817 g/dL in the epoetin group. The mean baseline Hbs and mean baseline ferritin were similar between Mircera and the reference group, respectively.

BA16738: A total of 324 patients from 82 centers were randomized to receive either Mircera once every 2 weeks (n=162) or darbepoetin alfa once every week (n=162). Among those 298 patients who completed the correction and evaluation period, 145 patients (89.5%) in the Mircera group and 153 patients (94.4%) in the darbepoetin alfa group. The total percentage of patients who were prematurely withdrawn for either safety or non-safety reasons during the correction and evaluation periods was 10% (n=17) in the Mircera treatment group and 6% (n=9) in the darbepoetin alfa treatment group.

Of the 324 patients randomized, the majority was females (Mircera group: 56.8%; darbepoetin alfa group: 50.6%) and Caucasians (69.8% in the Mircera group and 80.9% in the darbepoetin alfa group). Mean age \pm SD were 63.9 ± 14.1 years and 66.9 ± 12.8 years in Mircera and darbepoetin alfa groups, respectively. Mean body weight was 76.8 ± 16.2 kg and 80.5 ± 19.5 kg in the Mircera and darbepoetin alfa groups, respectively.

Mean baseline Hb values were similar in both treatment groups (10.22 ± 0.596 g/dL in the Mircera group and 10.15 ± 0.693 g/dL in the darbepoetin alfa group). Hb values ranged from 8.37 g/dL to 11.05 g/dL in the Mircera treatment group and 7.96 g/dL to 11.35 g/dL in the darbepoetin alfa dose group. There were no major differences in serum iron, ferritin, or transferrin saturation.

Table 4 Baseline Demographics and Characteristics: BA16736 and BA16738 (ITT)

	BA16736		BA16738	
	Mircera (N=135)	Epoetin (N=46)	Mircera (N=162)	Darbepoetin (N=162)
Gender				
Female	53 (39.3%)	14 (30.4%)	92 (54.8%)	82 (50.6%)
Male	82 (60.7%)	32 (69.6%)	70 (43.2%)	80 (49.4%)
Race				
Black	17 (12.6%)	7 (15.2%)	35 (21.6%)	19 (11.7%)
Caucasian	106 (78.5%)	33 (71.7%)	113 (69.8%)	131 (80.9%)
Oriental	8 (5.9%)	3 (6.5%)	7 (4.3%)	9 (5.6%)
Other	4 (3.0%)	3 (6.5%)	7 (4.3%)	3 (1.9%)
Age				
<65	99 (73.3%)	35 (76.1%)	70 (43.2%)	62 (38.3%)
65-75	23 (17.0%)	6 (13.0%)	44 (27.2%)	48 (29.6%)
75+	13 (9.6%)	5 (10.9%)	48 (29.6%)	52 (32.1%)
Mean \pm SD	54.7 \pm 14.4	53.4 \pm 15.2	63.9 \pm 14.1	66.9 \pm 12.8
Median	54.0	54.5	67.0	69.0
Country				
US	4 (3.0%)	2 (4.3%)	57 (35.2%)	58 (35.8%)
Non-US	131 (97.0%)	44 (95.7%)	105 (64.8%)	104 (64.2%)
Body Weight (kg)				
<65	65 (48.1%)	16 (34.8%)	35 (21.6%)	35 (21.6%)
65 - <80	41 (30.4%)	13 (28.3%)	65 (40.1%)	57 (35.2%)
80+	29 (21.5%)	17 (37.0%)	62 (38.3%)	70 (43.2%)
Mean \pm SD	67.9 \pm 14.1	73.9 \pm 15.6	76.8 \pm 16.2	80.5 \pm 19.5
Median	66.0	71.9	74.5	75.8
Mode of Current Dialysis				
Hemodialysis	132 (97.8%)	46 (100.0%)	--	--
Peritoneal dialysis	3 (2.2%)	--	--	--
Not on dialysis	--	--	162 (100.0%)	162 (100.0%)
Baseline Hemoglobin (g/dL)				
Mean \pm SD	9.39 \pm 0.876	9.40 \pm 0.817	10.22 \pm 0.596	10.15 \pm 0.693
Median	9.35	9.28	10.37	10.33
Baseline Ferritin (μg/L)				
Mean \pm SD	479.5 \pm 382.2	426.2 \pm 330.7	214.9 \pm 161.2	240.6 \pm 197.6
Median	376.3	325.8	174.7	185.8

3.1.1.5 Statistical Methodologies: BA16736 and BA16738

The Hb response rate was the primary efficacy endpoint in both studies. The assessment of response was based on the weekly Hb measurements and defined as an increase in Hb ≥ 1.0 g/dL from baseline and a single Hb concentration ≥ 11 g/dL without RBC transfusion before response during the 24 weeks after first dose.

The hypotheses to be tested for the primary efficacy analysis was H_0 : Hb response rate (r) $\leq 60\%$ versus H_1 : $r > 60\%$, using the correspondence between tests and confidence intervals (CI). A two-sided 95% CI based on the exact method of Clopper and Pearson was calculated. If the lower limit was above 60%, H_0 could be rejected with a significance level of 0.025.

In BA16738, the second primary efficacy endpoint was change in Hb concentration (g/dL) between the baseline and evaluation periods. If the null hypothesis for the first primary efficacy endpoint H_0 : Hb response rate (r) $\leq 60\%$ was rejected, then the non-inferiority in change in Hb concentration (g/dL) between the baseline and evaluation periods would be assessed. Analysis of covariance (ANCOVA) was used to compare the Mircera group to the darbepoetin alfa reference group for the second primary efficacy endpoint.

The independent variable in the model was treatment group and the covariates Hb at baseline and geographical region. Two-sided 95% confidence intervals for the difference in mean change in Hb between the baseline and evaluation periods between treatments were calculated. The Mircera group was regarded as non-inferior to the darbepoetin alfa reference group if the lower limit of the two-sided CI was greater than or equal to -0.75 g/dL. A non-inferiority limit of -0.75 g/dL for the difference in mean Hb was chosen since this difference was considered small and not clinically relevant.

The primary objective of the two correction studies was to demonstrate the efficacy of Mircera administered 1x/2 weeks in correcting anemia. The primary analysis of response rate and all secondary efficacy variables were based on the ITT population. For the non-inferiority comparison of the Mircera treatment group versus the darbepoetin alfa reference group (change in Hb) in BA16738, the efficacy analysis was based on the per-protocol (PP) population using all patients randomized without a major protocol violation. Additional PP analyses were conducted for the response rate and time to Hb response. Similarly, the non-inferiority comparison was also performed using the ITT, eligible and observed completion populations to test the robustness of analysis results based on the PP population.

