

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
BLA 125164

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

MEMORANDUM

To: Florence Moore, M.S., Project Manager
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Through: Hong Zhao, Ph.D., Team Leader
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Hong Zhao 11/2/07

From: Jang-Ik Lee, Pharm.D., Ph.D., Reviewer
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Jang-Ik Lee 11/2/07

Date: November 2, 2007

Re: Clinical Pharmacology Review of Resubmission for Mircera BLA (STN 125164)

Roche Pharmaceuticals submitted an original BLA (STN 125164) for the approval of Mircera for the treatment of anemia associated with chronic renal failure on April 19, 2006. The clinical pharmacology review of the original submission was completed on May 3, 2007 and the signed-off hard copy of the review was handed to the Project Manager, Ms Florence Moore on May 7, 2007. The Division of Medical Imaging and Hematology Product issued a complete response letter indicating clinical deficiencies to Roche on May 18, 2007. Subsequently, Oncology Drug and Cardio-Renal Advisory Committee meetings were held in May and September 2007 discussing the safe and effective target hemoglobin concentrations in the use of erythropoiesis stimulating agents for the treatment of anemia in cancer and renal diseases.

Roche resubmitted the BLA in response to the complete response letter on September 13, 2007. The PDUFA due date for completing the review of the resubmission is November 14, 2007. The resubmission contains Roche's proposal

~~_____~~, and on
~~_____~~ Since the resubmission does not contain any immediate issues that require an update of the previous clinical pharmacology review, the clinical pharmacology review completed on May 3, 2007 is the final version.

OFFICE OF CLINICAL PHARMACOLOGY REVIEW

BLA; STN	125164/0000
Submission Date(s)	4/19/06 (original), 12/4/07 (major safety amendment) 3/26/07 (clinical pharmacology amendment)
PDUFA Due Date	5/17/07
Brand Name	Mircera
Generic Name	pegserepoetin beta
Primary Reviewer	Jang-Ik Lee, Pharm.D., Ph.D.
Primary Review Team Leader	Hong Zhao, Ph.D.
Pharmacometrics Reviewer	Pravin Jadhav, Ph.D.
Pharmacometrics Team Leader	Joga Gobburu, Ph.D.
Secondary QT reviewer	Christine Garnette, Ph.D.
OCP Division	DCP 5
OND Division	OODP/DMIHP (HFD-160)
Sponsor	Hoffmann-La Roche Inc.
Relevant IND(s)	BB-IND 10,158
Submission Type	original BLA (NME)
Formulation	injectable solutions
Proposed indication	treatment of anemia associated with chronic renal failure
Proposed Dosage and Administration	Starting dose at 0.6 mcg/kg intravenously or subcutaneously administered as a single dose once every two weeks. Dose must be individualized to ensure hemoglobin maintained at an appropriate level for each patients

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1 EXECUTIVE SUMMARY

Pegserepoetin beta (Mircera[®]) being developed by Hoffmann-La Roche Inc. is a new molecular entity that activates erythropoietin receptor. Pegserepoetin beta differs from erythropoietin beta in the integration of methoxy polyethylene glycol moiety into its protein backbone to prolong the terminal half-life. The proposed indication for pegserepoetin beta in this original BLA is the treatment of anemia associated with chronic renal failure (CRF). This BLA was initially under 10-month standard review. However, to resolve the issues associated with 9 sudden death cases that appeared only in the active treatment group, the BLA was amended with additional safety data submission and therefore the PDUFA due date was extended by 3 months.

1.1 Recommendation

From a clinical pharmacology standpoint, this BLA is acceptable for the approval of pegserepoetin beta for the treatment of anemia associated with chronic renal failure. The proposed labeling is under revision at the time of completion of this review (see 3. DETAILED LABELING RECOMMENDATIONS).

1.2 Phase 4 Study Commitments

No Phase 4 commitment studies are recommended in the area of clinical pharmacology.

1.3 Summary of Clinical Pharmacology and Biopharmaceutics Findings

Exposure-Response Relationships

The effectiveness of pegserepoetin beta was well established in 6 clinical studies. All studies show consistent success in correction/maintaining hemoglobin levels within the defined threshold. The patients are treated by periodic monitoring of hemoglobin levels and assessing the change from previous measurement to adjust the dose. For example, if the rate of rise in hemoglobin is greater than 2 g/dL over a month, the dose is to be reduced by approximately 50%. However, the risk-benefit of pegserepoetin beta and overall erythropoiesis-stimulating agents (ESAs) is questionable. At this time, it is not possible to optimize the treatment given uncertainties in dose effect, hemoglobin target (partial or complete correction), hemoglobin minimum to start ESA treatment (baseline risk) or any other predictors (such as, slope of hemoglobin response) that would maximize overall benefit.

Pharmacokinetics

Table 1 shows a summary of pharmacokinetic parameters of pegserepoetin beta determined following a single intravenous (IV) or subcutaneous (SC) dose to healthy subjects or patients with CRF. 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 (V_{ss} , approx. 4 L) 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 apparently

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.

Table 1: Pharmacokinetic parameter values (mean ± SD) of pegserepoetin beta determined following a single dose

Subject	Healthy Subjects		Patients with Chronic Renal Failure			
	BP16239	BP16198	BP18034 (not on Dialysis)		BP16779 (on Peritoneal Dialysis)	
Study	BP16239	BP16198	BP18034 (not on Dialysis)		BP16779 (on Peritoneal Dialysis)	
Route	IV	SC	IV	SC	IV	SC
Dose (mcg/kg)	0.4	0.8	0.8	1.2	0.4	0.8
Number (n)	7 - 8	6 - 8	8 - 12	6 - 9	11 - 16	11 - 16
T _{max} (hr)*		72 (24-120)		94 (48-144)		72 (24-192)
C _{max} (ng/mL)	8.2 ± 3.3	1.86 ± 1.07	16.1 ± 4.7	3.2 ± 2.2	9.1 ± 3.0	4.6 ± 2.3
AUC _{clast} (ng·hr/mL)	533 ± 294	363 ± 269	949 ± 914	771 ± 704	1028 ± 1090	1106 ± 1065
AUC _∞ (ng·hr/mL)	629 ± 218	504 ± 276	1380 ± 880	1141 ± 710	898 ± 281	1047 ± 397
CL or CL/F (mL/hr/kg)	0.82 ± 0.27	2.43 ± 2.37	0.93 ± 0.75	1.67 ± 1.33	0.49 ± 0.18	0.90 ± 0.42
V _{ss} (mL/kg)	NC	NC	57.6 ± 12.8	NC	66.6 ± 27.5	NC
t _{1/2} (hr)	70 ± 35	102 ± 62	77 ± 54	142 ± 64	134 ± 65	139 ± 67

* median (range), NC not calculated

Following a similar single SC dose, the dose-normalized mean AUC value of pegserepoetin beta determined in CRF patients on peritoneal dialysis were much greater (approx. 3 fold) than the values determined in healthy subjects. The values determined in CRF patients not on dialysis showed a similar trend with a lesser extent (approx. 1.4 fold). The ratio of the dose-normalized mean AUC value in patients on peritoneal dialysis to the value in patients not on dialysis was approximately 2.1. These trends are reflected by slower mean CL values in CRF patients. After discussing with the clinical review team, the pharmacokinetic data in CRF patients not on dialysis were not included in the labeling since CRF patients not on dialysis would not have greater safety risks compared with CRF patients on peritoneal dialysis due to the pharmacokinetic difference.

Pharmacodynamics

Reticulocyte counts were selected as the primary pharmacodynamic marker in all clinical pharmacology studies. 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. At later time points, reticulocyte counts decreased further, slightly below baseline values, and then returned slowly towards baseline values. After repeated SC administrations of pegserepoetin beta every 2 weeks, the reticulocyte count response diminished over time. In contrast, the reticulocyte count response remained nearly constant over time after IV dosing every three weeks. The difference appears to be due to the difference in dosing interval rather than the difference in route of administration. For both SC and IV dosing, the relationship between reticulocyte response and dose was nearly linear. At the highest dose

level tested (3.2 mcg/kg), the maximum observed reticulocyte response was 251% of baseline value after SC dosing and 334% after IV dosing.

Hemoglobin was selected as the secondary pharmacodynamic marker in clinical pharmacology studies, whereas hemoglobin was used as an efficacy endpoint in clinical studies. 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. A slow decline in hemoglobin levels after the last drug administration was observed with a similar rebound effect as seen in reticulocyte counts.

Effect of Intrinsic Factors

Based on population analyses, the pharmacokinetics of pegserepoetin beta are not significantly altered due to common demographic characteristics. Results of these analyses showed that no dose adjustments are necessary for age, gender and race. The safety and efficacy of pegserepoetin beta therapy has not been established in patients with hemoglobinopathies, severe liver disease, seizures or with platelet level greater than $500 \times 10^9/L$.

Effect of Extrinsic Factors

No formal drug-drug interaction studies have been performed. There was no indication in clinical studies of an effect of concomitant medications on the pharmacokinetics of pegserepoetin beta.

Immunogenicity

No subjects received pegserepoetin beta showed an induction of anti-pegserepoetin beta or anti-erythropoietin antibodies in any of the studies submitted in this BLA. One patient treated with pegserepoetin beta had detectable levels of anti-erythropoietin antibody at baseline, Day 90 and Day 365. One patient who received a reference comparator (epoetin alfa) had positive anti-erythropoietin antibodies.

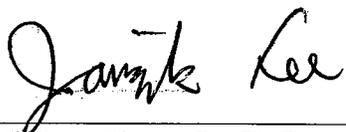
Product Comparability

A pharmacokinetic comparability study was conducted in healthy subjects to compare the exposure of pegserepoetin beta between Formulation A (used in some phase 1 and phase 2 studies) versus Formulation B (used in some phase 1 and phase studies, and all phase 3 studies) following an SC administration of 3.2 mcg/kg. The mean C_{max} values are comparable (geometric mean ratio, GMR = 0.98; 90% confidence interval, 90% CI = 0.83 - 1.17). However, the mean AUC_{last} was somewhat smaller in Formulation B than Formulation A (GMR = 0.89; 90% CI = 0.77 - 1.04); a similar result was obtained for AUC_{inf} (GMR = 0.84; 90% CI = 0.73 - 0.96).

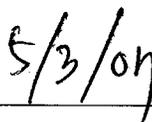
For both formulations, maximum numbers of reticulocytes were reached 8 to 10 days after drug administration. The baseline-corrected values of area under the effect-time curve determined from Day 1 to Day 36 of drug administration (AUE_{1-36days}) for reticulocytes were similar for both

formulations (GMR = 1.03; 90% CI = 1.00 - 1.06). The absolute and relative maximum changes from baseline in reticulocyte counts were also comparable for both formulations.

Considering the variability in the pharmacokinetics of pegserepoetin beta and the similarity in reticulocyte counts, Formulations A and B are considered to be comparable.



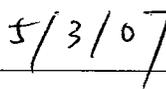
Date: _____



Jang-Ik Lee, Pharm.D., Ph.D.
Clinical Pharmacology Reviewer
Division of Clinical Pharmacology 5
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Date: _____



Hong Zhao, Ph.D.
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Attendees to the required office-level clinical pharmacology briefing held on April 20, 2007

IO: Shiew-Mei Huang, Felix Frueh, Mike Orr
DCP2: Tayo Fadiran, Ting Ong,
DCP3: Dennis Bashaw, Myong Jin Kim, Jane Bai,
DCP4: John Lazor, Kelly Reynolds, Derek Zhang, Assad Noory
DCP5: Atik Rahman, Young Moon Choi, Jang-Ik Lee, Leslie Kenna, Angela Men, Qi Liu
PM: Joga Gobburu, Yaning Wang, Pravin Jadhav
DMIHP: Dwaine Rieves, Kathy Robie Suh, John Lee, Faranak Jamali, Ruyi He

2 QUESTION-BASED REVIEW

2.1 General Attributes of pegserepoetin beta

2.1.1 *What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product?*

Pegserepoetin beta is a new molecular entity that activates erythropoietin receptor. Pegserepoetin beta differs from erythropoietin beta through integration of an amide bond between either the N-terminal amino group or the ϵ -amino group of lysine, predominantly Lys52 and Lys45 and methoxy polyethylene glycol butanoic acid. This results in a molecular weight of approximately 60,000 daltons. Pegserepoetin beta is formulated as a sterile, preservative-free protein solution for intravenous (IV) or subcutaneous (SC) administration. Single use vials are available containing 50, 100, 200, 300, 400, 600 or 1000 mcg in 1 mL solution of pegserepoetin beta. Single use prefilled syringes are available containing 50, 75, 100, 150, 200, or 250 mcg in 0.3 mL solution of pegserepoetin beta and 400, 600 or 800 mcg in 0.6 mL solution of pegserepoetin beta. Injectable solutions of pegserepoetin beta in vials and prefilled syringes contain sodium phosphate, sodium sulphate, mannitol, methionine and poloxamer 188. The solution is clear, colorless to slightly yellowish and the pH is 6.2 ± 0.2 .

2.1.2 *What are the proposed mechanism(s) of action and therapeutic indication(s)?*

Pegserepoetin beta is indicated for the treatment of anemia associated with chronic renal failure (CRF) including patients on dialysis and patients not on dialysis.

A primary growth factor for erythroid development, erythropoietin is produced in the kidney and released into the bloodstream in response to hypoxia. Erythropoietin interacts with erythroid progenitor cells to increase red blood cell production. Production of endogenous erythropoietin is impaired in patients with CRF, and erythropoietin deficiency is the primary cause of their anemia.

In comparison to erythropoietin, pegserepoetin beta 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.

2.1.3 *What are the proposed dosage(s) and route(s) of administration?*

IMPORTANT:

Due to the longer serum half-life, pegserepoetin beta should be administered less frequently than other erythropoiesis-stimulating agents (ESAs). The dosages recommended below are based upon those used in clinical studies supporting marketing approval.

Pegserepoetin beta is administered either IV or SC. In patients on hemodialysis, the IV route is recommended. The dose should be started and slowly adjusted as described below based on hemoglobin levels. When administered SC, pegserepoetin beta should be injected in the abdomen, arm or thigh.

When pegserepoetin beta therapy is initiated or adjusted, the hemoglobin should be monitored every two weeks until stabilized, and every two to four weeks thereafter. If a patient fails to respond or maintain a response, causes of non-response should be evaluated.

For patients who respond to pegserepoetin beta with a rapid increase in hemoglobin (i.e., more than 1.0 g/dL in any 2-week period), the dose of pegserepoetin beta should be reduced. A clinically significant decrease in hemoglobin may not be observed for several weeks following dose reduction or interruption of dosing. Dose adjustments should not be made more often than once a month. If one dose of pegserepoetin beta is missed, the missed dose is to be administered as soon as possible and administration of pegserepoetin beta is to be restarted at the prescribed dosing frequency.

Starting Dose for Patients Not Currently Treated with an ESA

The recommended starting dose of pegserepoetin beta for the treatment of anemia in CRF patients is 0.6 mcg/kg body weight administered as a single IV or SC injection once every two weeks.

Starting Dose for Patients Currently Treated with an ESA

When converting from epoetin alfa or darbepoetin alfa, pegserepoetin beta can be administered once monthly or, if desired, once every two weeks. The dose of pegserepoetin beta, given as a single IV or SC injection, should be based on the total weekly epoetin or darbepoetin alfa dose at the time of conversion.

Conversion from Epoetin alfa

Previous Weekly Epoetin alfa Dose (Units/week)	pegserepoetin beta Dose (mcg)	
	Once Monthly	Once Every Two Weeks
< 8000	120	60
8000 - 16000	200	100
> 16000	360	180

Conversion from Darbepoetin alfa

Previous Weekly Darbepoetin alfa Dose (mcg/week)	pegserepoetin beta Dose (mcg)	
	Once Monthly	Once Every Two Weeks
< 40	120	60
40 - 80	200	100
> 80	360	180

Dose Adjustment for Patients Not Currently Treated with an ESA

The dose of pegserepoetin beta may be increased by approximately 25% of the previous dose if

2.2.4.3 Does this drug prolong the QT or QTc interval?

Refer to Dr. Pravin Jadhav's pharmacometrics review attached separately.

2.2.4.4 Is the dose and dosing regimen selected by the Sponsor consistent with the known relationship between dose-concentration-response, and are there any unresolved dosing or administration issues?

Refer to Dr. Pravin Jadhav's pharmacometrics review attached separately.

2.2.5 What are the pharmacokinetic characteristics of the drug and its major metabolite?

2.2.5.1 What are the single dose and multiple dose pharmacokinetic parameters?

Single Intravenous Dose Pharmacokinetics

Table 2 shows a summary of pharmacokinetic parameter values of pegserepoetin beta determined following a single IV administration to healthy volunteers (Study BP16239), CRF patients on peritoneal dialysis (Study BP16779), and CRF patients not on dialysis (Study 18034). The mean values of total body clearance (CL) were slow and ranged from 28 mL/hr - 58 mL/hr in healthy subjects. The mean terminal half-life ($t_{1/2}$) value determined in CRF patients on peritoneal dialysis is apparently longer than the values determined in healthy subjects or CRF patients not on dialysis at similar doses.

Table 2: Pharmacokinetic parameter values (mean \pm SD) of pegserepoetin beta determined following a single intravenous dose

Subject Study	Healthy Volunteers BP16239				CRF Patients	
	0.4	0.8	1.6	3.2	BP16779 [#]	BP18034 [§]
Dose (mcg/kg)	0.4	0.8	1.6	3.2	0.4	0.8
Number (n)	7 - 8	7	8	6	11 - 16	8 - 12
C _{max} (ng/mL)	8.2 \pm 3.3	17.8 \pm 4.9	38.8 \pm 6.2	105.0 \pm 25.8	9.1 \pm 3.0	16.1 \pm 4.7
C _{max} / Dose	20.6	22.3	24.2	32.8	22.8	20.1
AUC _{last} (ng·hr/mL)	533 \pm 294	1405 \pm 221	3043 \pm 773	9349 \pm 2156	1028 \pm 1090	949 \pm 914
AUC _{last} / Dose	1333	1756	1902	2922	2570	1183
AUC _∞ (ng·hr/mL)	629 \pm 218	1421 \pm 219	3094 \pm 807	9522 \pm 2227	898 \pm 281	1380 \pm 880
AUC _∞ / Dose	1573	1776	1934	2975	2245	1725
CL (mL/hr)	57.1 \pm 19.2	45.3 \pm 9.6	42.7 \pm 9.3	27.5 \pm 3.1	0.49 \pm 0.18 [^]	0.93 \pm 0.75 [^]
V _{ss} (mL/kg)	not calculated				66.6 \pm 27.5	57.6 \pm 12.8
t _{1/2} (hr)	70 \pm 35	90 \pm 49	90 \pm 45	122 \pm 35	134 \pm 65	77 \pm 54

[#] on peritoneal dialysis [§] not on dialysis [^] mL/hr/kg

Single Subcutaneous Dose Pharmacokinetics

Table 3 shows a summary of pharmacokinetic parameter values of pegserepoetin beta determined following a single SC administration to healthy volunteers (Study BP16239), CRF

patients on peritoneal dialysis (Study BP16779), and CRF patients not on dialysis (Study BP18034). A C_{max} was achieved approximately 3 days following a single SC dose in the majority of subjects. The mean t_{1/2} values determined in CRF patients are longer than the values determined in healthy subjects at similar doses.

Table 3: Pharmacokinetic parameter values (mean ± SD) of pegserepoetin beta determined following a single subcutaneous dose

Subject	Healthy Volunteers				CRF Patients	
	BP16198				BP16779 [#]	BP18034 [§]
Dose (mcg/kg)	0.4	0.8	1.6	3.2	0.8	1.2
Number (n)	3 - 6	6 - 8	4 - 8	8	11 - 16	6 - 9
T _{max} (hr)*	120 (3-168)	72 (24-120)	72 (12-168)	72 (36-120)	72 (24-192)	94 (48-144)
C _{max} (ng/mL)	0.67 ± 0.43	1.86 ± 1.07	2.63 ± 1.96	15.59 ± 3.53	4.6 ± 2.3	3.2 ± 2.2
C _{max} / Dose	1.7	2.3	1.6	4.9	5.8	2.7
AUC _{clast} (ng-hr/mL)	192 ± 174	363 ± 269	627 ± 659	3102 ± 701	1106 ± 1065	771 ± 704
AUC _{clast} / Dose	480	454	392	969	1382	643
AUC _∞ (ng-hr/mL)	287 ± 165	504 ± 276	1234 ± 511	3195 ± 784	1047 ± 397	1141 ± 710
AUC _∞ / Dose	717	603	771	998	1309	951
CL/F (mL/hr)	146 ± 112*	170 ± 166	111 ± 65	79 ± 19	0.90 ± 0.42 [^]	1.67 ± 1.33 [^]
t _{1/2} (hr)	147 ± 64	102 ± 62	125 ± 70	105 ± 60	139 ± 67	142 ± 64

[#] on peritoneal dialysis [§] not on dialysis * median (range) [^] mL/hr/kg

There are apparent inconsistencies in the mean t_{1/2} values of pegserepoetin beta determined in single dose pharmacokinetic studies. Following an IV dose, the mean t_{1/2} value determined in CRF patients not on dialysis (77 ± 54 hour at 0.8 mcg/kg dose) is similar to the mean value determined in healthy subjects (70 ± 35 hr at 0.4 mcg/kg dose), but much shorter than the mean value determined in the CRF patients on peritoneal dialysis (134 ± 65 hr at 0.4 mcg/kg dose, Table 2). In contrast, following an SC administration, the mean value in CRF patients not on dialysis (142 ± 64 hr at 1.2 mcg/kg dose) is much longer than the mean value in healthy subjects (102 ± 62 hour at 0.8 mcg/kg dose), but similar to the mean value in CRF patients on peritoneal dialysis (139 ± 67 hr at 0.8 mcg/kg dose, Table 3). The reasons for such inconsistencies are not clearly known. The Sponsor explained that the inconsistencies are attributed to the variability in the pharmacokinetics of pegserepoetin beta and the small number of subjects used to calculate the mean value.

Multiple Intravenous Dose Pharmacokinetics

Table 4 shows a summary of pharmacokinetic parameter values of pegserepoetin beta determined following 3 IV doses every 3 weeks to healthy volunteers (Study BP16346). Whereas T_{max} was reached at the completion of IV injection in most subjects, T_{max} was reached as late as 2 - 4 days after dose in a few subjects. Mean CL values were low and ranged from 28 mL/hr - 61 mL/hr. The mean values of volume of distribution at steady state (V_{ss}) is similar to serum volume of normal healthy adults and ranged from 3.0 L to 5.4 L. At all dose levels, the AUC_{clast} values after the last dose are greater than the values after the first or second doses. The t_{1/2} values show a similar trend. Since blood samples were collected for a longer period of time (408 hours) after the last dose than after the first or second doses (264 hours),

these findings are probably an artifact. Therefore, AUC_{τ} appear to be more reliable than AUC_{last} in this study. Whereas the $t_{1/2}$ values determined after the first or second doses appear to be the better estimates for effective half-life during dosing, the $t_{1/2}$ values determined after the last doses seem to be the better estimates for the terminal $t_{1/2}$. Five subjects demonstrated much lower systemic exposure (e.g., $AUC < 15\%$ of the group mean or $t_{1/2} < 10$ hr) compared with other subjects in the same dose group.

Table 4: Pharmacokinetic parameter values (mean \pm SD) of pegserepoetin beta determined following 3 intravenous doses every 3 weeks to healthy subjects (Study BP16346)

Dose (mcg/kg)		0.4	0.8	1.6	3.2
Number of Subjects (n)		10	10	10	10
C_{max} (ng/mL)	Day 1	11.6 \pm 2.7	24.6 \pm 7.4	43.6 \pm 12.1	71.2 \pm 27.4
	Day 43	12.9 \pm 2.3	19.5 \pm 9.0	46.1 \pm 10.5	68.4 \pm 16.2
C_{max} / Dose	Day 1	29.0	30.8	27.1	22.3
	Day 43	32.3	24.4	28.8	21.4
	Day 43 / Day 1	1.11	0.79	1.06	0.96
AUC_{last} (ng hr/mL)	Day 1	734 \pm 131	1365 \pm 795	2919 \pm 598	5666 \pm 2918
	Day 43	1007 \pm 219	1405 \pm 886	3955 \pm 1454	6809 \pm 3154
AUC_{last} / Dose	Day 1	1838	1706	1824	1770
	Day 43	2517	1756	2471	2127
	Day 43 / Day 1	1.37	1.03	1.35	1.20
AUC_{τ} (ng hr/mL)	Day 1	790 \pm 112	1451 \pm 810	3304 \pm 1010	6098 \pm 3247
	Day 43	1049 \pm 220	1477 \pm 897	4133 \pm 1547	7099 \pm 3290
AUC_{τ} / Dose	Day 1	1975	1814	2065	1905
	Day 43	2623	1846	2583	2218
	Day 43 / Day 1	1.33	1.02	1.25	1.16
CL (mL/hr)	Day 1	35.9 \pm 7.1	37.1 (18.9-1031)	41.6 \pm 14.7	60.7 \pm 57.0
	Day 43	27.6 \pm 8.3	33.1 (17.7-1319)	43.6 \pm 46.6	50.9 \pm 57.2
V_{ss} (mL)	Day 1	3307 \pm 807	3484 \pm 2163	3329 \pm 778	5293 \pm 5085
	Day 43	3605 \pm 600	5517 \pm 3058	4351 \pm 785	4144 \pm 1511
$t_{1/2}$ (hr)	Day 1	85 \pm 32	71 \pm 43	63 \pm 21	66 \pm 37
	Day 43	135 \pm 62	108 \pm 64	120 \pm 46	91 \pm 38

* median (range)

Multiple Subcutaneous Dose Pharmacokinetics

Table 5 shows a summary of pharmacokinetic parameter values of pegserepoetin beta determined following 4 SC doses every 2 weeks to healthy volunteers (Study WP16422). At each dose and dosing day, the median value for T_{max} was 72 hr. Apparent systemic clearance (CL/F) was low and ranged from 97 mL/hr to 167 mL/hr. At all dose levels, the AUC_{last} values after the last dose are greater than the values after the first or second doses. The $t_{1/2}$ values show a similar trend. Since blood samples were collected for a longer period of time (672 hours) after the last dose than the first dose (336 hours), these findings are probably an artifact. Whereas the $t_{1/2}$ values determined after the first dose appear to be the better estimates for effective $t_{1/2}$ during multiple dosing, the $t_{1/2}$ determined after the last doses seem to be the better estimates for the terminal $t_{1/2}$.

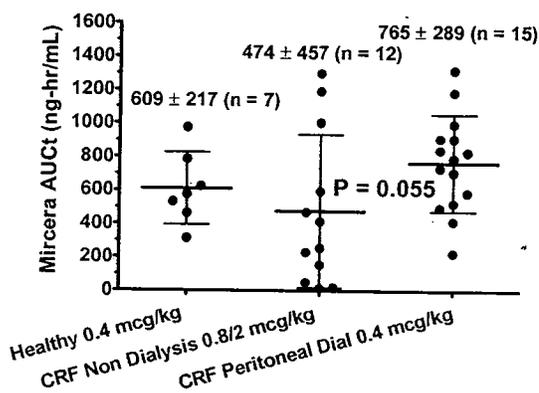
Table 5: Pharmacokinetic parameter values (mean \pm SD) of pegserepoetin beta determined following 4 subcutaneous doses to healthy subjects every 2 weeks (Study WP16422)

Dose (mcg/kg)		0.4	0.8	1.6	3.2
Number of Subjects (n)		7 - 9	6 - 9	6 - 8	8 - 9
T_{max}^* (hr)	Day 1	72 (12 - 216)	72 (6 - 72)	72 (72 - 120)	72 (24 - 120)
	Day 43	72 (24 - 120)	72 (12 - 120)	72 (12 - 168)	72 (72 - 168)
C_{max} (ng/mL)	Day 1	1.2 \pm 0.5	2.1 \pm 0.7	4.7 \pm 1.9	10.7 \pm 3.4
	Day 43	1.6 \pm 0.5	2.7 \pm 1.1	6.2 \pm 3.3	15.4 \pm 6.6
C_{max} / Dose	Day 1	3.0	2.6	2.9	3.3
	Day 43	4.0	3.4	3.9	4.8
	Day 43 / Day 1	1.33	1.29	1.34	1.44
AUC _{last} (ng hr/mL)	Day 1	164 \pm 61	341 \pm 105	741 \pm 216	1848 \pm 638
	Day 43	330 \pm 98	471 \pm 159	1223 \pm 720	3485 \pm 1468
AUC _{last} / Dose	Day 1	410	426	463	578
	Day 43	825	589	764	1089
	Day 43 / Day 1	2.01	1.38	1.65	1.88
AUC _T (ng hr/mL)	Day 1	219 \pm 73	426 \pm 79	816 \pm 189	2132 \pm 810
	Day 43	410 \pm 143	615 \pm 178	1600 \pm 916	4955 \pm 2334
AUC _T / Dose	Day 1	548	533	510	666
	Day 43	1025	769	1000	1548
	Day 43 / Day 1	1.87	1.44	1.96	2.32
CL/F (mL/hr)	Day 1	146 \pm 65	153 \pm 25	167 \pm 39	119 \pm 77
	Day 43	105 \pm 38	137 \pm 37	115 \pm 65	97 \pm 96
$t_{1/2}$ (hr)	Day 1	88 \pm 58	73 \pm 29	76 \pm 35	98 \pm 26
	Day 43	130 \pm 44	135 \pm 55	137 \pm 62	170 \pm 61

* median (range)

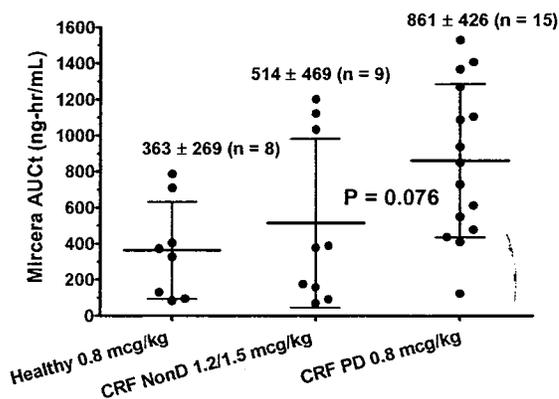
2.2.5.2 How do the pharmacokinetics in healthy volunteers compare to those in patients?

Following a similar single IV dose, the dose-normalized (0.4 mcg/kg) mean AUC_{last} value of pegserepoetin beta determined in CRF patients on peritoneal dialysis are numerically greater (approx. 1.9 fold, $p > 0.05$) than the values determined in healthy subjects (see figure below). The values determined in CRF patients not on dialysis show an opposite trend (approx. 0.89 fold, $p > 0.05$).



The ratio of the dose-normalized mean AUC_{last} value in patients on peritoneal dialysis to the value in patients not on dialysis is approximately 2.2 without statistical significance ($p > 0.05$). The statistical insignificance appears to be due to large variability of AUC data (CV up to 100%). The mean $t_{1/2}$ value determined in CRF patients on peritoneal dialysis is greater by approximately 2 fold than the values determined in healthy subjects or CRF patients not on dialysis. The V_{ss} values determined in CRF patients following a single dose are slightly larger than the values determined in healthy subjects following multiple doses.

Following a single SC dose, the dose-normalized (0.8 mcg/kg) mean AUC_{last} value of pegserepoetin beta determined in CRF patients on peritoneal dialysis are numerically much greater (approx. 3 fold, $p > 0.05$) than the values determined in healthy subjects (see Figure below).



The values determined in CRF patients not on dialysis show a similar trend with a lesser extent (approx. 1.4 fold, $p > 0.05$). The ratio of the dose-normalized mean AUC_{last} value in patients on peritoneal dialysis to the value in patients not on dialysis is approximately 2.1 without statistical significance ($p > 0.05$). These trends are reflected by slower mean CL values in CRF patients. The statistical insignificance appears to be due to large variability of AUC data (CV up to 100%). The mean $t_{1/2}$ value determined in CRF patients not on dialysis or on peritoneal dialysis is greater by 1.4 fold than the values determined in healthy subjects.

The pharmacokinetic parameter values of pegserepoetin beta were not assessed in CRF patients following multiple IV or SC doses.

2.2.5.3 What are the characteristics of drug absorption?

Absolute Bioavailability of Subcutaneous Injection

The absolute bioavailability of pegserepoetin beta following an SC dose was assessed in patients with CRF (Study BP16779) by administering crossover doses of 0.4 mcg/kg IV and 0.8 mcg/kg SC 6 weeks apart. The mean \pm SD (median, range) bioavailability value was $62 \pm 36\%$ (52%, 7 - 153%) based on AUC_{last} ratio or $71 \pm 38\%$ (59%, 36 - 149%) based on AUC $_{\infty}$ ratio (Table 6). As shown in coefficients of variation (58% based on AUC_{last}) and range, the determined absolute bioavailability showed a large inter-patient variation.

Table 6: Absolute bioavailability and pharmacokinetic parameter values (mean \pm SD) of pegserepoetin beta determined following intravenous (0.4 mcg/kg) and subcutaneous (0.8 mcg/kg) administration 6 weeks apart to 16 patients on peritoneal dialysis (Study BP16779)

Pharmacokinetic Parameter	Dose and Route of Administration		Absolute Bioavailability (%)
	0.4 mcg/kg IV	0.8 mcg/kg SC	
Tmax* (hr)	2 (0.25-13.2)	72 (24-192)	
Cmax (ng/mL)	9.1 \pm 3.0	4.6 \pm 2.3	
AUClast (ng-hr/mL)	1028 \pm 1090	1106 \pm 1065	62 \pm 36
AUC ∞ (ng-hr/mL)	898 \pm 281	1047 \pm 397	71 \pm 38 [#]
CL or CL/F [^] (mL/hr/kg)	0.49 \pm 0.18	0.90 \pm 0.42	
t $\frac{1}{2}$ [^] (hr)	134 \pm 65	139 \pm 67	

*median (range) [^] n = 11, [#] n = 8

The time course of reticulocyte counts between the two routes of administration was comparable at the selected doses in Study 16779. After both 0.8 μ g/kg SC and 0.4 μ g/kg IV injections of pegserepoetin beta, a peak increase in reticulocyte counts was observed after 8 days (Figure 1). Thereafter, reticulocyte counts decreased and returned to levels close to baseline.