3.1.1.6 Results and Conclusions: BA16736 and BA16738

Primary efficacy results of Hemoglobin Response: Based on the ITT population, the hemoglobin response rates were 93.3% (95% CI: 87.7%, 96.9%) and 91.3% (95% CI: 79.2%, 97.6%) for Mircera and epoetin groups, respective, in BA16736. Similarly, the hemoglobin response rates were 97.5% (95% CI: 93.8%, 99.3%) and 96.3% (95% CI: 92.1%, 98.6%) for Mircera and Darbepoetin alfa groups, respective, in BA16738.

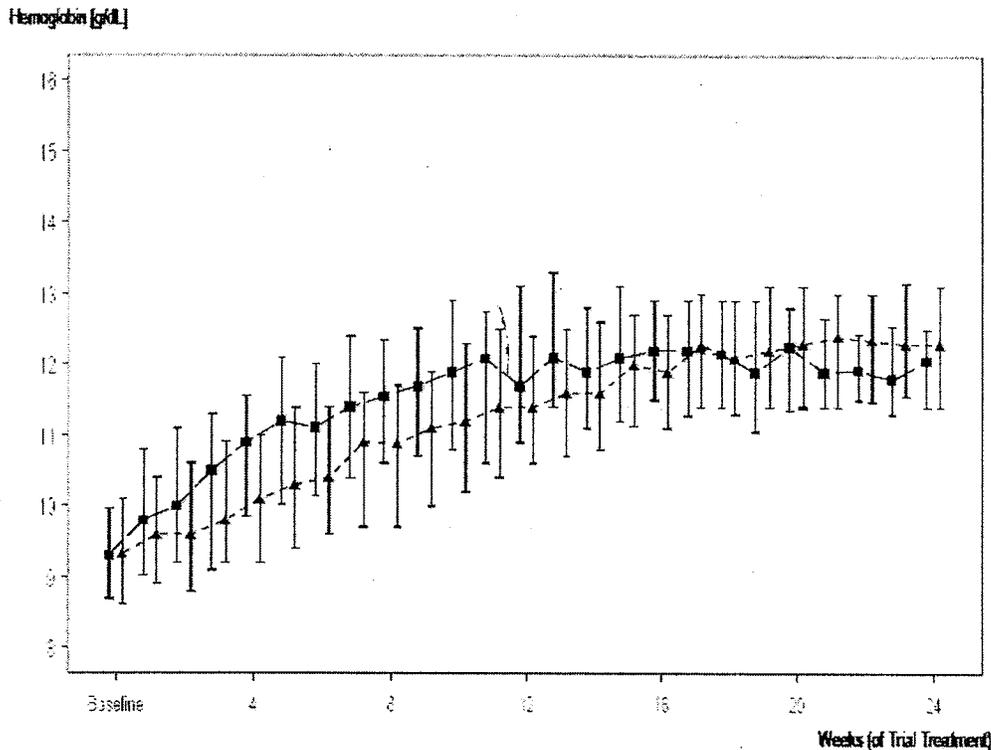
Table 7 shows the summary of hemoglobin response rates by gender, age, race, and region. Results from the subgroup analysis were consistent with the overall Hb response in both BA16736 and BA16738 for Mircera and the reference groups. Subgroups of race (Oriental, other and Black), age (65-75 & 75+ in BA16736), and Region (US in BA16736) were too small to draw any conclusions.

**Table 7 Summary of Responders in Phase III Correction Studies (ITT Population)
Overall and by Subgroup**

	BA16736		BA16738	
	Mircera (N=135)	Epoetin (N=46)	Mircera (N=162)	Darbepoetin (N=162)
Overall	93.3% (126/135) (87.7%, 96.9%)	91.3% (42/46) (79.2%, 97.6%)	97.5% (158/162) (93.8%, 99.3%)	96.3% (156/162) (92.1%, 98.6%)
Gender				
Female	88.7% (47/53) (77.0%, 95.7%)	92.9% (13/14) (66.1%, 99.8%)	98.9% (91/92) (94.1%, 99.9%)	97.6% (80/82) (91.5%, 99.7%)
Male	96.3% (79/82) (89.7%, 99.2%)	90.6% (29/32) (75.0%, 98.0%)	95.7% (67/70) (88.0%, 99.1%)	95.0% (76/80) (87.7%, 98.6%)
Race				
Black	100.0% (17/17) (80.5%, 100.0%)	100.0% (7/7) (59.0%, 100.0%)	94.3% (33/35) (80.8%, 99.3%)	89.5% (17/19) (66.9%, 98.7%)
Caucasian	93.4% (99/106) (86.9%, 97.3%)	93.9% (31/33) (79.8%, 99.3%)	98.2% (111/113) (93.8%, 99.8%)	97.0% (127/131) (92.4%, 99.2%)
Oriental	100.0% (8/8) (63.1%, 100.0%)	66.7% (2/3) (9.4%, 99.2%)	100.0% (7/7) (59.0%, 100.0%)	100.0% (9/9) (66.4%, 100.0%)
Other	50.0% (2/4) (6.8%, 93.2%)	66.7% (2/3) (9.4%, 99.2%)	100.0% (7/7) (59.0%, 100.0%)	100.0% (3/3) (29.3%, 100.0%)
Age				
<65	91.9% (91/99) (84.7%, 96.5%)	88.6% (31/35) (73.3%, 96.8%)	97.1% (68/70) (90.1%, 99.7%)	95.2% (59/62) (86.5%, 99.0%)
65-75	100.0% (23/23) (85.2%, 100.0%)	100.0% (6/6) (54.1%, 100.0%)	97.7% (43/44) (88.0%, 99.9%)	95.8% (46/48) (85.8%, 99.5%)
75+	92.3% (12/13) (64.0%, 99.8%)	100.0% (5/5) (47.8%, 100.0%)	97.9% (47/48) (88.9%, 99.9%)	98.1% (51/52) (89.7%, 99.9%)
Country				
US	75.0% (3/4) (19.4%, 99.4%)	100.0% (2/2) (15.8%, 100.0%)	98.5% (56/57) (90.6%, 99.9%)	96.6% (56/58) (88.1%, 99.6%)
Non-US	93.9% (123/131) (88.3%, 97.3%)	90.9% (40/44) (78.3%, 97.5%)	97.1% (102/105) (91.9%, 99.4%)	96.2% (100/104) (0.49%, 98.9%)

Secondary efficacy results in BA16736: A plot of the median Hb values over time for the correction period in BA16736 is presented in Figure 1. Median time to response in BA16736 was 57 days in Mircera group and 31 days in the epoetin group. Seven patients (5.2%) in the Mircera group and two patients (4.3%) in the epoetin group received RBC transfusion during the correction period.