Figure 1: Reticulocyte counts (mean \pm SE) measured after intravenous (0.4 mcg/kg) and subcutaneous (0.8 mcg/kg) administration of pegserepoetin beta 6 weeks apart to 16 patients on peritoneal dialysis (Study BP16779)

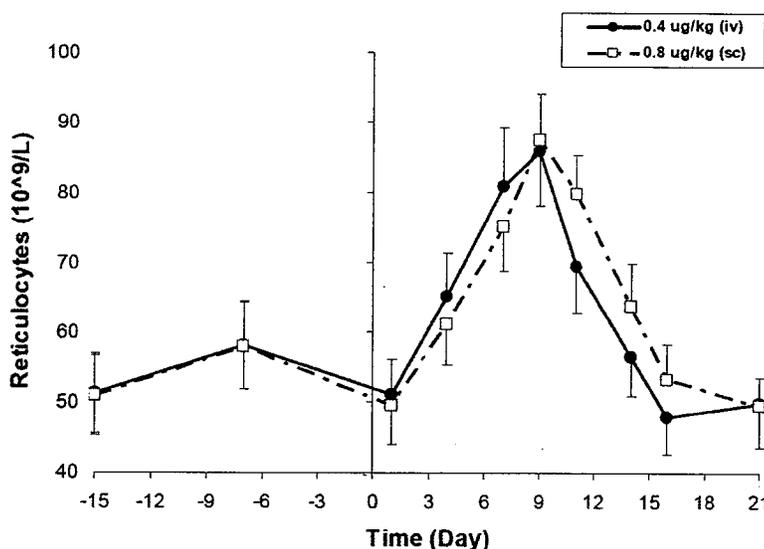


Table 7 shows a summary of the pharmacodynamic parameters for reticulocyte counts following the IV and SC administrations of pegserepoetin beta in Study BP16779. The mean AUE values measured after 0.4 mcg/kg IV and 0.8 mcg/kg SC were almost identical (geometric mean ratio, GMR, 1.02; 90% confidence interval, 90% CI, 0.92 - 1.14). For the maximum increase in reticulocyte counts, the absolute changes from baseline were similar, whereas for the relative change from baseline, the mean value appeared to be higher after SC administration (0.8 mcg/kg) than after IV dosing (0.4 mcg/kg).

Table 7: Reticulocyte counts (mean \pm SD) measured after intravenous (0.4 mcg/kg) and subcutaneous (0.8 mcg/kg) administration of pegserepoetin beta 6 weeks apart to 16 patients on peritoneal dialysis (Study BP16779)

Dose and Route	T_{max}^* (day)	Maximum Change from Baseline		$AUE_{0-21days}$ ($10^9 \cdot day/mL$)
		Absolute ($10^9/L$)	Relative (%)	
0.4 mcg/kg IV	8 (6 - 10)	36 \pm 19	73 \pm 38	1.19 \pm 0.47
0.8 mcg/kg SC	8 (6 - 13)	41 \pm 20	92 \pm 59	1.19 \pm 0.36
Geometric Mean Ratio		1.11		1.02
90% Confidence interval		0.73 - 1.70		0.92 - 1.14

* median (range)

The bioavailability of pegserepoetin beta administered subcutaneously was also assessed in patients with CRF (Study BP18034) with a parallel group study design. The patients enrolled on the study received a single dose of pegserepoetin beta 0.8 mcg/kg IV or 1.2 mcg/kg SC. The bioavailability was 54% or 55% based on the comparison of the mean values of AUC_{last} or AUC_{∞} respectively. The bioavailability values determined in this study with a parallel group design appear to be less reliable than the values determined in Study BP16779 with a crossover design.

The absolute SC bioavailability of pegserepoetin beta was also assessed in healthy subjects (Study WP16383) in an incomplete three-way crossover design (0.8 mcg/kg IV, 0.8 mcg/kg SC, or 1.6 mcg/kg SC followed by 3.2 mcg/kg SC every 2 weeks). The mean \pm SD bioavailability values were 46 \pm 27% for 0.8 mcg/kg SC, 62 \pm 56% for 1.6 mcg/kg SC, 109 \pm 204 for 3.2 mcg/kg SC. The bioavailability values determined in this study do not appear to be reliable since there were significant period effect and large variability due to drug accumulation over time by insufficient washout between doses and incomplete crossover design, particularly at the dose of 3.2 mcg/kg always administered lastly.

Relative Bioavailability between Subcutaneous Injections into Abdomen, Arm, Thigh

In a clinical pharmacology study (BP18035), the relative bioavailability of pegserepoetin beta was compared after single SC doses of 3.0 mcg/kg through the abdomen, arm and thigh. Study BP18035 was a three-way crossover study conducted in healthy subjects who were randomized to receive three doses of pegserepoetin beta in six possible treatment sequences with a seven-week interval between administrations. The pharmacokinetic parameters were similar for the three sites of administration. As shown in Table 8, the GMR for AUC_{last} were 1.01, 1.11 and 1.10 when comparing the abdomen to the arm, the thigh to the arm and the thigh to the abdomen, respectively. For C_{max} , the ratios were 1.09, 1.21 and 1.11, respectively. Terminal half-life values were also similar for the three sites (means between 160 and 164 hours). These results indicate that for the three sites of administration, systemic exposure (AUC_{last} and C_{max}) was similar, although the C_{max} value was observed to be 10 to 20% higher after injection in the thigh compared with the arm and abdomen.

Table 8: Comparison of pharmacokinetic parameter values (mean ± SD) of pegserepoetin beta determined following a single subcutaneous dose of 3.2 µg/kg through different sites of injection (Study BP18035).

Pharmacokinetic Parameter	A: Abdomen (n = 40)	B: Arm (n = 42)	C: Thigh (n = 42)	Geometric Mean Ratio [90% CI]		
				A / B	C / B	C / A
<i>T</i> _{max} * (hr)	96 (24 - 168)	97 (48 - 216)	96 (48 - 120)			
<i>C</i> _{max} (ng/mL)	15.7 ± 5.6	14.2 ± 5.8	16.5 ± 5.7	1.09 [0.95 1.25]	1.21 [1.07 1.37]	1.11 [1.02 1.22]
<i>AUC</i> _{clast} (ng hr/mL)	4151 ± 1380	4088 ± 1567	4323 ± 1521	1.01 [0.90 1.17]	1.11 [1.01 1.22]	1.10 [1.02 1.18]
<i>AUC</i> _∞ (ng hr/mL)	4241 ± 1410	4449 ± 1525 [^]	4558 ± 1461 [#]			
<i>t</i> _{1/2} (hr)	160 ± 48	164 ± 41 [^]	160 ± 46 [#]			

* median (range) [^] n = 38 [#] n = 39

The trends in the changes of mean reticulocyte counts were similar for the three sites after SC injection (Figure 2). The slightly higher mean reticulocyte counts observed after SC injection into the thigh compared with the arm or abdomen is consistent with the pharmacokinetic result of a slightly higher *C*_{max} after injection into the thigh. Independent of the site of injection, a peak increase in reticulocyte counts was observed after approximately 10 days. Thereafter, reticulocyte counts decreased and returned to levels close to baseline on approximately Day 29.

Figure 2: Time course of mean reticulocyte counts determined following a single subcutaneous dose of pegserepoetin beta 3.0 mcg/kg into the abdomen, (n = 41), arm (n = 41) and thigh (n = 42) of healthy subjects (Study BP18035)

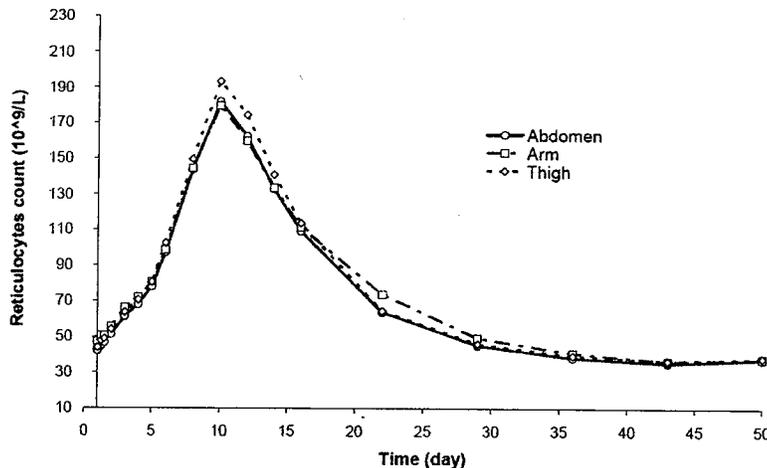


Table 9 shows the *T*_{max}, maximum changes from baseline, and *AUE*_{1-50days} of reticulocyte counts following SC injection of pegserepoetin beta into the abdomen, arm and thigh. The median values of *T*_{max} were the same, occurring 10 days after administration, independent of the site of injection. For the maximum increase in reticulocyte counts from baseline and *AUE*_{1-50days}, the mean values were comparable between the three sites of injection (90% CIs of GMRs within the range of 80% to 125%).

Table 9: Comparison of mean reticulocyte counts (mean \pm SD) determined following a single subcutaneous dose of pegserepoetin beta 3.0 mcg/kg into the abdomen; (n = 41), arm (n = 41) and thigh of healthy subjects (Study BP18035)

Pharmacodynamic Parameter	A: Abdomen (n = 41)	B: Arm (n = 41)	C: Thigh (n = 42)	Geometric Mean Ratio [90% Confidence Interval]		
				A / B	C / B	C / A
<i>T</i> _{max} (d)*	10 (8 - 14)	10 (6 - 14)	10 (6 - 12)			
Maximum Change from Baseline (%)	269 \pm 133	258 \pm 130	273 \pm 141	1.02 [0.92 1.13]	1.04 [0.94 1.15]	1.03 [0.93 1.14]
<i>AUE</i> _{1-50days} (10 ⁹ day/mL)	3.5 \pm 0.6	3.6 \pm 0.8	3.6 \pm 0.7	0.96 [0.94 0.99]	1.00 [0.97 1.02]	1.03 [1.01 1.06]

* median (range)

Considering the variability in the pharmacokinetics of pegserepoetin beta and the similarity in reticulocyte counts following pegserepoetin beta administration, the SC injection sites of abdomen, arm, and thigh are considered to be comparable though the 90% CIs of the GMR of C_{max} are outside the bioequivalence range of 90% - 125%.

2.2.5.4 What are the characteristics of drug distribution?

Pegserepoetin beta appears to be distributed mainly intravascularly. The mean volume of distribution at steady state (V_{ss}) determined in healthy subjects (approx. 3 - 5 L, Table 2) is similar to or slightly larger than the serum volume in adults. The V_{ss} values determined in CRF patients weighing 70 kg following a single dose (approx. 4.5 L) are similar to or slightly larger than the values determined in healthy subjects following multiple doses (Table 2).

2.2.5.5 Does the mass balance study suggest renal or hepatic as the major route of elimination?

Not applicable to biologics.

2.2.5.6 What are the characteristics of drug metabolism?

Not applicable to biologics.

2.2.5.7 What are the characteristics of drug excretion?

Not applicable to biologics.

2.2.5.8 Based on pharmacokinetic parameters, what is the degree of linearity or nonlinearity in the dose-concentration relationship?

The degree of linearity in the dose concentration relationship of pegserepoetin beta was determined in Studies BP16198, BP16239, JP16690, BP16346, and WP16422 (see 4.2. **Summary of Individual Studies**). For each of these studies, values of C_{max} and AUC_{last} were dose-normalized and mean values were compared using an analysis of variance (ANOVA). Results from Studies BP16198 (Table 3) and BP16239 (Table 2) showed a statistically significant difference between dose levels for both C_{max} and AUC_{last}, indicating a deviation

from linearity in the dose-concentration relationship. In these studies, a greater than dose proportional increase in AUC_{last} and C_{max} was observed, especially at the highest dose tested (3.2 mcg/kg). For example, in study BP16239, the mean AUC_{last} value measured at the dose of 3.2 mcg/kg was 54% greater than the expected value from the measured value at 1.6 mcg/kg based on linearity predictions. In contrast, the ANOVA did not show any significant differences between doses in Studies BP16346, WP16422 and JP16690.

The apparent inconsistency between studies in the degree of linearity in the dose concentration relationship may be due to a result of a small deviation from linear pharmacokinetics. The small deviation is not likely to make a significant impact on the clinical use of pegserepoetin beta considering the high variability in the pharmacokinetics of pegserepoetin beta and the dose adjustment based on hemoglobin response.

2.2.5.9 How do the pharmacokinetic parameters change with time following chronic dosing?

The accumulation of pegserepoetin beta following repeated doses was low to moderate at the tested dosing intervals. When pegserepoetin beta was administered intravenously every 3 weeks in Study BP16346, the accumulation ratio based on the AUC_{τ} value determined on Day 43 compared to the value on Day 1 ranged from 1.02 to 1.33 (Table 4). The accumulation ratio based on C_{max} ranged from 0.79 to 1.11. When pegserepoetin beta was administered SC every 2 weeks in Study WP16422, the accumulation ratio based on the C_{max} and AUC_{τ} values determined on Day 43 compared to the values on Day 1 ranged from 1.29 to 1.44 and from 1.44 to 2.32, respectively (Table 5). The higher mean accumulation ratio values in Study WP16422 compared with BP16436 seems to be related to the shorter dosing interval.

2.2.5.10 What is the inter- and intra-subject variability of pharmacokinetic parameters in volunteers and patients, and what are the major causes of variability?

The variability in the pharmacokinetics of pegserepoetin beta was moderate to high. When determined in 42 healthy subjects following the subcutaneous injections of pegserepoetin beta 3.0 mcg/kg into abdomen, arm, and thigh in a 7-week interval (Study BP18035), the inter-subject variability of C_{max} and AUC_{last} ($CV = SD/mean$) was 37% and 36%, respectively. The intra-subject variability based on the CV calculated from the residual error variance in the ANOVA was 33% and 27%, respectively.

Low Exposure to Pegserepoetin beta

Very low or no systemic exposure to pegserepoetin beta was observed in approximately 7% of healthy subjects enrolled in clinical pharmacology studies. In these subjects, a low or no pharmacodynamic response (reticulocyte count) was observed in the corresponding time period post-drug administration. The low systemic exposure after multiple administrations of pegserepoetin beta falls into two main patterns. In subjects with Pattern A, very low pegserepoetin beta concentrations in serum are observed after each dose with a short $t_{1/2}$ for pegserepoetin beta (approximately one fifth of that in subjects with normal systemic exposure). This pattern is related to high clearance of pegserepoetin beta. In subjects with Pattern B, very low pegserepoetin beta concentrations are observed after one but not all doses. Pattern B

suggests inter-occasion variability in the absorption of the pegserepoetin beta in case of SC administration or other unknown phenomenon in case of IV administration.

An exploratory study (BP17570, see 4.2 Summary of Individual Studies) was conducted to determine whether such findings were reproducible. In Study BP17570, some of the same subjects identified from previous studies (WP16422 and WP16383) as having low serum concentrations of pegserepoetin beta were recruited. In addition, healthy volunteers with no previous exposure to pegserepoetin beta were also recruited as control subjects. To test whether low systemic exposure occurs consistently, two doses of pegserepoetin beta (0.8 mcg/kg) were administered 4 weeks apart.

As shown in Table 10, 3 (Subjects 3, 12 and 14) out of 12 subjects showed low systemic exposure to pegserepoetin beta after repeated administrations. These three subjects had a very small or undetectable reticulocyte response. The terminal half-life could not be estimated for these subjects. These subjects showed reproducible low levels of exposure after receiving repeated doses. This suggests that inter-occasion variability within the time-frame of this study (i.e. 4 weeks) is small and not the explanation for the low exposures observed. However, the subjects identified previously as having low systemic exposure (Subjects 1, 13, 19) were not the same subjects who exhibited low exposure in this study. There is no clear explanation for this finding. There was no change in baseline characteristics from previous studies to this study for these subjects that could explain the difference in response to pegserepoetin beta. These results indicate that reproducibility in terms of exposure levels occurs within a short time-frame (i.e. 4 weeks) but is not observed over a much longer period of time (i.e. two to three years since the previous studies were conducted).

Table 10: Pharmacokinetic parameters of pegserepoetin beta determined in healthy subjects with or without lower previous exposure to pegserepoetin beta (Study BP17570)

Subject	Previous Exposure	$t_{1/2}$ (hr)				AUC_{last} (ng hr/mL)			
		Value at Previous Dose	Dose 1	Dose 2	Dose 3	Value at Previous Dose	Dose 1	Dose 2	Dose 3
			0.8 mcg/kg	0.8 mcg/kg	3.2 mcg/kg		0.8 mcg/kg	0.8 mcg/kg	3.2 mcg/kg
1	0.8 mcg/kg IV	18.2	46.9	34.7	NC	134.6	797	834	NC
2	No		80.1	110.7	126.3		1870	1840	9150
3	No		NC	NC	NC		158	148	NC
4	No		47.8	83.3	161.3		1020	1420	8980
5	No		34.8	112.4	107.3		1420	1820	8820
12	No		NC	NC	NC		87	79	1650
13	1.6 mcg/kg SC	NC	NC	17.7	74.3	NC	441	487	7760
14	No		NC	NC	NC		99.4	59	167
15	No		39.9	116.7	163.7		1270	1720	9900
16	No		105.8	NC	NC		1500	NC	NC
17	No		21.1	13.1	55.9		426	275	4610
19	1.6 mcg/kg SC	25.0	18.2	104.1	54.2	192.3	770	701	5380

IV, intravenous; NC, not calculable; SC, subcutaneous

It is suggested that Pattern A low systemic exposure to pegserepoetin beta may be dose dependent since Pattern A low exposure was observed in most clinical pharmacology studies at lower doses but not in studies with higher doses only (i.e., 3.2 and 3.0 mcg/kg in BP16964 and

BP18035, respectively). It is also suggested that there may be an unknown elimination pathway that is responsible for the high clearance and that would be saturated when the dose is increased. Therefore, Study BP17570 was also designed to test whether low systemic exposure may be dependent on dose. Subjects were, therefore, administered a third and higher dose (3.2 mcg/kg) of pegserepoetin beta 4 weeks after the two lower doses (0.8 mcg/kg). Only two (Subjects 12 and 14) of the three subjects showing low exposure received this third dose (Table 10). This low number of subjects precludes any conclusions on the dose dependency.

A low systemic exposure to pegserepoetin beta was also observed in clinical studies conducted in patients with CRF (Table 11). However, the incidence of low exposure was relatively smaller (2% - 4% of patients) and the low systemic exposure does not always predict lack of efficacy. Similar results of isolated cases of patients with very low systemic exposure have been reported following administration of single doses of darbepoetin alfa (1 patient in a cohort of 8 and 1 patient in another cohort of 17) and epoetin alfa (1 patient in a cohort of 15). These results suggest that the very low systemic exposure observed in a small number of patients is not specific to pegserepoetin beta but may be shared with other drugs of the same pharmacologic class.

Table 11: Frequency of low systemic exposure to pegserepoetin beta by pattern and associated hemoglobin response in patients with chronic renal failure

Study (Phase)	Number of Patients				
	Total	Pattern A		Pattern B	
		n	Hb Response	n	Hb Response
BA16260 (2)	61	2 (3%)	2 NR	7 (11%)	1 NR, 6 R
BA16528 (2)	65	2 (3%)	2 NR	5 (8%)	3 NR, 2 R
BA16736 (3)	135	0		6 (4%)	6 R
BA16739 (3)	122	0		2 (2%)	1 S, 1 D
BA16740 (3)	143	0		4 (3%)	2 S, 2 I

Hb, hemoglobin; NR, non-responder; R, responder; S, stable; D, decrease by > 1 g/dL, I, increase by > 1 g/dL

2.2.6 What are the PD characteristics of the drug? (Frequently applicable to Biologics, Include PD parameters that are not addressed in 2.2.4 but important to understand the clinical pharmacology of the drug)

2.2.6.1 Are the PD changes appropriately identified and measured? (If yes, refer to 2.6, Analytical Section; if no, describe the reasons.)

Yes, please refer to Section 2.6. Analytical.

2.2.6.2 What are the characteristics of PD markers?

Reticulocyte Counts

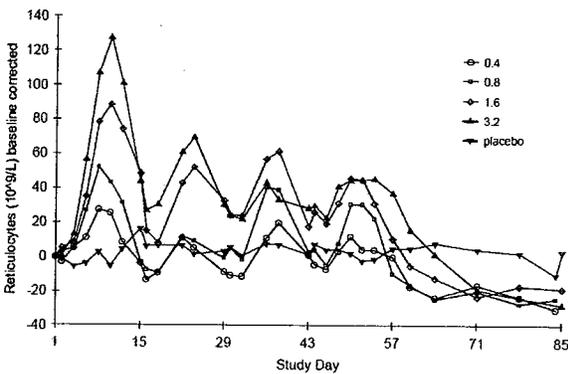
Changes in reticulocyte counts from baseline were selected as the primary pharmacodynamic marker in all clinical pharmacology studies. Following a single IV or SC dose of pegserepoetin

beta to CRF patients on peritoneal dialysis, the reticulocyte response was characterized by an increase with a rapid onset and a peak 8 to 10 days post-dose (Study BP16779, Figure 1). Thereafter, reticulocyte counts declined and returned to levels near baseline 20 - 30 days post dose. At later time points, reticulocyte counts decreased further, slightly below baseline levels, and then returned slowly towards baseline levels. This rebound effect appears to be the result of a physiologic negative feedback mechanism that decreases the production of reticulocytes after a strong stimulation of erythropoiesis.

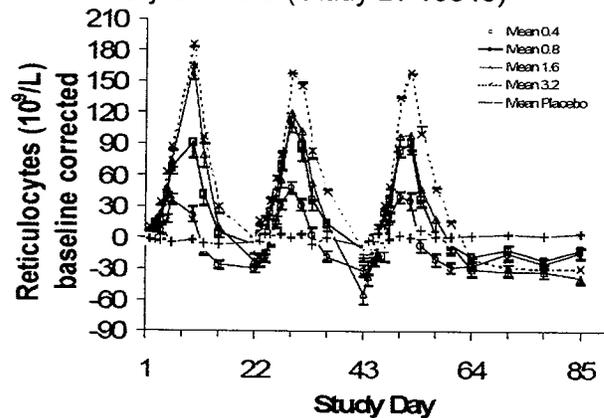
After repeated administrations of pegserepoetin beta every 2 weeks, the reticulocyte count response diminished over time after SC dosing (Study WP16422, Figure 3A). In contrast, the reticulocyte count response remained nearly constant over time after IV dosing every three weeks (study BP16346, Figure 3B).

Figure 3: Baseline corrected mean reticulocyte counts after multiple doses of pegserepoetin beta to healthy subjects

A. SC every 2 weeks (Study WP16422)



B. IV every 3 weeks (Study BP16346)

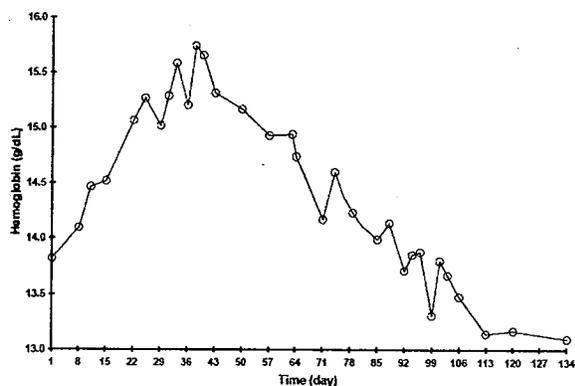


Hemoglobin

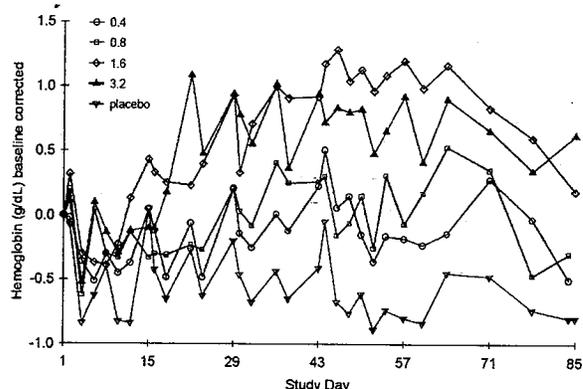
Hemoglobin was selected as the secondary pharmacodynamic marker in clinical pharmacology studies, whereas hemoglobin was used as an efficacy endpoint in clinical studies. Hemoglobin increase defined as an increase > 0.4 g/dL from baseline was observed after 7 to 15 days after the first dose. After multiple dose administrations of pegserepoetin beta to healthy volunteers, a cumulative increase in hemoglobin levels were observed over time (Figure 4). A slow decline in hemoglobin levels after the last drug administration was observed with a similar rebound effect as seen in reticulocyte counts.

Figure 4: Mean hemoglobin levels measured over time from healthy subjects following multiple doses of pegserepoetin beta every 2 weeks

A. Following 3 IV doses of 3.2 mcg/kg (Study BP17278, n = 19)



B. Following 4 SC doses (Study WP16422, n = 10 each)



Other Pharmacodynamic Parameters

Hematocrit, red blood cell counts, and iron-related parameters such as serum iron, serum ferritin, soluble transferrin receptor, and transferrin saturation were also assessed as secondary pharmacodynamic parameters in clinical pharmacology. In brief reviews, the results showed consistency with changes in erythropoiesis following erythropoietin administrations.

2.2.6.3 *How does the PD of the drug in healthy volunteers compare to that in patients?*

Reticulocyte Counts

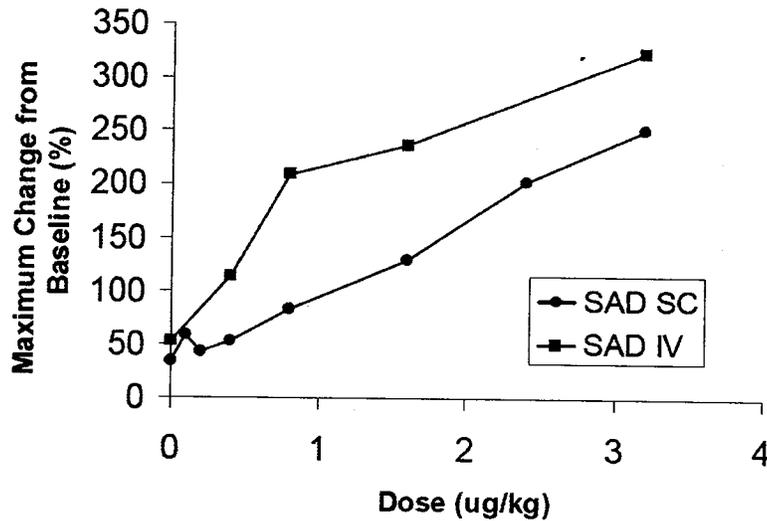
The pattern of reticulocyte response was similar in CRF patients and healthy subjects (Study BP16239).

2.2.6.4 *Based on PD parameters, what is the degree of linearity or nonlinearity in the dose-response relationship?*

Reticulocyte Counts

For both IV and SC dosing, the relationship between reticulocyte response and dose was nearly linear (Figure 5). At the highest dose level tested (3.2 mcg/kg), the maximum observed reticulocyte response was 251% and 334% after SC and IV dosing, respectively.

Figure 5: Maximum change from baseline in reticulocyte counts as a function of dose after intravenous and subcutaneous administrations of pegserepoetin beta to healthy subjects (Studies BP16239 and BP16198, respectively).



Hemoglobin

After single dose administrations of pegserepoetin beta, there was an increasing trend in hemoglobin response with dose. However, the hemoglobin response was very variable and no clear dose dependency could be observed in both healthy volunteers (Studies BP16239 and BP16198) and CRF patients (Studies BP16779 and BP18034). After multiple dose administrations of pegserepoetin beta to healthy volunteers, the increase in hemoglobin levels over time showed a rough dose-dependent fashion (Figure 4B).

2.2.6.5. *How do the PD parameters change with time following chronic dosing? (This may include time to steady-state; single dose prediction of multiple dose PD.)*

Reticulocyte Counts

As described in the previous question 2.2.6.4., after repeated administrations of pegserepoetin beta every 2 weeks, the reticulocyte count response diminished over time after SC dosing (Study WP16422, Figure 3A). In contrast, the reticulocyte count response remained nearly constant over time after IV dosing every three weeks (study BP16346, Figure 3B). The difference appears to be due to the difference in dosing interval rather than the difference in route of administration: the reticulocyte count response also diminished in Study BP16346 with IV pegserepoetin beta dosing every 2 weeks. Similar to the rebound effect seen after single dosing, this decrease in response after dosing every 2 weeks appears to be the result of a physiologic negative feedback mechanism that decreases the production of reticulocytes after a strong stimulation of erythropoiesis. Decreases in endogenous erythropoietin production or exhaustion of the pool of precursor cells in the bone marrow after repeated stimulation of erythropoiesis are possible hypotheses to explain these observations.

2.2.6.6 What is the inter- and intra-subject variability of PD parameters in volunteers and patients, and what are the major causes of variability?

The CV of AUE in reticulocyte counts determined in healthy subjects was approximately 20%. No clinical pharmacology studies were adequately conducted to determine the intra-subject variability of PD parameters and the cause of variability.

2.3 Intrinsic Factors

2.3.1 What intrinsic factors influence exposure and/or response, and what is the impact of any differences in exposure on efficacy or safety responses?

Refer to Dr. Pravin Jadhav's pharmacometrics review attached separately.

2.3.2 Based upon what is known about exposure-response relationships and their variability and the groups studied, healthy volunteers vs. patients vs. specific populations, what dosage regimen adjustments, if any, are recommended for each of these groups? If dosage regimen adjustments are not based upon exposure-response relationships, describe the alternative basis for the recommendation.

2.3.2.1 Elderly

Refer to Dr. Pravin Jadhav's pharmacometrics review attached separately.

2.3.2.2 Pediatric Patients

Refer to Dr. Pravin Jadhav's pharmacometrics review attached separately.

2.3.2.3 Gender

Refer to Dr. Pravin Jadhav's pharmacometrics review attached separately.

2.3.2.4 Race

Japanese versus Caucasians

When determined in 30 Japanese and 30 Caucasian healthy subjects following a single IV dose of pegserepoetin beta (Study JP16690), the exposure was comparable. For C_{max}, when all doses were considered, the GMR of Japanese to Caucasian subjects was 1.19 (90% CI, 1.06-1.34). Although the ratio was close to one for the 1.6 and 3.2 µg/kg doses, it was 1.67 for the 0.8 µg/kg dose, indicating that C_{max} was 67% higher in Japanese than in Caucasian subjects for this dose. For AUC_{last}, the GMR was 1.09 (90% CI, 0.84-1.40) when all doses were considered. Although the bioequivalence criterion was not met for the upper pre-defined limit of 1.25, the result indicated similarity in exposure between Japanese and Caucasian subjects.

Also refer to Dr. Pravin Jadhav's pharmacometrics review attached separately.

2.3.2.5 Renal impairment

Refer to Dr. Pravin Jadhav's pharmacometrics review attached separately.

2.3.2.6 Hepatic impairment

Refer to Dr. Pravin Jadhav's pharmacometrics review attached separately.

2.3.2.7 What pregnancy and lactation use information is there in the application?

There are no adequate and well-controlled studies in pregnant women. Pegserepoetin beta should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. It is unknown whether pegserepoetin beta is excreted in human breast milk.

2.3.3 Immunogenicity (added specifically for Biologics)

2.3.3.1 Are the anti-drug antibodies in serum (or other biological fluid) appropriately identified and measured to assess immunogenicity? (If yes, refer to 2.6, Analytical Section; if no, describe the reasons.)

Yes, please refer to **2.6, Analytical**.

2.3.3.2 What is the incidence (rate) of the production of the anti-drug antibodies?

Even though no specific study was conducted to test for immunogenicity of pegserepoetin beta, the immunogenicity was monitored in all clinical and clinical pharmacology studies trials undertaken with pegserepoetin beta. No subjects received pegserepoetin beta showed an induction of anti-pegserepoetin beta or anti-erythropoietin antibodies in any of the studies. One patient in study BA16739 treated with pegserepoetin beta had detectable levels of anti-erythropoietin antibodies (above the limit of quantification of 5 ng/ml) at baseline, Day 90 and Day 365 (range, 6.1 - 7.0 ng/mL). Samples taken at days 197 and 281, in contrast, were negative. These findings indicate that the patient had low levels of anti-erythropoietin antibodies before treatment with pegserepoetin beta and the antibody titer did not increase as the patient continued the treatment. One patient who received a reference comparator (epoetin beta) had positive anti-erythropoietin antibody findings. This patient had detectable levels of anti-erythropoietin antibodies at Days 89, 142, 201, 257, 285, 313, and 369 (range 10.6 to 14300 ng/mL).

2.3.3.3 Do the anti-drug antibodies neutralize the effect of the drug? (If yes, include a neutralization assay method(s) in **2.6 Analytical section**)

Not applicable: no subject received pegserepoetin beta developed anti-pegserepoetin beta and therefore neutralization effect could not be studied.

2.3.3.4 Does the immunogenicity affect the PK and/or PD of the drug?

Not applicable: no subject received pegserepoetin beta developed anti-pegserepoetin beta and therefore such effect could not be studied.

2.3.3.5 What is the clinical impact of the production of anti-drug antibodies on the efficacy and safety?

Not applicable: no subject received pegserepoetin beta developed anti-pegserepoetin beta and therefore such effect could not be studied.

2.4 Extrinsic Factors

2.4.1 What extrinsic factors (drugs, herbal products, diet, smoking, and alcohol use) influence dose-exposure and/or -response and what is the impact of any differences in exposure on response?

Effect of Hemodialysis

The effect of hemodialysis on the serum concentration of pegserepoetin beta was determined in 41 CRF patients on hemodialysis (Study BA16260). The geometric mean ratio of the concentration of pegserepoetin beta after hemodialysis to the concentration before hemodialysis was 1.01 (90% confidence interval, 0.87 - 1.16). Thus, hemodialysis has no effect on the serum concentration of pegserepoetin beta.

Also refer to Dr. Pravin Jadhav's pharmacometrics review attached separately.

2.4.2 Drug-drug interactions

Refer to Dr. Pravin Jadhav's pharmacometrics review attached separately.

2.4.3 What issues related to dose, dosing regimens, or administration are unresolved and represent significant omissions?