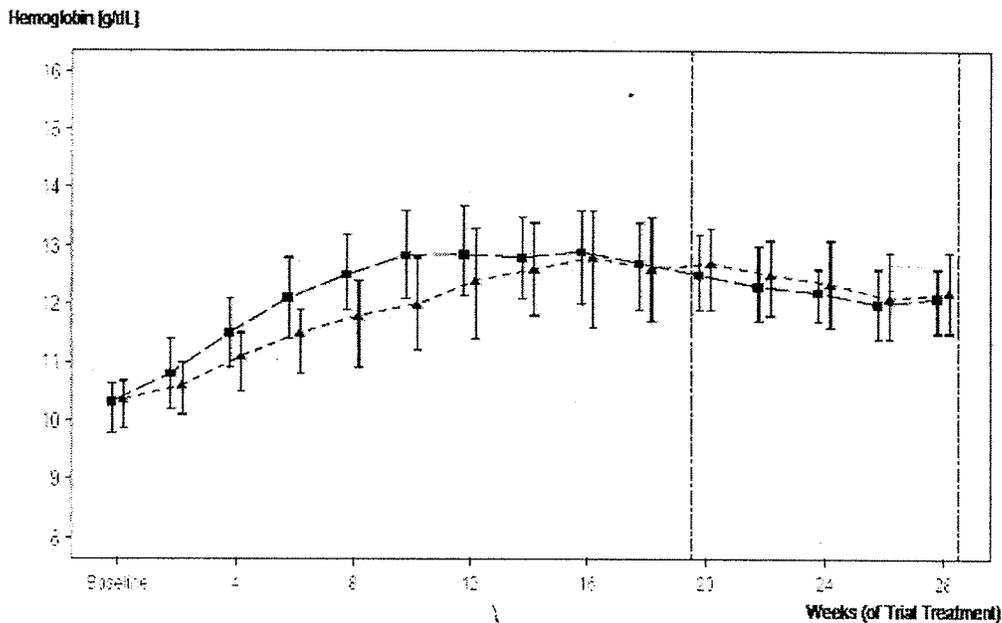
Figure 1 Median Hemoglobin Values Over Time in BA16736 (ITT Population)



Secondary efficacy results in BA16738: A plot of the median Hb values over time for the correction and evaluation periods in BA16738 is presented in Figure 2. Median time to response in BA16736 was 43 days in Mircera group and 29 days in the epoetin group. Eleven patients (6.8%) in the epoetin group and four patients (2.5%) in the Mircera group received RBC transfusion during the correction period.

In BA16378, 62.9% (n=95) of patients in Mircera group and 65.8% (n=102) patients in darbepoetin alfa group maintained Hb values within ± 1 g/dL of the response value during the evaluation period. These results were similar to those obtained for the PP and eligible populations.

Figure 2 Median Hemoglobin Values Over Time in BA16738 (ITT Population)



3.1.2 Maintenance Studies: BA16739, BA16740, BA17283 and BA17284

The four maintenance studies, BA16739, BA16740, BA17283 and BA17284, had a similar design of study in efficacy endpoints, sample size calculation, analysis population and statistical analysis method. All of them were randomized, controlled, open-label, multi-center, parallel group (3-arm or 2-arm), non-inferiority trials comparing Mircera to reference.

3.1.2.1 Study Design and Efficacy Endpoints: BA16739, BA16740, BA17283 and BA17284

The duration of the four trials were initiated with 4 weeks screening/baseline period and followed by 28-week titration and then 8-week evaluation periods (weeks 29 to 36). Weeks 1 to 28 were used for dose titration and stabilization of Hb concentration. All 4 studies, except BA17284, had a 16-week follow-up to assess the long-term safety observation of Mircera (weeks 37 to 52). Patients received a starting dose of Mircera that was based on the epoetin dose administered during the week preceding the switch to the study drug.

There were some minor differences among the four maintenance trials in study design. Those included: (1) BA16739 had a IV administered epoetin alfa/beta as the reference; (2) BA16739 and BA16740 had two dosing intervals of Mircera, once every two weeks and once every four weeks; (3) In BA16739 and BA17283, experimental drugs were administered intravenously; (4) In BA17284, Mircera was administered with prefilled syringes IV or SC.

Primary and Secondary Efficacy Variables: The primary efficacy variable for all four studies was the change in Hb concentration (g/dL) between the baseline and evaluation periods. The secondary efficacy variables were (1) the number of patients maintaining average Hb concentration during the evaluation period within ± 1 g/dL of their baseline Hb concentration and (2) the incidence of RBC transfusions during the dose titration and evaluation periods

3.1.2.2 Analysis Populations

Five different populations were defined for efficacy and safety analyses. The definitions of the analysis populations were the same as those in correction studies. The primary efficacy analysis for all four maintenance studies was based on the Per-Protocol population.

The Intent-to-Treat (ITT) Population was defined as all randomized patients. The ITT population was used for all baseline outputs as well as analyses for the efficacy endpoints.

The **Eligible Population** was defined for additional confirmatory analysis of the primary efficacy parameter. The eligible population included all patients randomized who had received at least one dose of trial medication (safety population) with the exception of: (1) Patients who did not fulfill the inclusion criterion of a stable baseline Hb concentration; (2) Patients with inadequate iron status defined as mean serum ferritin < 100 ng/mL **and** mean TSAT $< 20\%$ (or mean hypochromic RBCs $\geq 10\%$) during baseline; (3) Patients who do fulfill the exclusion criterion of emoglobinopathies or hemolysis; (4) Patients with RBC transfusions or blood loss during baseline.

The **Per-Protocol (PP) Population** was a subset of the eligible population and consisted of all patients randomized with the exception of: (1) Patients who did not have a stable baseline Hb concentration; (2) Patients with inadequate iron status at baseline or at evaluation; (3) Patients who do fulfill the exclusion criterion of hemoglobinopathies or hemolysis; (4) Patients with RBC transfusions or blood loss during baseline or within weeks 21 to 33; (5) Patients with less than five recorded Hb values during the evaluation period; and (6) Patients with missing administrations of the study drug or reference drug in weeks 26 to 35.

The **Observation Complete Population:** An additional subset of the data was defined. No imputation for missing values was performed and the analyses only included Hb values for those patients with a complete set of observations during the evaluation period.

The **Safety Population** was defined as all patients who received at least one dose of Mircera or reference drug and a safety follow-up, whether withdrawn prematurely or not. This population was used for the analysis of all safety endpoints.

3.1.2.3 Planned Sample Size

The assumptions for sample size calculation and the non-inferiority margin were the same for all four studies. Due to adjusting for multiplicity, a two-sided 97.5% confidence interval was used for BA16739 and BA16740. In contrast, the 95% confidence interval was calculated for BA17283 and BA17284.

BA16739 and BA16740: Based on a non-inferiority limit of -0.75 g/dL and a two-sided confidence interval approach with a coverage probability of 97.5 % with the assumption of SD = 1 g/dL for all groups, 124 patients per treatment group were required in the per-protocol population to conclude non-inferiority with 90% power. Assuming 20% of the patients were not eligible for inclusion in the per-protocol population, approximately 155 patients per treatment group were planned for recruiting to the study.

BA17283 and BA17284: Based on a non-inferiority limit of -0.75 g/dL and a two-sided confidence interval approach with a coverage probability of 95% with the same assumptions for sample size estimation previously, 105 patients per treatment group were required in the per-protocol population to conclude non-inferiority with 90% power. The sample size for each arm required 132 patients in BA17283 and BA17284 with taking 20% of ineligible patients for inclusion in the per-protocol population into account.

3.1.2.4 Patient Population and Demographic Characteristics: BA16739 and BA16740

BA16739: A total of 673 patients were recruited at 91 centers in 8 countries. More patients were recruited into the study than planned because all eligible patients who had signed an informed consent form and had entered the screening/baseline period were randomized in the study.

The majority of patients was males (56.2% to 59.6%), Caucasian (58.5% to 62.8%), and recruited from USA centers (67%). The mean age \pm SD in years was 59.0 ± 15.2 years and 61.8 ± 14.7 years in the Mircerca 1x/2 weeks and Mircerca 1x/4 weeks groups, respectively, and 58.6 ± 15.1 years in the epoetin group.

The mean baseline Hb values were similar in all the treatment groups (11.97 ± 0.652 g/dL in the Mircerca 1x/2 weeks, 11.85 ± 0.649 g/dL in the Mircerca 1x/4 weeks, and 11.91 ± 0.640 g/dL in the epoetin groups). There were no major differences in serum iron, ferritin, or TSAT. In this study, all of the patients received hemolysis. Table 8 shows the baseline demographics and characteristics of BA16739 in ITT population.

Table 8 Baseline Demographics and Characteristics: BA16739 (ITT Population)

	BA16739		
	Mircera 1*/2 weeks (N=223)	Mircera 1*/4 weeks (N=224)	Epoetin (N=226)
Gender			
Female	60 (36.3%)	98 (43.8%)	92 (40.7%)
Male	133 (63.7%)	126 (56.2%)	134 (59.3%)
Race			
Black	74 (33.2%)	82 (36.6%)	82 (36.3%)
Caucasian	140 (62.8%)	131 (58.5%)	133 (58.8%)
Oriental	9 (4.0%)	7 (3.1%)	11 (4.9%)
Other	0 (0.0%)	4 (1.8%)	0 (0.0%)
Age			
<65	134 (60.1%)	134 (59.8%)	141 (63.4%)
65-75	47 (21.1%)	52 (23.2%)	50 (22.1%)
75+	42 (18.8%)	38 (17.0%)	35 (15.5%)
Mean±SD	59.0 ± 15.2	61.8 ± 14.7	58.6 ± 15.1
Median	61.0	64.0	60.5
Country			
US	151 (67.7%)	152 (67.9%)	152 (67.3%)
Non-US	72 (32.3%)	72 (32.1%)	74 (32.7%)
Body Weight (kg)			
<65	70 (31.4%)	55 (24.6%)	52 (23.0%)
65 - <80	68 (30.5%)	83 (37.1%)	81 (35.8%)
80+	85 (38.1%)	86 (38.4%)	93 (41.2%)
Mean±SD	77.2 ± 19.7	70.3 ± 16.5	80.6 ± 22.0
Median	73.7	69.0	75.7
Mode of Current Dialysis			
Hemodialysis	223 (100.0%)	224 (100.0%)	226 (100.0%)
Peritoneal dialysis	0 (0.0%)	0 (0.0%)	0 (0.0%)
Baseline Hemoglobin (g/dL)			
Mean±SD	11.97 ± 0.652	11.85 ± 0.649	11.91 ± 0.640
Median	11.97	11.91	11.97
Baseline Ferritin (µg/L)			
Mean±SD	529.6 ± 384.9	556.5 ± 347.7	555.8 ± 380.8
Median	453.0	521.5	504.5

BA16740: A total of 572 patients were recruited at 89 centers in 20 countries. The largest number of premature withdrawals from the study occurred during the titration period (26 patients in the Mircera 1x/2 weeks group, 22 patients in the Mircera 1x/4 weeks group, and 13 patients in the epoetin group). During the evaluation and the safety follow-up periods, 3 and 7 patients, respectively, in the Mircera 1x/2 weeks group, 4 and 16 patients, respectively in the Mircera 1x/4 weeks group, and 4 and 15 patients, respectively in the epoetin group withdrew. In all three treatment groups, the majority of the patients was males (56.2% to 63.7%), Caucasian (77.5% to 81.8%), and recruited from non-USA centers (88%).

The mean age \pm SD was 60.5 ± 15.4 years, 62.3 ± 15.4 years, and 60.4 ± 14.7 years in the Mircera 1x/2 weeks, Mircera 1x/4 weeks, and the epoetin groups, respectively. The mean baseline Hb values were similar in all the treatment groups (11.7 ± 0.724 g/dL in the Mircera 1x/2 weeks, 11.66 ± 0.713 g/dL in the Mircera 1x/4 weeks, and 11.65 ± 0.697 g/dL in the epoetin groups). There were no major differences in serum iron, ferritin, or TSAT. In this study, the majority of the patients received HD (92.6% in the Mircera 1x/2 weeks, 92.7% in the Mircera 1x/4 weeks, and 89.5% in the epoetin groups). Table 9 shows the baseline demographics and characteristics of BA16740 in ITT population.