No unresolved issues or omissions related to dose, dosing regimens, or administration are identified in this submission.

2.5 General Biopharmaceutics

None of the general biopharmaceutics questions in the QBR is applicable to this injectable biologics product, pegserepoetin beta. Only the comparability questions in Section 2.5.10 added specifically for biologics are applicable to this BLA.

2.5.10 What is the PK and/or PD comparability of the proposed to-be-marketed formulation to the pivotal clinical trial? (Applicable to Biologics only)

During the manufacturing process development for pegserepoetin beta, several changes were implemented (Table 12). The process changes from the preliminary

Table 12: Pegserepoetin beta supply (drug substance and drug product) used in clinical studies

	Preliminary Preliminary Formulation	Final Formulation	Final Formulation	Final Formulation
Drug Substance				
Manufacturing Process	Preliminary	Final	Final	Final
Scale of Starting Material (g)	Pilot	Pilot	Final	Final
Facility	Pilot	Pilot	Pilot	Final
Drug Product Formulation	Preliminary	Final	Final	Final
Drug Supply for Clinical Studies	<u>Phase I</u> BP16198 BP16239 WP16422 BP16346 WP16383 BP16779 BP16964 JP16417 JP16690 <u>Phase II Renal</u> BA16285 BA16286 BA16528 BA16260 <u>Phase I/II Oncology</u> BA16558	<u>Phase I</u> BP17278 BP16964 BP17570 <u>Phase II Renal Extension</u> BA16285 BA16286 BA16528 <u>Phase II Oncology</u> BA16728 NA17101	<u>Phase I</u> BP18034 BP18035 Phase II Renal Extension BA16285 BA16286 <u>Phase III Renal</u> BA16739 BA16740*** BA16736 BA16738 BA17283 BA17284 <u>Phase III Renal Extension</u> BH18387	<u>Phase III renal extension</u> BH18387 <u>Phase II and III oncology</u> <u>To Be Marketed</u>

A clinical pharmacology study (BP16964) was conducted to compare the pharmacokinetics of pegserepoetin beta between Formulations A versus B following an SC administration of 3.2

mcg/kg (Table 13). Study BP16964 was a randomized, single dose, open label, two-way crossover study conducted in 35 healthy subjects.

Table 13 compares the pharmacokinetic parameters of pegserepoetin beta determined in Study BP16964 following an SC injection of Formulations A and B (3.2 mcg/kg). The median and range of Tmax values was identical for both formulations. The mean Cmax values are comparable. However, the mean AUC_{last} was somewhat smaller in Formulation B than A (GMR = 0.89; 90% CI = 0.77 - 1.04); a similar result was obtained for AUC_{inf} (GMR = 0.84; 90% CI = 0.73 - 0.96). Although t_{1/2} could not be calculated in 3 occasions, no major differences were observed for the mean t_{1/2} values. The mean values of the apparent volume of distribution in the post-distribution phase (Vz/F) and the apparent clearance (CL/F) of pegserepoetin beta were also comparable.

Table 13: Comparison of pharmacokinetic parameter values (mean ± SD) of pegserepoetin beta determined following a single subcutaneous injection of Formulations A and B 3.2 mcg/kg (n = 35, Study BP16964).

Pharmacokinetic Parameter	Formulation A	Formulation B	Geometric Mean Ratio (B/A)	90% Confidence Interval
Tmax (hr) [#]	72 (12 - 216)	72 (12 - 216)		
Cmax (ng/mL)	19.5 ± 10.5	19.0 ± 9.9	0.98	0.83 - 1.17
AUC _{last} (ng hr/mL)	3829 ± 1757	3362 ± 1429	0.89	0.77 - 1.04
AUC _∞ (ng hr/mL)	5334 ± 2473*	4283 ± 1561 [^]	0.84	0.73 - 0.96
CL/F (mL/hr)	67.0 ± 87.5*	65.2 ± 35.8 [^]		
Vz/F (L)	13.3 ± 10.9*	13.0 ± 8.5 [^]		
t _{1/2} (hr)	169 ± 88*	141 ± 53 [^]		

[#] median (range), * n = 33, [^] n = 34

For both formulations, maximum reticulocyte counts were reached 8 to 10 days after drug administration (Table 14). The baseline-corrected values of area under the effect-time curve determined from Day 1 to Day 36 of drug administration (AUE_{1-36days}) for reticulocytes were similar for both formulations. The absolute and relative maximum changes from baseline in reticulocyte counts were also comparable for both formulations.

Table 14: Comparison of reticulocyte counts (mean ± SD) determined following a single subcutaneous dose of pegserepoetin beta 3.2 µg/kg (n = 35, BP16964)

Pharmacodynamic Parameter		Formulation A	Formulation B	Geometric Mean Ratio (B/A)	90% Confidence Interval
Tmax (hr) [*]		8.0 (4.0 - 14.0)	8.0 (5.0 - 16.0)		
Maximum Change	Absolute (10 ⁹ /mL)	0.12 ± 0.05	0.12 ± 0.05		
	Relative (%)	171 ± 106	161 ± 90.8		
AUE _{1-36day} (10 ⁹ day/mL)		0.91 ± 0.72	0.93 ± 0.78	1.03	1.00 - 1.06

^{*} median (range)

There was a similar increase in hemoglobin levels following administration of Formulations A and B (data not shown). Hemoglobin concentrations increased during the first 2 weeks and then

reached a plateau. The maximum absolute increase from baseline in hemoglobin concentration was about 1 g/dL for both formulations

Considering the variability in the pharmacokinetics of pegserepoetin beta and the similarity in reticulocyte counts following pegserepoetin beta administration, Formulations A and B are considered to be comparable though the 90% CIs of the GMR of AUC are outside the bioequivalence range of 80% - 125%.

2.5.10.1 What data support or do not support a waiver of a human PK or comparability study if no PK or PD comparability study was conducted in humans? (e.g., demonstration of CMC, Pharm/Tox or Clinical comparability)

Not applicable. The Sponsor conducted a PK comparability study.

2.5.10.2 What are the safety or efficacy issues, if any, for comparability studies that fail to meet the 90% CI using comparability limits? (Comparability limits for Biologics are not necessarily the same as bioequivalence limits of 80 - 125% for synthetic drugs.)

Not applicable. The PK comparability study results are not considered to be a failure in demonstrating PK comparability

2.5.10.3 If the drug products do not meet the standard criteria for comparability, what clinical pharmacology and/or clinical safety and efficacy data support the approval of the to-be-marketed product?

Not applicable. The PK comparability study results are not considered to be a failure in demonstrating PK comparability

2.6 Analytical

This section should address issues related to the analytical and bioanalytical methods used to support the CPB studies. (For Biologics, see 2.6.5, 2.6.6 and 2.6.7 only. Other analytical questions are not applicable to Biologics.)

2.6.5 What bioanalytical methods were used to assess the concentrations of the drug in serum or other biological fluids?

Validated enzyme-linked immunosorbent assay (ELISA) methods were used for the determination of serum concentrations of pegserepoetin beta and erythropoietin. The methods for determination of pegserepoetin beta in serum was developed to study the pharmacokinetics of the drug, whereas the assay for determination of erythropoietin in serum was used primarily to measure the endogenous erythropoietin at baseline (before drug administration). Table 15 shows a summary of ELISA methods used in the clinical studies to measure serum concentrations of pegserepoetin beta and erythropoietin.

Table 15: Summary of ELISA methods used in the clinical studies to measure serum concentrations of pegserepoetin beta, erythropoietin, and antibodies

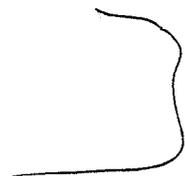
Clinical Studies	Pegserepoetin Beta			Erythropoietin	Antibodies	
	Original Assay	Updated Assay	Optimized Assay	Erythropoietin Assay	Anti-Pegserepoetin Beta Assay	Anti-Erythropoietin Assay
<i>Phase I</i>						
BP16198		X		X		X*
BP16239	X			X		X*
WP16422		X		X		X*
BP16346		X		X		X*
JP16690		X		X	X	
WP16383		X		X		X*
BP17278		X	X	X	X	
BP17570			X	X	X	
BP16964		X		X	X	
BP18035			X		X	X
BP18034			X	X	X	X
BP16779		X		X	X	
JP16417		X		X		X*
<i>Phase II</i>						
BA16285	N/A	N/A	N/A		X	
BA16286	N/A	N/A	N/A		X	
BA16260		X			X	
BA16528		X			X	
BA16558		X			X	
BA16728		X			X	
NA17101			X		X	
<i>Phase III</i>						
BA16739			X		X	X
BA16740			X	X	X	X
BA16736			X		X	X
BA16738	N/A	N/A	N/A		X	X
BA17283	N/A	N/A	N/A		X	X
BA17284	N/A	N/A	N/A		X	X

N/A, not applicable, * original anti-erythropoietin assay developed at _____

Pegserepoetin Beta

Three versions of the validated _____ ELISA were used in the clinical and clinical pharmacology studies to determine the concentrations of pegserepoetin beta in human serum samples. They are referred to as original, updated, and optimized assays.

The original assay for the determination of pegserepoetin beta was an adaptation of the assay used in the nonclinical studies for the determination of serum concentrations of pegserepoetin beta in dogs and rats.



This assay was established and validated at [redacted]
 The performance of the original assay is summarized in Table 16. This assay was used in Study BP16239 only.

Table 16: Performance summary of the ELISA used in the determination of pegserepoetin beta concentrations in serum

Validation Site	Assay Range (pg/mL)	Accuracy (%)		Precision (%)	
		Intra-Assay	Inter-Assay	Intra-Assay	Inter-Assay
<i>Original Assay</i>					
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
<i>Updated Assay</i>					
Hoffmann-La Roche	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
<i>Optimized Assay</i>					
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]



The performance of the updated assay is summarized in Table 16. The optimized assay was used in some clinical pharmacology studies, a phase 2 clinical study, and all phase 3 clinical studies (Table 15).

Erythropoietin Assay

Table 17: Performance summary of the ELISA used in the determination of erythropoietin concentrations in serum

Validation Site	Assay Range (pg/mL)	Accuracy (%)		Precision (%)	
		Intra-Assay	Inter-Assay	Intra-Assay	Inter-Assay

2.6.5.1 Do the measured concentrations reflect the amount (e.g., immunoassay) or activity (e.g., bioassay) of the drug in biological fluids?

The ELISA methods used in the concentration measurement for pegserepoetin beta and erythropoietin reflect the amount of pegserepoetin beta and erythropoietin in serum.

2.6.5.2 What are the limitations, if any, of the concentration values measured by the analytical methods to be used for the PK, PD or clinical assessment of the drug?

There are no apparent limitations of the ELISA methods used in the determination of pegserepoetin beta and erythropoietin.

2.6.6 What bioanalytical methods were used to detect anti-drug antibodies in serum or other biological fluids?

Validated ELISA methods were used for the detection of pegserepoetin beta antibodies and anti-erythropoietin antibodies in serum. Table 15 also shows a summary of ELISA methods used in the clinical studies to measure serum concentrations of the antibodies.

Anti-pegserepoetin beta Antibody Assay



Performance summary is summarized in Table 18.

Table 18: Performance summary of the ELISA methods used in the detection of anti-pegserepoetin beta antibodies

Validation Site	Assay Range (pg/mL)	Accuracy (%)		Precision (%)	
		Intra-Assay	Inter-Assay	Intra-Assay	Inter-Assay

Anti-erythropoietin Antibody Assay



This assay was used in Studies BP16198, BP16239, BP16346, JP16417, WP16383 and WP16422.

Table 19: Performance summary of the ELISA method used in the detection of anti-erythropoietin antibodies (First Assay)

Validation Site	Assay Range (pg/mL)	Accuracy (%)		Precision (%)	
		Back-Calculated Concentration	Absorbance Decrease	Back-Calculated Concentration	Absorbance Decrease

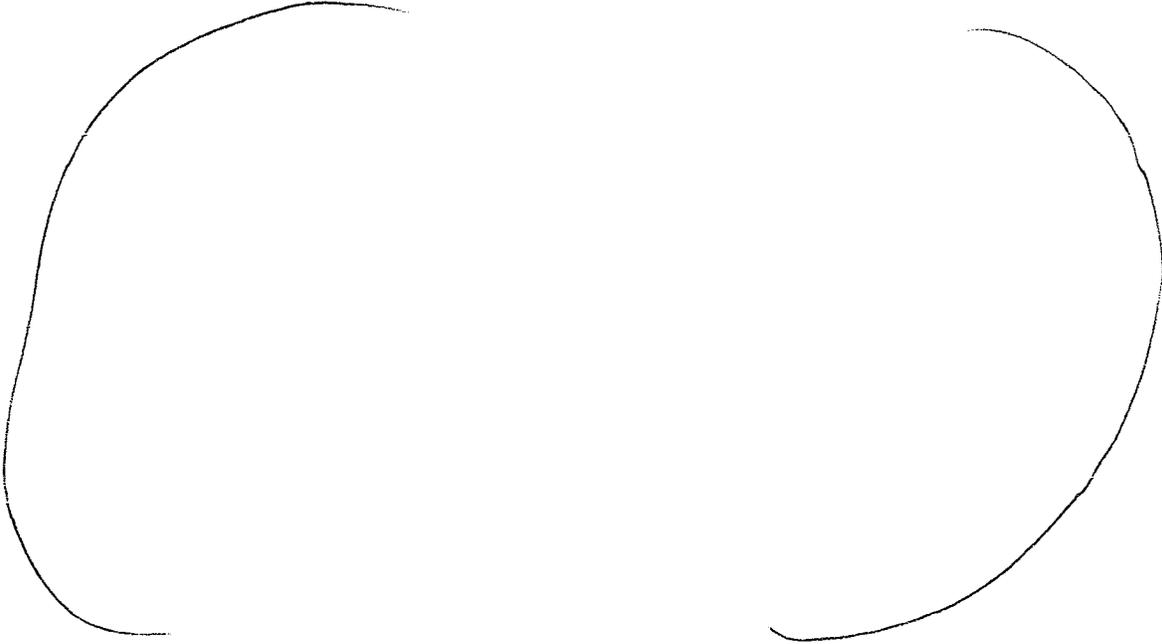


Table 20: Performance summary of the ELISA used in the detection of anti-pegserepoetin beta antibodies

Validation Site	Assay Range (pg/mL)	Accuracy (%)		Precision (%)	
		Intra-Assay	Inter-Assay	Intra-Assay	Inter-Assay

2.6.6.1 What criteria were used to conclude whether the anti-drug antibody production was positive or negative?

In the ELISA methods described above, if the decrease in absorbance due to the presence of erythropoietin was less than 49%, the test result was considered 'negative'. If the decrease in absorbance was 50% or more, the test result was considered 'positive.'

2.6.6.2 If the anti-drug antibodies neutralize the effect of the drug, how was the neutralization effect measured?

It is not known whether anti-pegseroepoetin beta antibodies neutralize the effect of pegseroepoetin beta since anti-pegseroepoetin beta antibodies were not detected in clinical studies.

2.6.7 What bioanalytical methods were used to assess the pharmacodynamic effect of the drug?

Reticulocyte counts, hemoglobin levels, hematocrit, red blood cell counts, and iron-related parameters such as serum iron, serum ferritin, soluble transferrin receptor, and transferrin saturation were measured using routine clinical laboratory tests.