Table 9 Baseline Demographics and Characteristics: BA16740 (ITT Population)

	BA16740		
	Mircera 1*/2 weeks (N=190)	Mircera 1*/4 weeks (N=191)	Epoetin (N=191)
Gender			
Female	82 (36.3%)	74 (43.8%)	81 (42.4%)
Male	108 (63.7%)	117 (56.2%)	110 (57.6%)
Race			
Black	13 (6.8%)	15 (7.9%)	17 (8.9%)
Caucasian	155 (81.6%)	156 (81.8%)	148 (77.5%)
Oriental	15 (7.9%)	16 (8.4%)	19 (9.9%)
Other	7 (3.7%)	4 (2.0%)	7 (3.7%)
Age			
<65	103 (54.2%)	94 (49.2%)	107 (56.0%)
65-75	46 (24.2%)	49 (25.7%)	43 (22.5%)
75+	41 (21.6%)	48 (25.1%)	41 (21.5%)
Mean \pm SD	60.5 \pm 15.4	62.3 \pm 15.4	60.4 \pm 14.7
Median	63.0	65.0	61.0
Country			
US	22 (11.6%)	23 (12.0%)	23 (12.0%)
Non-US	168 (88.4%)	168 (88.0%)	168 (88.0%)
Body Weight (kg)			
<65	75 (39.5%)	71 (37.2%)	75 (39.3%)
65 - <80	74 (38.9%)	80 (41.9%)	73 (38.2%)
80+	41 (21.6%)	40 (20.9%)	43 (22.5%)
Mean \pm SD	70.8 \pm 15.7	69.0 \pm 14.9	69.3 \pm 14.7
Median	70.1	68.5	61.0
Mode of Current Dialysis			
Hemodialysis	176 (92.6%)	177 (92.7%)	171 (89.5%)
Peritoneal dialysis	14 (7.4%)	14 (7.3%)	20 (10.5%)
Baseline Hemoglobin (g/dL)			
Mean \pm SD	11.70 \pm 0.724	11.66 \pm 0.713	11.65 \pm 0.697
Median	11.68	11.64	11.62
Baseline Ferritin (μg/L)			
Mean \pm SD	520.9 \pm 414.7	520.6 \pm 423.8	530.4 \pm 401.6
Median	417.8	426.5	435.0

3.1.2.5 Patient Population and Demographic Characteristics: BA17283 and BA17284

BA17283: A total of 313 patients were recruited at 48 sites in 12 countries. In the two treatment groups, the largest number of premature withdrawals from study treatment occurred during the titration period (8.9% for Mircera and 8.3 % for darbepoetin alfa). Additionally, in the darbepoetin alfa group, 1 patient withdrew upon completion of the titration period.

Of the 313 patients randomized, 181 were male (57.8%) and 132 were female (42.2%). The percentage of male patients in the Mircera group (63.7%) was higher than in the darbepoetin alfa group (51.9%). The majority of the patients were Caucasian (91.1% in the Mircera group and 92.3% in the darbepoetin alfa group).

The distribution of baseline hemoglobin levels in the treatment groups was similar, with a mean of approximately 12 g/dL in both groups and similar variation. There were no major differences in serum iron, ferritin or transferrin saturation.

BA17284: A total of 336 patients were recruited at 62 centers in 11 countries. The total percentage of patients who were prematurely withdrawn from the study for either safety or non-safety reasons was 21.4% (n=36) in the Mircera group and 10.7% (n=18) in the epoetin group.

The majority of patients was males (61.9% in the Mircera group and 67.3% in the epoetin group), Caucasian (61.9% in the Mircera group and 51.8% in the epoetin group) and recruited from USA centers (57.1% in the Mircera group and 55.4% in the epoetin group). The mean \pm SD age was 59.8 ± 14.4 years and 60.1 ± 13.9 years in the Mircera and epoetin groups, respectively.

The mean \pm SD baseline Hb values were similar in both treatment groups (11.85 ± 0.660 g/dL in the Mircera group and 11.83 ± 0.688 g/dL in the epoetin group). There were no major differences in the serum iron, ferritin or TSAT. The percentages of patients taking either epoetin beta or alfa were equally distributed among the treatment groups.

**Table 10 Baseline Demographics and Characteristics: BA17283 and BA17284
(ITT Population)**

	BA17283		BA17284	
	Mircera (N=157)	Darbepoetin (N=156)	Mircera (N=168)	Epoetin (N=168)
Gender				
Female	57 (36.3%)	75 (48.1%)	64 (38.1%)	55 (32.7%)
Male	100 (63.7%)	81 (51.9%)	100 (61.9%)	133 (67.3%)
Race				
Black	5 (3.2%)	4 (2.6%)	49 (29.1%)	57 (33.9%)
Caucasian	143 (91.1%)	144 (92.3%)	104 (61.9%)	87 (51.8%)
Oriental	4 (2.5%)	5 (3.2%)	10 (6.0%)	13 (7.7%)
Other	5 (3.2%)	3 (1.9%)	5 (3.0%)	11 (6.6%)
Age				
<65	76 (48.4%)	79 (50.6%)	104 (61.9%)	104 (61.9%)
65-75	39 (24.8%)	41 (26.3%)	37 (22.0%)	34 (20.2%)
75+	42 (26.8%)	36 (23.1%)	27 (16.1%)	30 (17.9%)
Mean±SD	62.4 ± 16.2	61.8 ± 14.7	59.8 ± 14.4	60.1 ± 13.9
Median	65.0	64.0	60.0	60.0
Country				
US	0 (0.0%)	0 (0.0%)	96 (57.1%)	93 (55.4%)
Non-US	157 (100.0%)	156 (100.0%)	72 (42.9%)	75 (44.6%)
Body Weight (kg)				
<65	70 (44.6%)	64 (41.0%)	56 (33.3%)	45 (26.8%)
65 - <80	57 (36.3%)	56 (35.9%)	49 (29.2%)	56 (33.3%)
80+	30 (19.1%)	36 (23.1%)	62 (36.9%)	66 (39.3%)
Mean±SD	68.9 ± 16.7	70.3 ± 16.5	75.5 ± 19.7	77.4 ± 19.7
Median	66.9	69.0	72.5	73.4
Mode of Current Dialysis				
Hemodialysis	157 (100.0%)	155 (99.4%)	159 (94.6%)	158 (94.0%)
Peritoneal dialysis	0 (0.0%)	1 (0.6%)	9 (5.4%)	10 (6.0%)
Baseline Hemoglobin (g/dL)				
Mean±SD	12.01 ± 0.676	11.93 ± 0.664	11.85 ± 0.660	11.83 ± 0.688
Median	12.00	12.00	11.91	11.75
Baseline Ferritin (µg/L)				
Mean±SD	424.2 ± 334.8	432.6 ± 271.2	529.3 ± 268.9	517.3 ± 301.3
Median	376.8	382.3	515.0	481.5

3.1.2.6 Statistical Methodologies: BA16739, BA16740, BA17283 and BA17284

Analysis of the Primary Efficacy Variable: The primary objective of BA16739, BA16740 was to demonstrate the efficacy of two Mircera dosing schedules (once every two weeks and once every four weeks) in maintaining Hb levels. Similarly, the primary objective of BA17283, BA17284 was to demonstrate the efficacy of Mircera dosing schedule of once every two weeks in maintaining Hb levels.

The primary analysis of all the four studies was based on the per-protocol population. Additional analysis was performed to test the robustness of the results based on the ITT population and the observation analysis population.

The primary efficacy endpoint of all four studies was the change in Hemoglobin 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. The evaluation period was between weeks 29 and 36. Subtracting the baseline value from the evaluation period value gave the final endpoint.

Data missing at the end of the evaluation period was handled using the last value carried forward method. In case of a RBC transfusion during the evaluation period, the Hb values measured within 3 weeks after the RBC transfusion were replaced by the Hb value measured immediately before the RBC transfusion to correct for the increase caused by the RBC transfusion.

In BA16739, BA16740, the differences in the mean change in hemoglobin between the baseline and evaluation periods were assessed for Mircera administered once every two weeks vs. reference and Mircera administered once every four weeks vs. reference.

Analysis of covariance (ANCOVA) was used to compare the Mircera to the epoetin reference group. The independent variables in the model were treatment group and the covariates Hb at baseline, geographical region and type of epoetin preparation at screening. Two-sided 97.5% CI (BA16739, BA16740) or 95% CI (BA17283, BA17284) for the between-group difference in mean change in Hb between the baseline and evaluation periods were calculated using the estimates from this model.

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. The confidence level of 97.5% was chosen to adjust for the multiplicity resulting from the independent comparisons of the two Mircera groups with the reference group. A non-inferiority limit of -0.75 g/dL for the difference in mean Hb was chosen since a decline of 0.75 g/dL over a 36-week period was considered reasonable.

Analysis of the Secondary Efficacy Variables: The secondary efficacy endpoints were (1) The number of patients maintaining average hemoglobin concentration during the evaluation period within ± 1 g/dL of their average baseline hemoglobin level and (2) The incidence of RBC transfusions during the dose titration and evaluation periods. The number of patients able to maintain their hemoglobin levels and the incidence of RBC transfusions were summarized using descriptive methods.

3.1.2.7 Results and Conclusions

Primary efficacy results: The primary efficacy analysis for all the four studies was based on the per-protocol population. Analyses using ITT, eligible and observation complete populations were also performed to test the robustness of the results from the per-protocol population.

BA16739: The primary analysis was performed in the PP population. The difference in the mean change in Hb between the baseline and week 36 was assessed for Mircerca administered 1x/2 weeks and 1x/4 weeks versus epoetin. Table 11 shows the lower bound of 97.5% confidence was -0.215 and -0.173 for the difference in the mean change in Hb of (Mircerca 1x/4 weeks minus epoetin) and (Mircerca 1x/2 weeks minus epoetin), respectively.

Additional analyses in the other three populations were performed as well. Treatment with Mircerca 1x/2 weeks and 1x/4 weeks was non-inferior to treatment with epoetin in maintaining Hb levels in all four populations tested (PP, ITT, eligible, and observation complete). Table 11 shows the mean Hb change difference between Mircerca 1x/2 weeks and epoetin group and the mean Hb change difference between Mircerca 1x/4 weeks and epoetin group based on all four populations. The corresponding 97.5% confidence interval can be seen in Table as well.

BA16740: The primary efficacy analysis was performed in the PP population for BA16740 and the rest of two studies, BA17283 and BA17284. Table 11 shows the lower bound of 97.5% confidence was -0.098 and -0.262 for the difference in the mean change in Hb of (Mircerca 1x/4 weeks minus epoetin) and (Mircerca 1x/2 weeks minus epoetin), respectively. It confirmed that Mircerca 1x/2 weeks and 1x/4 weeks was non-inferior to treatment with epoetin in maintaining Hb levels.

In addition, analyses in ITT, eligible and observation complete populations were performed to test the robustness. Again, in BA16740, treatment with Mircerca 1x/2 weeks and 1x/4 weeks was non-inferior to treatment with epoetin in maintaining Hb levels in all of ITT, eligible, and observation complete populations. Table 11 shows the results of mean Hb change differences and the corresponding 97.5% confidence intervals of Mircerca 1x/2 weeks and 1x/4 weeks compared to epoetin group based on all four populations.

BA17283 and BA17284: As mentioned above, the primary efficacy analysis was performed in the PP population for BA17283 and BA17284. Table 11 shows the lower bound of 95% confidence was -0.049 and -0.116 for the difference in the mean change in Hb of between Mircerca 1x/2 weeks and darbepoetin in BA17283 and difference in the mean change in Hb between Mircerca 1x/2 weeks and epoetin in BA17284, respectively. In both studies, the Mircerca 1x/2 weeks was non-inferior to reference treatment in maintaining Hb levels.

The non-inferiority analysis results based on ITT, eligible and observation complete populations were performed to test the robustness. In both BA17284 and BA17284, treatment with Mircera 1x/2 weeks was non-inferior to references in maintaining Hb levels in all of ITT, eligible, and observation complete populations. Table 12 shows the results of mean Hb change differences and the corresponding 95% confidence intervals of Mircera 1x/2 weeks compared to reference groups based on all four populations.

Table 11 Mean Changes in Hemoglobin from Baseline to Evaluation Period, Between-Group Difference and the Corresponding Confidence Interval, by Study (Per-Protocol Population)

	Mircera Mean Change (n)	Reference Mean Change (n)	Difference (SE)	Lower 97.5%/95% CI[#]	Upper 97.5%/95% CI[#]
BA16739					
Mircera 1*/2 weeks	-0.071 (188)	-0.075 (180)	0.004 (0.0973)	-0.215	0.223
Mircera 1*/4 weeks	-0.025 (172)	-0.075 (180)	0.051 (0.0997)	-0.173	0.275
BA16740					
Mircera 1*/2 weeks	0.032 (154)	-0.109 (167)	0.141 (0.1063)	-0.098	0.380
Mircera 1*/4 weeks	-0.131 (153)	-0.109 (167)	-0.022 (0.1065)	-0.262	0.217
BA17283					
Mircera 1*/2 weeks	0.063 (123)	-0.116 (126)	0.180 (0.1162)	-0.049	0.408
BA17284					
Mircera 1*/2 weeks	0.088 (123)	-0.030 (133)	0.118 (0.1190)	-0.116	0.353

Note: [#] indicates 97.5% CI for BA16739 & BA16740 due to adjusting for multiplicity and 95% CI for BA17283 & BA17284

In all, the lower bound of 97.5% confidence interval (BA16739 and BA16740) or lower bound of 95% confidence interval (BA17283 and BA17284) were similar in different analysis populations and were greater than the pre-specified margin of -0.75 g/dL. It demonstrated the robustness of primary efficacy results from using the PP population.