6 Page(s) Withheld

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

X § 552(b)(4) Draft Labeling

 § 552(b)(5) Deliberative Process

4.2 Summary of Individual Studies

Protocol No. (Country)	Objectives	Study Design	Subjects*, Gender, Race, Age	Dose Regimen	Remark
Single Dose Pharmacokinetics in Healthy Subjects					
BP16198 (France)	Safety, tolerability, pharmacokinetic and PD assessment after single doses	Single blind, randomized, parallel, placebo controlled, single center	62 healthy subjects, all males, mostly whites, 19 - 45 years	Single 0.1, 0.2, 0.4, 0.8, 1.6, 2.4 or 3.2 mcg/kg SC	
BP16239 (England)	Safety, tolerability, pharmacokinetic and PD assessment after single doses	Single blind, randomized, parallel, placebo controlled, single center	30 healthy subjects, all males, all whites, 18 - 50 years	Single 0.4, 0.8, 1.6 or 3.2 mcg/kg IV	
JP16417 (England)	Safety, tolerability, pharmacokinetic and PD assessment after single doses in Caucasians and Japanese	Single blind, randomized, parallel, placebo controlled, single center	Not reviewed	0.8 mcg/kg IV	Prematurely terminated due to admin reasons, not reviewed
Single Dose Pharmacokinetics in Patients					
BP16779 (worldwide)	PD and pharmacokinetic comparison after IV and SC administration in patients	Open label, randomized, two-way crossover, multicenter	16 patients with chronic renal failure on peritoneal dialysis, 14 males / 2 females, mostly whites, 37 - 80 years	0.4 mcg/kg IV and 0.8 mcg/kg SC (crossover, 6 weeks apart)	
BP18034 (New Zealand)	pharmacokinetic and PD comparison after SC and IV administration in patients	Open label, randomized, parallel, single center	21 chronic renal failure patients not on dialysis, 8 males / 13 females, mostly whites, 28 - 79 years	0.8 mcg/kg IV or 1.2 mcg/kg SC	

Protocol No. (Country)	Objectives	Study Design	Subjects*, Gender, Race, Age	Dose Regimen	Remark
Multiple Dose Pharmacokinetics in Healthy Subjects					
BP16346 (France)	PD, pharmacokinetic, safety and tolerability assessment after multiple doses	Open label, randomized, parallel, placebo controlled, single center	51 healthy subjects, 46 males / 5 females, mostly whites, 18 - 59 years	0.4, 0.8, 1.6 or 3.2 mcg/kg IV every 3 weeks for 6 weeks	
WP16422 (England)	Safety, tolerability, PD and pharmacokinetic assessment after multiple doses	Open label, randomized, parallel, placebo controlled, single center	38 healthy subjects, 27 males / 11 females, mostly whites, 20 - 60 years	0.4, 0.8, 1.6 or 3.2 mcg/kg SC every 2 weeks for 6 weeks	
Dose Proportionality in Healthy Subjects (see BP16198, BP16239, JP16690, BP16346, WP16422)					
Absolute Bioavailability in Healthy Subjects					
WP16383 (England)	Absolute bioavailability safety, tolerability in healthy subjects	Open label, randomized, crossover, single center	43 healthy subjects, 43 males, mostly whites, 18 - 50 years	0.8 mcg/kg IV, 0.8 mcg/kg SC, or 1.6 mcg/kg SC on days 1, 15, or 29; and 3.2 mcg/kg SC on day 43	Insufficient wash-out between doses
Absolute Bioavailability in Patients (see BP16779, BP18034)					
Relative Bioavailability in Healthy Subjects					
BP18035 (England)	Effect on pharmacokinetic and PD of 3 different sites of SC administration	Open label, randomized, three-way crossover, single center	42 healthy subjects, 25 males / 17 females, mostly whites, 20 - 64 years	3.0 mcg/kg SC in abdomen, arm and thigh, 7 weeks apart	
Comparability in Healthy Subjects					
BP16964 (Germany)	Relative bioavailability after SC administration of 2 different Formulations	Open label, randomized, two-way crossover, single center	35 healthy subjects, 19 males / 16 females, mostly whites, 22 - 64 years	3.2 mcg/kg SC, formulations A and B, 6 months apart	

Protocol No. (Country)	Objectives	Study Design	Subjects*, Gender, Race, Age	Dose Regimen	Remark
QT Prolongation in Healthy Subjects					
BP17278 (New Zealand)	Effect of pegserapoetin beta on QT interval	Double blind, randomized, placebo controlled, two-way crossover, single center	39 healthy subjects, 20 males / 19 females, all whites, 19 - 64 years	3.2 mcg/kg IV 3 doses, 2 weeks apart	
Special Population					
BP17570 (England)	pharmacokinetic and PD after multiple IV administration in healthy subjects with different pharmacokinetic characteristics	Open label, randomized, fixed sequence, two-center	12 healthy subjects, all males, all whites, 20 - 52 years	0.8, 0.8, and 3.2 mcg/kg IV on days 1, 29, and 57, respectively	low exposure
JP16690 (USA)	Safety, tolerability, pharmacokinetic and PD assessment after single doses in Caucasians and Japanese	Single blind, randomized, parallel, placebo controlled, single center	60 healthy subjects, all males, 30 Caucasians / 30 Japanese, 20 - 47 years	0.8, 1.6 and 3.2 mcg/kg IV	racial difference

* evaluable subjects with active treatment; PD, pharmacodynamics; pharmacokinetic, pharmacokinetics; IV, intravenously; SC, subcutaneously

4.3 Consult Reviews

See Pharmacometrics Review attached separately

4.4 OCPB Filing/Review Form

Office of Clinical Pharmacology BLA Filing and Review Form				
General Information About the Submission				
	Information		Information	
Application Number	STN 125164/0		Brand Name	Mircera
OCPB Division	DCP 5		Generic Name	pegserepoetin beta
Medical Division	DOB		Drug Class	Biologics: Hematopoetin
OCPB Reviewer	Jang-Ik Lee		Indication(s)	Anemia
OCPB Team Leader	Hong Zhao		Dosage Form and Strengths	Injectable solution, 10, 100, 200, 300, 400, 500, 600, 1000 µg/mL
Date of Submission	4/18/06		Dosing Regimen	
Estimated Due Date of OCP Review	12/18/06		Route of Administration	IV, SC
PDUFA Due Date	2/18/07		Sponsor	Roche
Division Due Date	1/18/07		Priority Classification	standard
Clin. Pharm. and Biopharm. Information				
	"Yes" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	Yes			
Tabular Listing of All Human Studies	Yes			
Hpharmacokinetic Summary	Yes			
Labeling	Yes			
Reference Bioanalytical and Analytical Methods	Yes			
I. Clinical Pharmacology				
Mass balance:	NA			Biologics
Isozyme characterization:	NA			Biologics
Blood/plasma ratio:	NA			Biologics
Plasma protein binding:	NA			Biologics
Tissue binding:	Yes	1		In vitro study
Pharmacokinetics (e.g., Phase I)				
<i>Healthy Volunteers-</i>				
single dose:	Yes	BP16198, BP16239, JP16417, JP16690	BP16198, BP16239	
multiple dose:	Yes	BP16346, WP16422	BP16346, WP16422	
<i>Patients-</i>				
single dose:	Yes	BP16779, BP18034	BP16779, BP18034	
multiple dose:	No			
Dose proportionality -				
fasting / non-fasting single dose:	Yes	BP16198, BP16239	BP16198, BP16239	
fasting / non-fasting multiple dose:	Yes	BP16346, WP16422	BP16346, WP16422	
Drug-drug interaction studies -				
In-vivo effects on primary drug:	No			FDA agreed
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:	Yes	BP17570	BP17570	pharmacokinetic in pts with low exposure
gender:	Yes			
pediatrics:	No			
geriatrics:	Yes/No			No dedicated study
renal impairment:	Yes/No			dialysis
hepatic impairment:	No			
PD:				
In vitro	Yes	1	1	Cell proliferation study
Phase 2:	Yes	7 studies	7 studies	Hb production vs conc
Phase 3:	Yes	3 studies	3 studies	Hb production vs conc
Phase 3:	Yes	3 studies	3 studies	Hb production vs conc
QT Prolongation	Yes	BP17278	BP17278	Negative

pharmacokinetic/PD:	Yes	10 studies including 2 phase II and 3 phase III studies	10 studies including 2 phase II and 3 phase III studies	To explore route, dose, interval
Phase I and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:	Yes/No			Exploratory in cancer pts with anemia
Data sparse:				
Immunogenicity	Yes/No			Determined in selected clinical study (no incidence)
II. Biopharmaceutics				
Absolute bioavailability:	Yes	WP16383	WP16383	SC vs IV (healthy) SC vs IV (patients)
Relative bioavailability -	Yes	BP18035	BP18035	Abdomen vs arm vs thigh SC,
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -	NA			biologics
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:	NA			injection
Dissolution:	NA			injection
(IVIVC):	NA			injection
Bio-wavier request based on BCS	NA			injection
BCS class	NA			injection
Comparability		BP16964	BP16964	
III. Other CPB Studies				
Genotype/phenotype studies:	No			
Chronopharmacokinetics	No			
Pediatric development plan	No			Requested waiver
Literature References	Yes			
Total Number of Studies		13	12	In addition to 4 phase II and 6 phase III clinical studies
Filability and QBR comments				
	"X" if yes	Comments		
Application fileable?	Yes			
Comments sent to firm?		Not at the time of filing		
QBR questions (key issues to be considered)	To follow GRP MAPP in clinical pharmacology review with modification for Biologics			
Other comments or information not included above				
Primary reviewer Signature and Date	Jang-Ik Lee			
PM reviewer Signature and Date	Pravin Jadhav			
Secondary reviewer Signature and Date	Hong Zhao			

End of Document

PHARMACOMETRICS REVIEW

BLA Number:	STN125164
Generic Name:	Pegserepoetin alfa
Brand Name:	Mircera
Proposed Indication:	Treatment of anemia associated with chronic kidney disease
Sponsor:	Hoffmann-La Roche Inc.
Type of submission:	Original BLA
Pharmacometrics (PM) reviewer:	Pravin Jadhav Ph.D.
PM Team Leader:	Jogarao Gobburu Ph.D.
Proposed Dosage and Administration	0.6 mcg/kg intravenously or subcutaneously administered as a single dose once every two weeks

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Abbreviations

CRF	Chronic kidney disease
ESA	Erythropoetin stimulating agents
Hb	Hemoglobin
IV	Intravenous administration
PK	Pharmacokinetics
PD	Pharmacodynamics
POPPK	Pouplation pharmacokinetic analysis
RO-503821	Roche nomenclature for mircera
SC	Subcutaneous administration
STN125164	Internal submission number for micera

1. Executive summary

Mircera is a chemically synthesized continuous erythropoietin receptor activator, for the treatment of anemia in patients with chronic renal failure (CRF). Mircera was studied in the correction and maintenance studies. The correction studies assessed the treatment of anemia associated with CRF in patients not treated with an erythropoietin stimulating agent (ESA). The maintenance studies assessed the treatment of anemia associated with CRF in patients converting from an ESA to treatment with mircera. The current review is focused on five major questions as outlined below.

Is there an exposure-response relationship to assess effectiveness of mircera?

The effectiveness of mircera was well established in 6 clinical studies. All studies show consistent success in correction/maintaining Hb levels within the defined threshold. Mircera shows exposure dependent effect on Hb in the correction as well as maintenance setting. Here, the treatment goal is titration to effect and exposure-response relationship supports dose adjustment for effectiveness.

Are there any exposure-safety concerns that could justify upper dose limit for mircera?

The exposure safety analyses of mircera presented a challenging scenario. Overall, the proportion of deaths seemed similar across the treatment arms. The review question was raised based on discrepancy observed in the number of fatal events which mapped to the MedDRA preferred term of 'sudden death' occurred in the mircera group (nine) and none in the reference arm. However, 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%]), the overall incidence of events of this nature is similar between the treatment arms. There was some trend towards the dose effect of ESAs on mortality, however, the effect is confounded by disease severity status. In other words, there is an indication that proportion of deaths increases with dose. At the same time, severely ill patients need higher doses of mircera for maintaining Hb levels.

Hence, the risk-benefit of mircera and overall ESA agents is questionable. At this time, it is not possible to optimize the treatment given uncertainties in dose effect, Hb target (partial or complete correction), Hb minimum to start ESA treatment (baseline risk) or any other predictors (such as, slope of Hb response) that would maximize overall benefit.

Are claims based on population PK analyses acceptable?

Based on population PK analyses, the sponsor investigated the effect of age, gender, race, dialysis status and potential for drug-drug interaction. The population PK analyses and the associated claims are acceptable. The suggested changes are noted in the recommendation section.

Is titration scheme proposed by the sponsor acceptable?

The time to reach steady state effect was not found to be a major issue. Given the controversies associated with the Hb correction (complete vs partial correction), in the clinical setting, the preference would be to use less aggressive correction methods. In

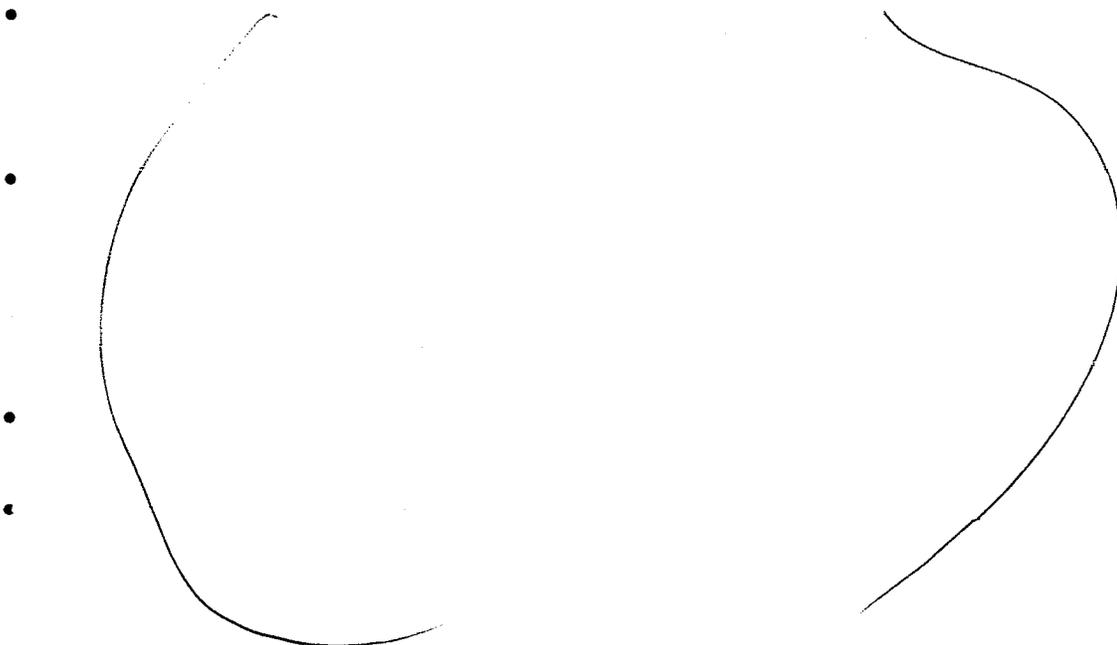
addition, steady state kinetics of Hb are driven by the pharmacodynamic half life, hence, the reversal of over correction could be an issue. Therefore, the current titration seems reasonable.

Given that body weight was not identified as a major covariate, is $\mu\text{g}/\text{kg}$ dosing supported?

Two important patient related outcomes, time to first overshoot (defined as Hb level > 13 g/dL) and time to response defined as an increase in Hb = 1.0 g/dL from baseline and a single Hb concentration = 11.0 g/dL, without RBC transfusion, during the first 24 weeks after first dose (until day 173, end of correction period), were used. The patients were stratified based on body weights into low and high weight groups. There was no difference between two weight groups for time to first overshoot or time to response within the mircera group. Therefore, no clinically relevant differences are expected between body weight based dosing versus fixed dosing in selecting the starting dose.

2. Recommendations

- 2.1. Mircera seems more appealing alternative to the current ESAs due to less frequent administration option. However, the risk-benefit profile of mircera as well as all other ESAs is questionable at this time. For patients, the benefit of less frequent administration does not seem to translate into overall benefit in the presence of current safety concerns.
- 2.2. The labeling claims proposed based on the population analyses supported by additional early phase data are acceptable with the following changes to the proposed language.



3. Introduction

Mircera is a chemically synthesized continuous erythropoietin receptor activator, for the treatment of anemia in patients with chronic renal failure (CRF). The current treatment options (epoetin alfa, epoetin beta, and darbepoetin alfa), require frequent administration, from three to seven times per week to once every 2 weeks. In contrast with erythropoietin, mircera is claimed to show 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 claimed to be relevant in order to achieve a once monthly dosing regimen with mircera in patients.

The sponsor claims that mircera administered intravenously (IV) or subcutaneously (SC) is safe and effective in the correction of anemia in patients with anemia associated with CRF who are on dialysis or not on dialysis and who are not currently treated with an erythropoiesis stimulating agent (ESA). In addition, patients with anemia associated with CRF who are currently treated with an ESA may be effectively converted to treatment with mircera IV or SC, thereby maintaining control of anemia but with a much less intensive dosing regimen.

4. Major questions

4.1. Is there an exposure-response relationship to assess effectiveness of mircera?

Mircera was studied in the correction and maintenance studies. The correction studies assessed the treatment of anemia associated with CRF in patients not treated with an ESA. The maintenance studies assessed the treatment of anemia associated with CRF in patients converting from an ESA to treatment with mircera. In the correction setting, the sponsor's proposed 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. In study BA17638 (correction study), the median dose at the time of response was the same as the starting dose (ie, 0.6 µg/kg 1x/2 weeks SC). However, in study BA16736 (correction study), the median dose at the time of Hb response was 0.6 µg/kg 1x/2 weeks IV (compared with the starting dose of 0.4 µg/kg 1x/2 weeks IV) suggesting that this dose (0.6 µg/kg 1x/2 weeks) is appropriate for both IV and SC routes of administration.

The claim was investigated to assess safety and effectiveness of mircera for IV dosing as the starting dose in the clinical trial was lower than the proposed dose.

4.2. Are there any exposure-safety concerns that could justify upper dose limit for mircera?

The majority of patients had at least one AE during the study, with a similar percentage in the mircera group (89%) and the reference group (91%). The average number of AEs per patient was also similar between groups (approximately 5 AEs per patient in each group). The most frequent (10%) clinical AEs were hypertension, diarrhea, and

nasopharyngitis. The frequency of these common AEs was similar between the mircera and reference groups. However, a number of fatal events which mapped to the MedDRA preferred term of 'sudden death' occurred in the mircera group (eight) and none in the reference arm. However, 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%]), the overall incidence of events of this nature is similar between the treatment arms.

A dose-event relationship was investigated to assess if there is any upper limit on mircera dose.

4.3. Are claims based on population PK analyses acceptable?

The following claims were based on population analyses.