Table 12 Mean Changes in Hemoglobin from Baseline, Between-Group Difference and the Corresponding Confidence Interval, by Study and Analysis Population

BA16739	Mircera Mean Change (n)	Reference Mean Change (n)	Difference (SE)	Lower 97.5% CI	Upper 97.5% CI
<i>PP Population</i>					
Mircera 1*/2 weeks	-0.071 (188)	-0.075 (180)	0.004 (0.0973)	-0.215	0.223
Mircera 1*/4 weeks	-0.025 (172)	-0.075 (180)	0.051 (0.0997)	-0.173	0.275
<i>ITT Population</i>					
Mircera 1*/2 weeks	-0.192 (223)	-0.223 (225)	0.031 (0.1087)	-0.213	0.276
Mircera 1*/4 weeks	-0.198 (220)	-0.223 (225)	0.025 (0.1090)	-0.220	0.270
<i>Eligible Population</i>					
Mircera 1*/2 weeks	-0.167 (220)	-0.207 (222)	0.140 (0.1081)	-0.203	0.283
Mircera 1*/4 weeks	-0.155 (215)	-0.207 (222)	0.053 (0.1087)	-0.191	0.297
<i>Observation Complete</i>					
Mircera 1*/2 weeks	-0.067 (170)	-0.079 (172)	0.013 (0.0970)	-0.205	0.231
Mircera 1*/4 weeks	-0.062 (161)	-0.079 (172)	0.017 (0.0985)	-0.204	0.239
BA16740	Mircera Mean Change (n)	Reference Mean Change (n)	Difference (SE)	Lower 97.5% CI	Upper 97.5% CI
<i>PP Population</i>					
Mircera 1*/2 weeks	0.032 (154)	-0.109 (167)	0.141 (0.1063)	-0.098	0.380
Mircera 1*/4 weeks	-0.131 (153)	-0.109 (167)	-0.022 (0.1065)	-0.262	0.217
<i>ITT Population</i>					
Mircera 1*/2 weeks	-0.199 (190)	-0.227 (189)	0.028 (0.1209)	-0.244	0.300
Mircera 1*/4 weeks	-0.320 (153)	-0.227 (189)	-0.093 (0.1208)	-0.364	0.179
<i>Eligible Population</i>					
Mircera 1*/2 weeks	-0.206 (187)	-0.226 (189)	0.019 (0.1216)	-0.254	0.293
Mircera 1*/4 weeks	-0.324 (189)	-0.226 (189)	-0.098 (0.1212)	-0.371	0.174
<i>Observation Complete</i>					
Mircera 1*/2 weeks	0.119 (148)	0.036 (160)	0.084 (0.1051)	-0.153	0.320
Mircera 1*/4 weeks	-0.045 (149)	0.036 (160)	-0.081 (0.1047)	-0.316	0.155
BA17283	Mircera Mean Change (n)	Reference Mean Change (n)	Difference (SE)	Lower 95% CI	Upper 95% CI
<i>PP Population</i>					
Mircera 1*/2 weeks	0.063 (123)	-0.116 (126)	0.180 (0.1162)	-0.049	0.408
<i>ITT Population</i>					
Mircera 1*/2 weeks	-0.029 (163)	-0.316 (155)	0.287 (0.1352)	0.021	0.553
<i>Eligible Population</i>					
Mircera 1*/2 weeks	-0.050 (152)	-0.311 (153)	0.261 (0.1363)	-0.007	0.529
<i>Observation Complete</i>					
Mircera 1*/2 weeks	0.158 (112)	-0.086 (117)	0.245 (0.1194)	0.009	0.480
BA17284	Mircera Mean Change (n)	Reference Mean Change (n)	Difference (SE)	Lower 95% CI	Upper 95% CI
<i>PP Population</i>					
Mircera 1*/2 weeks	0.088 (123)	-0.030 (133)	0.118 (0.1190)	-0.116	0.353
<i>ITT Population</i>					
Mircera 1*/2 weeks	-0.021 (167)	-0.175 (168)	0.154 (0.1225)	-0.087	0.395
<i>Eligible Population</i>					
Mircera 1*/2 weeks	-0.002 (158)	-0.178 (161)	0.176 (0.1251)	-0.070	0.422
<i>Observation Complete</i>					
Mircera 1*/2 weeks	0.135 (112)	0.034 (129)	0.101 (0.1217)	-0.139	0.341

Secondary efficacy results: For the four maintenance studies of BA16739, BA16740, BA17283 and BA17284, the analysis population for all secondary endpoints was the ITT population. The secondary efficacy endpoints included (1) the number of patients maintaining their average Hb concentration during the evaluation period within ± 1 g/dL of their average baseline concentration and (2) the incidence of RBC transfusions during the dose titration and evaluation periods (descriptive analyses only).

BA16739: In the ITT population, during the evaluation period, a total of 124 patients (75.6%) in the Mircera 1x/2 weeks, 111 patients (66.1%) in the Mircera 1x/4 weeks, and 127 patients (72.2%) in the epoetin groups maintained a Hb within ± 1 g/dL of their average baseline. The incidence of RBC transfusions during the titration and evaluation periods was 9.5% in the Mircera 1x/2 weeks group, 7.3% in the Mircera 1x/4 weeks group, and 7.6% in the epoetin group.

BA16740: In the ITT population, during the evaluation period, a total of 124 patients (75.6%) in the Mircera 1x/2 weeks, 111 patients (66.1%) in the Mircera 1x/4 weeks, and 127 patients (72.2%) in the epoetin groups maintained a Hb within ± 1 g/dL of their average baseline. The incidence of RBC transfusions during the titration and evaluation periods was lowest in the Mircera 1x/2 weeks group (6.3%) and similar in the Mircera 1x/4 weeks (10.5%) and the epoetin (9.9%) treatment groups.

BA17283: In the ITT population during the evaluation period, a total of 91 patients (65.5%) in the Mircera group and 102 patients (71.8%) in the darbepoetin alfa group maintained a Hb concentration within ± 1 g/dL of their average baseline. In the PP population, similar percentages of patients maintained a Hb within ± 1 g/dL of their average baseline were seen for all 3 treatment groups. The incidence of RBC transfusions during the titration and evaluation periods was 12.4% in the Mircera group and 10.3% in the darbepoetin alfa group.