- 4.3.1. In CRF patients, the pharmacokinetics of mircera were studied after the first dose and after administrations on week 9 and week 19 or 21. Multiple dosing was found to have no effect on clearance, volume of distribution and bioavailability of mircera.
- 4.3.2. After administration every 4 weeks in CRF patients, there was virtually no accumulation of mircera, as demonstrated by a ratio of accumulation of 1.03. After administration every 2 weeks, the ratio of accumulation in serum was 1.12.
- 4.3.3. Population analyses evaluated the potential effects of demographic characteristics on the pharmacokinetics of mircera. Results of these analyses showed that no dose adjustments are necessary for age, gender, or race.
- 4.3.4. A population pharmacokinetic analysis also showed no pharmacokinetic differences between patients on dialysis and patients not on dialysis.
- 4.3.5. No formal drug-drug interaction studies have been performed. The effect of other drugs on the pharmacokinetics and pharmacodynamics of mircera was explored using a population analysis approach. There was no indication of an effect of concomitant medications on the pharmacokinetics and pharmacodynamics of mircera.

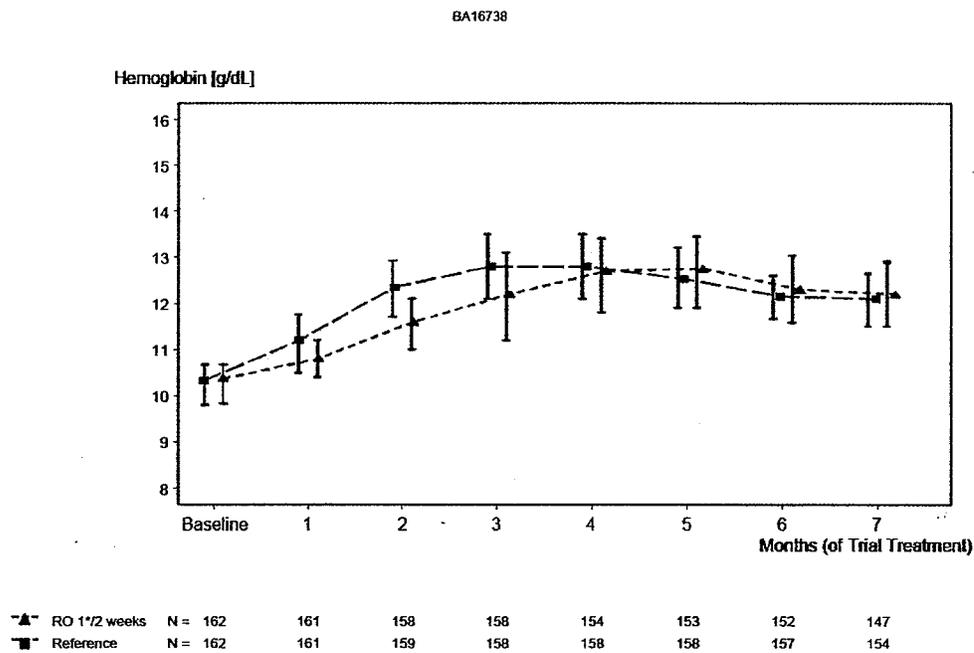
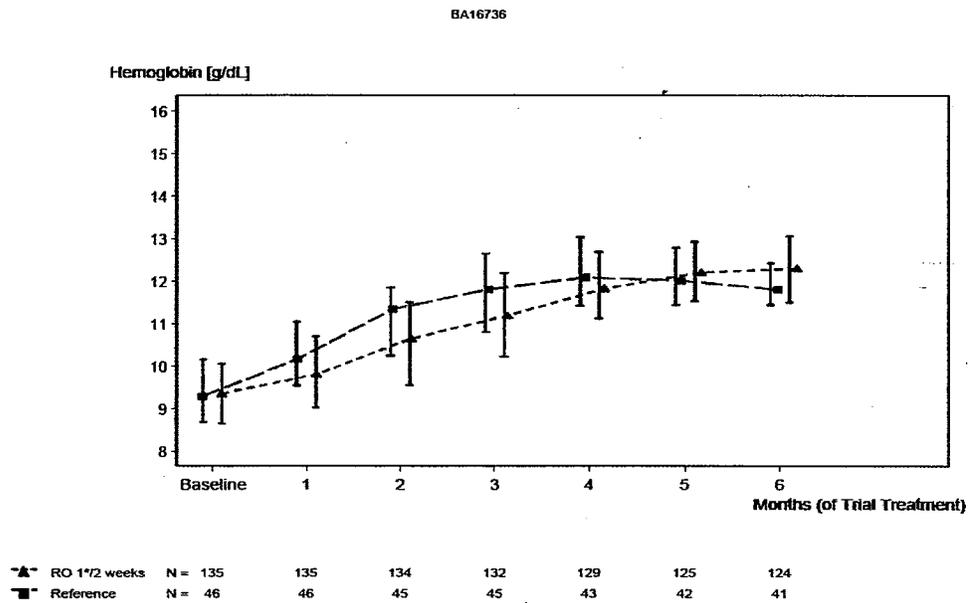
The validity of these claims out of the population PK analyses was investigated.

4.4. Is titration scheme proposed by the sponsor acceptable?

Hemoglobin values over time in studies BA16736 and BA16738 are depicted graphically in Figure 1 (ITT population). In both studies, median Hb concentrations reached levels \geq 11 g/dL during the correction period in all treatment groups. 11 g/dL is considered to be the lower limit of clinically acceptable Hb concentrations for this patient population. In both studies, the rate of increase was slower in the mircera group than in the reference group.

The appropriateness of the titration scheme was investigated to assess whether Hb concentrations on mircera could increase at the rate similar to that of the reference arm.

Figure 1: Plot of Median Hemoglobin Values Over Time, in the Phase III Correction Studies (BA16736 and BA16738 ITT Population)



4.5. Given that body weight was not identified as a major covariate, is $\mu\text{g}/\text{kg}$ dosing supported?

Population PKPD analysis did not identify body weight as a major covariate on important PKPD parameters. This could mean that 'one dose for all' is more appropriate than $\mu\text{g}/\text{kg}$ dosing. The sponsor also concluded in one of the early reports that $\mu\text{g}/\text{kg}$

dosing or 'one dose for all' would not make a difference. The body weight based dosing was investigated to assess whether fixed dose would be a better alternative.

5. Data

A total of 10 individual study reports and 4 additional (associated) quantitative analyses reports were used this review. Table 1 summarizes study numbers, the development phase, the number of patients on mircera and respective control arms.

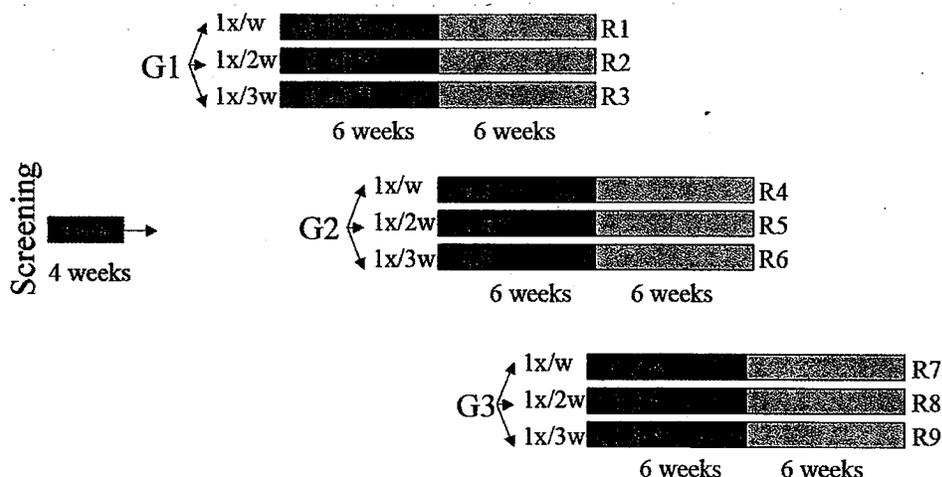
Table 1: Summary of patients included in the pooled phase II and III clinical studies with mircera

Study	Development Phase	RO0503821	Epoetin reference	Darbepoetin alfa reference
Induction Studies				
BA16260	II	61	--	--
BA16528	II	65	--	--
BA16736	III	135	46	--
BA16738	III	161	--	162
Maintenance Studies				
BA16285	II	91	--	--
BA16286	II	137	--	--
BA16739	III	441	225	--
BA16740	III	380	191	--
BA17283	III	153	--	156
BA17284	III	165	168	--
Total Overall		1789	630	318

BA16260 (phase II trial) was a randomized, open-label, multicenter, ascending-dose study evaluating efficacy and safety of different doses of mircera and different dosing schedules in patients with chronic kidney disease requiring correction of anemia and on hemodialysis or peritoneal dialysis treatment.

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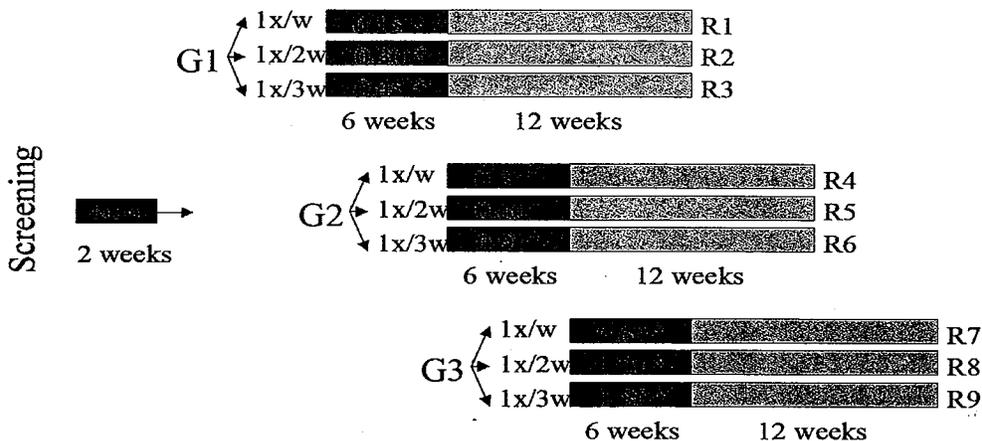
Figure 2: Study plan for BA16260



*, +, & total weekly dose per cohort identical
*, & pending confirmation

BA16528 (phase II trial) was an open-label, randomized, multi-centre, multiple-dose study designed to investigate the efficacy and safety of SC injections of mircera administered at different dosing intervals to patients with anemia and chronic kidney disease who were not on renal replacement therapy.

Figure 3: Study plan for BA16528

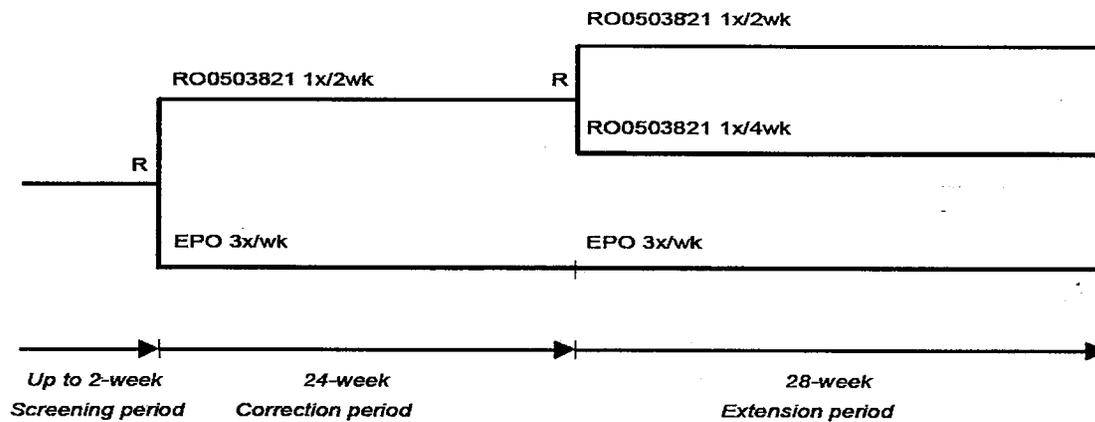


*, +, & total weekly dose per cohort identical

BA16736 (phase III trial) was a randomized, open-label, multi-center, parallel-group (2-arm) study that consisted of a correction period of 24-weeks, followed by an extension period of up to 28 weeks. There was one IV dosing interval for mircera during the correction period (once every 2 weeks) and two IV dosing intervals for mircera during the extension period (once every 2 weeks; once every 4 weeks). The dosing schedule for the reference arm, epoetin, remained the same during the correction and extension periods. The reference arm was not used for statistical analysis of the primary endpoint.

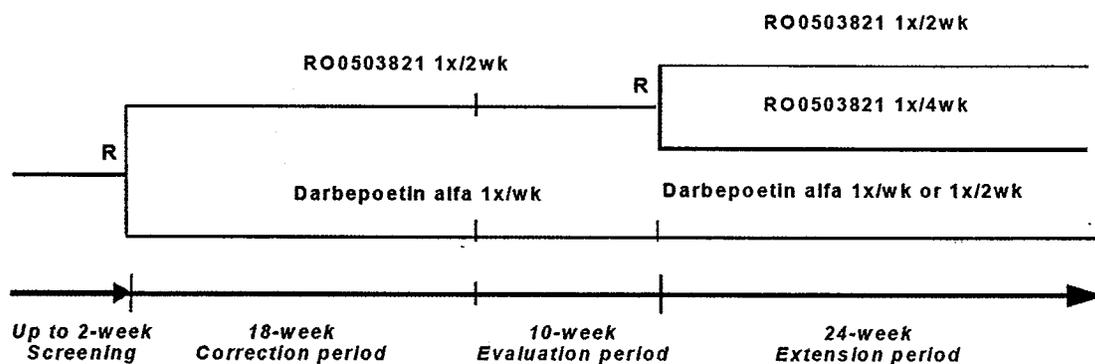
The primary objective of the study was to demonstrate the efficacy of IV mircera treatment for correction of anemia in patients with stage 5 CRF who are on dialysis.

Figure 4: Study plan for BA16736



BA16738 (phase III trial) was a randomized, open-label, multi-center, darbepoetin alfa-controlled, parallel-group (two-arm) study with one SC dosing interval for mircera (1x/2 weeks) during the correction and evaluation periods and two SC dosing intervals for mircera (1x/2 weeks; once every four weeks [1x/4 weeks]) during the extension period. The study consisted of a correction period of 18 weeks and an evaluation period of 10 weeks to address the main study questions, followed by an extension period of up to 24 weeks for documentation of safety. The primary objective of the study was to demonstrate the efficacy of mircera treatment administered SC once every 2 weeks (1x/2 weeks) for correction of anemia in CRF patients who were not on dialysis and were not treated with epoetin.

Figure 5: Study plan for BA16738



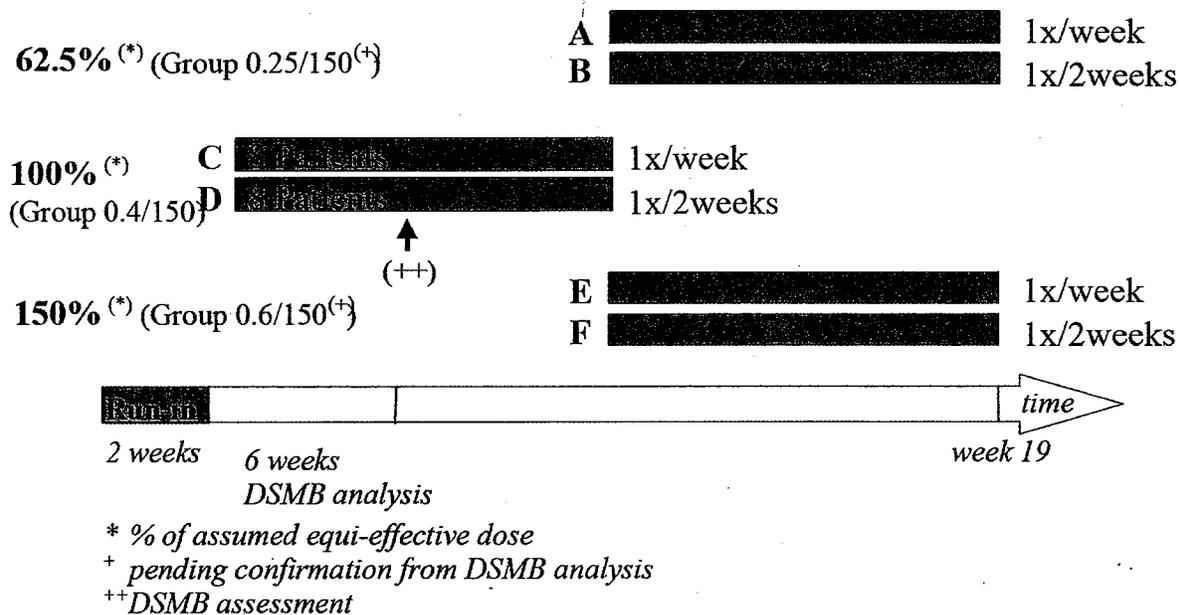
BA16285 (phase II trial) was a randomized, multicenter, open-label study, consisting of a two-week run-in period (to assess patients' baseline Hb levels and iron status under stable dosage) followed by the core treatment period of 19 weeks. After the core treatment period there were two optional treatment extension periods. The first optional extension period was up to 54 weeks after the core treatment period, and the second optional extension period was up to 54 weeks after the first optional extension period.