BA17284: In the ITT population, during the evaluation period, a total of 98 patients (68.5%) in the Mircera group and 107 patients (67.7%) in the epoetin group maintained Hb within ± 1 g/dL of their average baseline. In the PP population, similar percentages of patients maintained a Hb within ± 1 g/dL of their average baseline were seen for all 3 treatment groups. The incidence of RBC transfusions during the titration and evaluation periods was 9.7% in the Mircera group and 11.3% in the epoetin group.

For all four maintenance studies: In the PP population, similar percentages of patients maintained a Hb within ± 1 g/dL of their average baseline were seen for all 3 treatment groups. Table ?? presents the percentages of patients maintaining hemoglobin within ± 1 g/dL during the evaluation period in ITT and PP populations. Table 14 presents the incidence of RBC transfusions during the titration and evaluation periods in safety population.

Table 13 Percentage of Patients Maintaining Hemoglobin within ± 1 g/dL during the Evaluation Period

Study	Mircera 1*/4 weeks %	Mircera 1*/2 weeks %	Reference %
<u>BA16739</u>			
ITT	67.6% (127/188)	67.9% (133/196)	67.3% (138/205)
PP	69.8% (120/172)	69.7% (131/188)	71.7% (129/180)
<u>BA16740</u>			
ITT	66.1% (111/168)	75.6% (124/164)	72.2% (127/176)
PP	69.3% (106/153)	76.0% (117/154)	73.7% (123/167)
<u>BA17283</u>			
ITT	--	65.5% (91/139)	71.8% (102/142)
PP	--	67.5% (83/123)	77.0% (97/126)
<u>BA17284</u>			
ITT	--	68.5% (98/143)	67.7% (107/158)
PP	--	68.3% (84/123)	72.2% (96/133)

Table 14 Incidence of Red Blood Cells Transfusions during the Titration and Evaluation Periods (Safety Population)

Study	Mircera 1*/4 weeks %	Mircera 1*/2 weeks %	Reference %
BA16739	7.3% (16/230)	9.5% (21/221)	7.6% (17/2225)
BA16740	10.5% (20/190)	6.3% (12/190)	9.9% (19/191)
BA17283	--	12.4% (19/153)	9.7% (16/165)
BA17284	--	10.3% (16/156)	11.3% (19/168)

3.2 Evaluation of Safety

3.2.1 An apparent greater incidence of sudden deaths with Mircera than with reference agents was initially a major review concern. The Mircera safety database consisted of pooled results from four phase II and six phase III clinical studies involving 2737 (1789 receiving Mircera and 948 receiving a reference ESA). There were 9 cases of sudden death in Mircera patients and none in reference ($p=0.0287$). All studies terminated at 52 weeks and after 52 weeks, subjects were allowed to enroll in a long-term extension. Approximately half of all the patients enrolled in the long-term extension. When all long-term extension data included, sudden deaths incidence were 14 and 5 cases in Mircera and reference patients, respectively ($p=0.4431$).

3.2.2 C-Reactive Protein (CRP) is a blood protein that increases with infection/inflammation. An increased level has been importantly correlated with increased risk for cardiovascular events. The sponsor actively screened all patients to eliminate patients with chronically elevated CRP from their Phase II/III studies. The sponsor used a cut off of > 15 mg/L for nondialysis and 30 or 50 mg/L for dialysis patients. Usually CRP > 10 mg/L is regarded as high. That is, the truly most vulnerable patients were eliminated from the studies.

The Agency raised two questions regarding the CRP exclusion as an important limitation of the Mircera safety database and the sponsor's database limitation as sufficient to preclude licensure until additional data verify the product's safety.

Based on the Mircera safety database, baseline characteristics were similar across treatment groups. The analysis results suggested (1) Baseline CRP showed a significant effect on multiple composite cardiovascular toxicity endpoints as well as the components of the composites, including death, (2) no significant treatment by CRP interaction, and (3) Kaplan-Meier survival analyses generally confirmed the impact of baseline CRP > 10 mg/L on composite endpoints and on individual endpoints.

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4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race and Age

It is clear that the demographic factors had no effect on hemoglobin response in BA16736 and BA16738 (see Table 7). The demographic characteristics of gender, race and age did not affect the change in average Hb between baseline and the evaluation period in Mircera or reference groups for all 2 correction studies and 4 maintenance studies.

4.2 Other Special/Subgroup Populations

In general, hemoglobin response and hemoglobin change from baseline was similar among the subgroups of the factors in geographic region (US versus Non-US), diabetes status (diabetic versus non-diabetic) and previous ESA treatment.

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

There were no breaking blind or unblinded issues since all of the 6 pivotal trials were open label studies. No interim analyses were performed in any study. No change of primary endpoint occurred during conducting of the trial, nor had a change of sample size.

BA16739 and BA16740 had a 3-arm, non-inferiority design of study, Mircera 1x/2 weeks, Mircera 1x/4 weeks and reference groups. There lower bound of 97.5% CI, which had adjusted for multiplicity, was calculated to compare with the pre-specified margin of -0.75 g/dL.

Efficacy results were consistent across different subgroups. Based on the ITT, Per-protocol, eligible and observation complete analysis populations, efficacy analysis results presented the consistency in support of using Mircera in correction and maintenance of hemoglobin of anemic patients with CKD.

5.2 Conclusions and Recommendations

Based on the efficacy results presented by the sponsor and this reviewer's statistical evaluation, BLA Submission 125164/0 has presented the non-inferiority in efficacy of using Mircera both in correction and maintenance of hemoglobin level of anemic patients with chronic kidney disease (CKD) compared to reference. Two Phase III studies provided statistical support for the efficacy claim in hemoglobin correction and 4 Phase III studies provided statistical support for the efficacy claim in hemoglobin maintenance. However, the efficacy of this product has to be evaluated in the light of considerable safety concerns, and whether it is an appropriate usage will be a clinical decision.

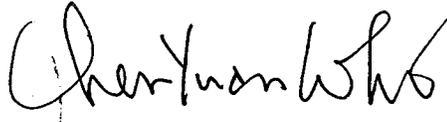
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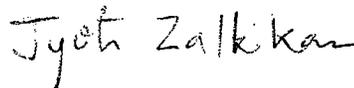
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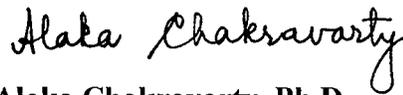
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