The following dose conversion factors and frequencies of administration were tested:

- 0.25/150 administered either once weekly (1x/week) or once every two weeks (1x/2 weeks)
- 0.4/150 administered either 1x/week or 1x/2 weeks
- 0.6/150 administered either 1x/week or 1x/2 weeks

The weekly dose of mircera IV was determined by multiplying the weekly epoetin alfa dose the patient received during the run-in period by one of the three conversion factors (0.25/150, 0.4/150, or 0.6/150. During the run-in period, patients continued to receive epoetin alfa IV at the same dose and frequency (three administrations per week) as during the previous two weeks. The first patients were randomized to cohorts C and D with the conversion factor of 0.4/150 (= 100% of the assumed equi-effective dose). When the first 16 patients) (eight patients from each cohort) had completed the first six weeks of treatment, a Data and Safety Monitoring Board (DSMB) reviewed the patients' safety and efficacy data and confirmed the conversion factors of 0.25/150 (= 62.5% of the assumed equi-effective dose) for cohorts A and B and 0.6/150 (= 150% of the assumed equi-effective dose) for cohorts E and F.

Figure 6: Study plan for BA16285



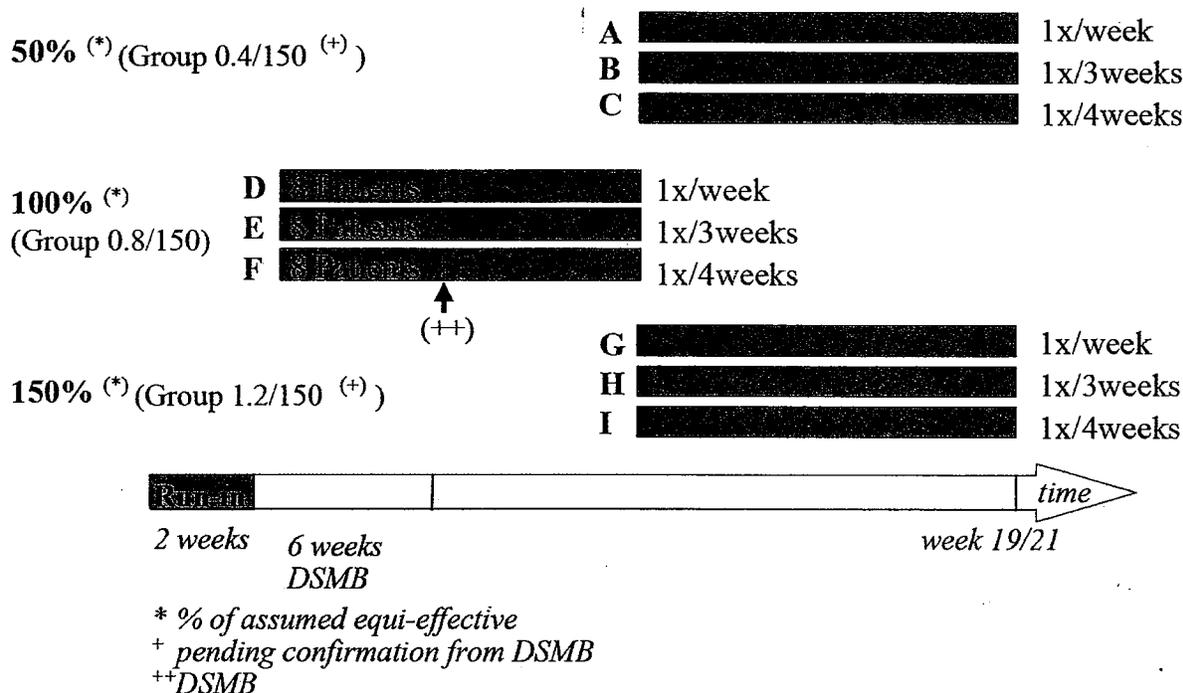
BA16286 (phase II trial) was a randomized, multicenter, open-label study, consisting of a two-week run-in period (to assess patients' baseline Hb levels and iron status under stable dosage) followed by the core treatment period of 19 weeks (or 21 weeks for the once every four weeks dosing schedule). After the core treatment period there were two optional treatment extension periods. The first optional extension period was up to 54 weeks after the core treatment period, and the second optional extension period was up to 54 weeks after the first optional extension period.

The following dose conversion factors and frequencies of administration were tested:

- 0.4/150 administered either once weekly (1x/week), once every three weeks (1x/3 weeks), or once every four weeks (1x/4 weeks)
- 0.8/150 administered either 1x/week, 1x/3 weeks, or 1x/4 weeks
- 1.2/150 administered either 1x/week, 1x/3 weeks, or 1x/4 weeks

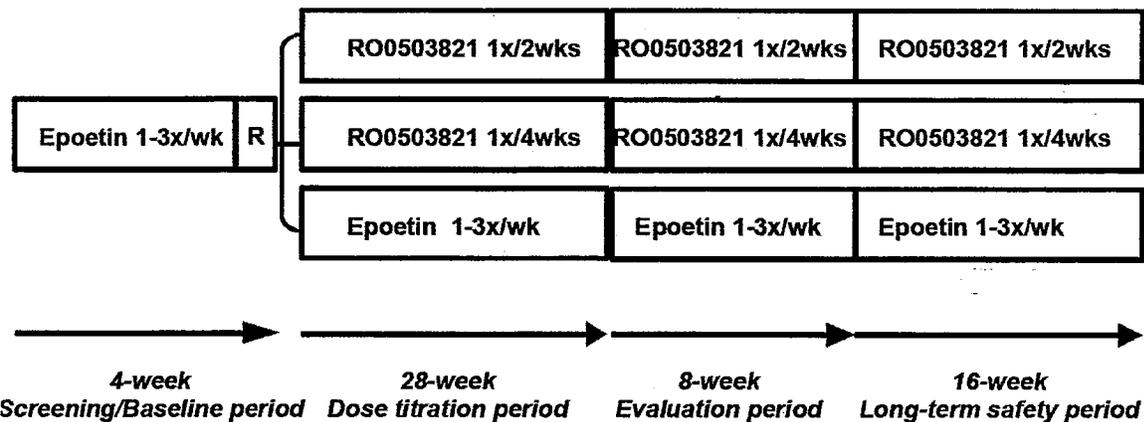
The weekly dose of mircera SC was determined by multiplying the weekly epoetin alfa or beta dose the patient received during the run-in period by one of the three conversion factors (0.4/150, 0.8/150, or 1.2/150). During the run-in period, patients continued to receive SC epoetin alfa or beta at the same dose and frequency (one to three administrations per week) as during the previous two weeks. The first patients were randomized to cohorts D, E, and F with the conversion factor of 0.8/150 (= 100% of the assumed equi-effective dose). When the first 24 patients (eight patients from each cohort) had completed the first six weeks of treatment, a Data and Safety Monitoring Board (DSMB) reviewed the patients' safety and efficacy data and confirmed the conversion factors of 0.4/150 (= 50% of the assumed equi-effective dose) for cohorts A, B, and C and 1.2/150 (= 150% of the assumed equi-effective dose) for cohorts G, H, and I.

Figure 7: Study plan for BA16286



BA16739 (phase III trial) was a randomized, controlled, open-label, multi-center, parallel-group (3- arm), non-inferiority study comparing two dosing intervals of mircera (once every two weeks and once every four weeks) to continued epoetin treatment. The primary study objective was to demonstrate that mircera administered iv maintains Hb concentrations in dialysis patients on prior iv epoetin maintenance treatment of chronic renal anemia.

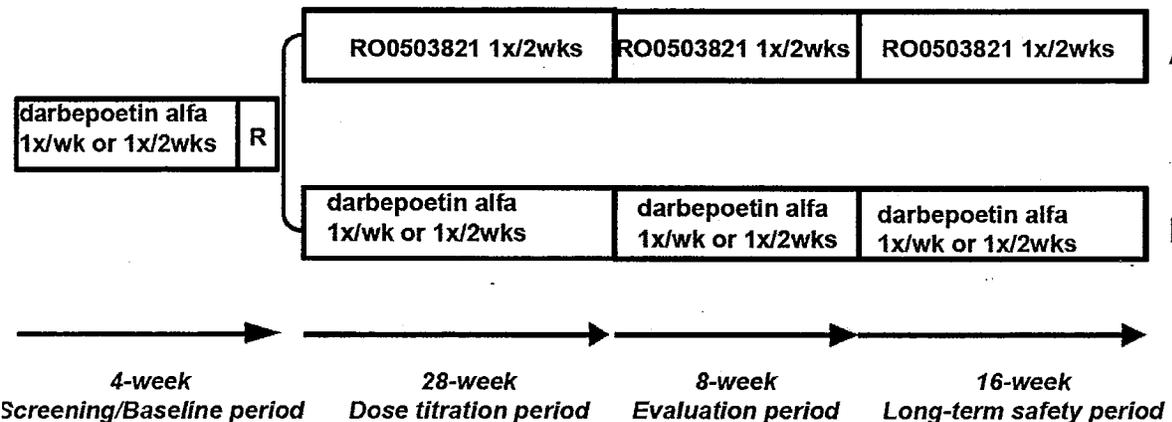
Figure 8: Study plan for BA16739



BA16740 (phase III trial) was a randomized, controlled, open-label, multi-center, parallel-group (3-arm), non-inferiority study comparing two dosing intervals of mircera (1x/2 weeks and 1x/4 weeks) to continued epoetin treatment. The primary objective was to demonstrate that mircera administered SC maintains Hb concentrations in dialysis patients on prior SC epoetin maintenance treatment of chronic renal anemia. The study plan was similar to the BA16739 study plan.

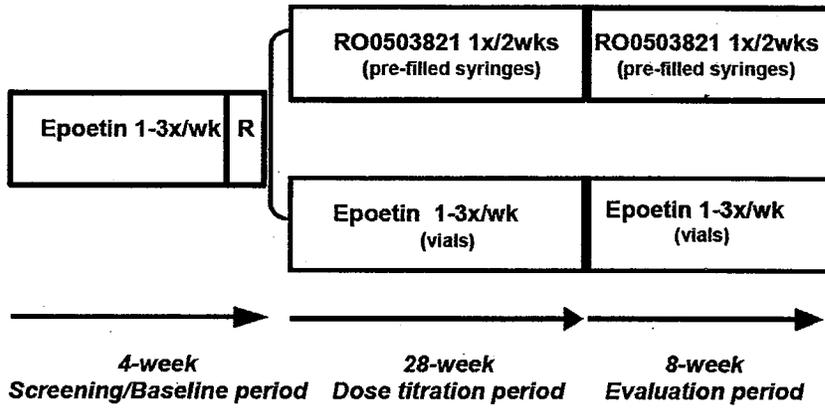
BA17283 (phase III trial) was a randomized, controlled, open-label, multi-center, parallel-group (2-arm), non-inferiority study comparing mircera (once every two weeks) to continued darbepoetin alfa treatment. The primary objective was to demonstrate that mircera administered intravenously maintains Hb concentrations in dialysis patients on prior IV darbepoetin alfa maintenance treatment of chronic renal anemia.

Figure 9: Study plan for BA17283



BA17284 (phase III trial) was a randomized, controlled, open-label, multi-center, parallel-group (2-arm), non-inferiority study comparing mircera once every two weeks (1x/2 weeks, pre-filled syringes) to epoetin treatment (vials). The primary objective was to demonstrate that mircera administered with pre-filled syringes maintains Hb concentrations in dialysis patients on prior IV or SC epoetin maintenance treatment of chronic renal anemia.

Figure 10: Study plan for BA17284



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6. Discussion

6.1. Is there an exposure-response relationship to assess effectiveness of mircera?

Overall, the phase III studies were able to demonstrate effectiveness of mircera. Briefly, In BA16736 (ITT population), the response rate* in the mircera group at the end of the correction period was 93% ($p < 0.0001$; 95% CI 87.7-96.9), and the lower limit of the confidence interval (CI) was well above 60%, confirming that mircera resulted in the correction of anemia. The response rate was comparable in the epoetin group, 91%. In BA16738 (ITT population), the response rate in the mircera group during the correction and evaluation periods was similar to that seen in study BA16736, 98% ($p < 0.0001$; 95% CI 93.8-99.3%) with the lower limit of the CI well above 60%, confirming that mircera resulted in correction of anemia. The response rate was comparable in the darbepoetin alfa group, 96%. The primary objective of studies BA16739, BA16740, BA17283, and BA17284 was to demonstrate that mircera administered IV or SC would maintain Hb concentrations in dialysis patients on prior IV or SC ESAs. The primary efficacy parameter was the change in Hb concentrations between baseline and the evaluation period. The change in Hb concentration between baseline and the evaluation period was comparable between the mircera treatment group(s) and the reference group within each of the four studies, and most were close to zero (no change). The largest changes from baseline occurred in the mircera 1x/4 weeks group of study BA16740 (-0.21 g/dL) and the mircera 1x/2 weeks group of study BA17284 (0.25g/dL). Both were within the range of expected variation over time in this patient population. For more detailed results, refer to summary of clinical efficacy or individual study reports.

Sponsor's analysis

The sponsor evaluated the relationship between serum concentration of mircera and Hb.

Early pharmacokinetic (PK)-pharmacodynamic (PD) modeling

The population PKPD modeling approach was used to explore the mircera dose-response relationship and assessment of exposure to mircera following dosing regimens used in BA16260 and BA16528 studies.

The population PK of mircera was extensively investigated in healthy volunteers following both intravenous (IV) and SC administrations. Utilizing intensive blood sampling, a one compartment PK model with first-order absorption and first-order elimination proved sufficient to describe the data. Therefore one compartment PK model was used for further analyses.

A semi- mechanistic model was developed using data from healthy volunteer, however, a simplified version of the model was employed to assess hemodynamic pattern. As Hb is mainly carried by RBCs, the life span of RBCs determines the duration of Hb elevations due to stimulation of erythropoiesis. This concept was implemented into a

* a Hb response is determined by a single Hb value = 11.0 g/dL and an increase in Hb from baseline = 1.0 g/dL.

mathematical structural pharmacodynamic model that describes the instantaneous relationship between production rate of Hb (expressed in g/dL/day) and serum concentrations of mircera by means of an Emax type model. The two drug-related parameters of this PD model were the maximum increase in Hb production rate relative to the Hb production rate at baseline (S_{max}) and the serum concentrations of mircera at which 50% of S_{max} was reached (SC_{50}). The apparent life span (LS) of RBCs and the Hb at baseline (Hb_0) were two additional, non-drug-related parameters of this pharmacodynamic model. The following equations describe the structural PKPD model.

$$Hb'(t) = S(t) - S(t - LS)$$

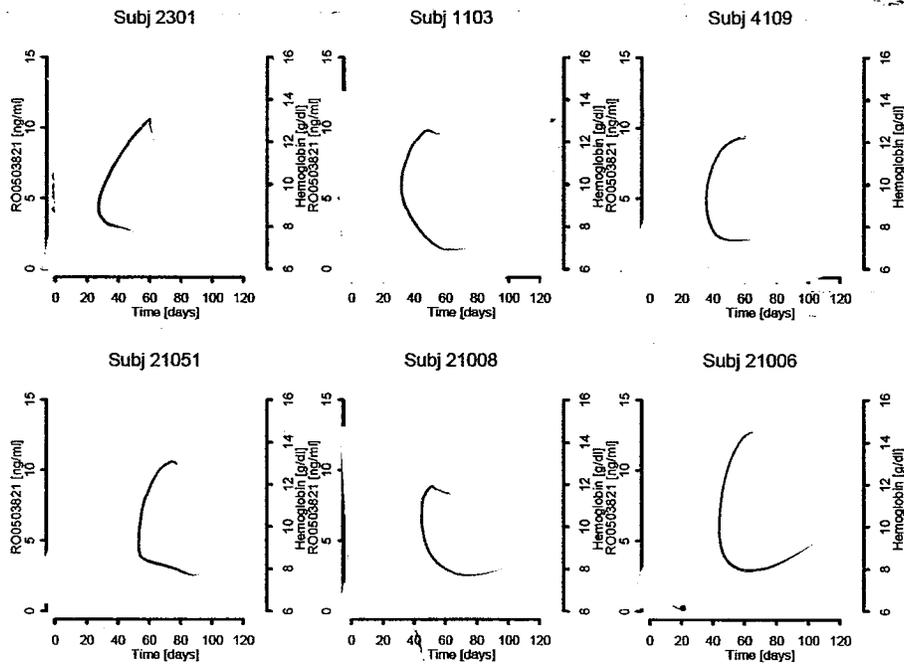
$$S(t) = Hb_0 / LS * (1 + E(C(t)))$$

$$E(C(t)) = S_{max} * C(t) / (SC_{50} + C(t))$$

where Hb' [(g/dL)/days] is the change in Hb over time, LS [days] the apparent lifespan of RBCs, and Hb_0 [g/dL] the Hb concentration at baseline. $S(t)$ [(g/dL)/days] and its LS-delayed value $S(t-LS)$ describe the production and elimination of Hb, respectively. Hb_0/LS is the production of Hb at baseline which was considered to be constant during one LS before time of Hb_0 assessment. $S(t)$ reflects the relative change in baseline Hb production and was related to $C(t)$ via an Emax type model with parameters S_{max} and SC_{50} . S_{max} is the maximum increase in Hb production relative to Hb baseline production and SC_{50} is the concentration of mircera at which 50% of the maximum increase is achieved.

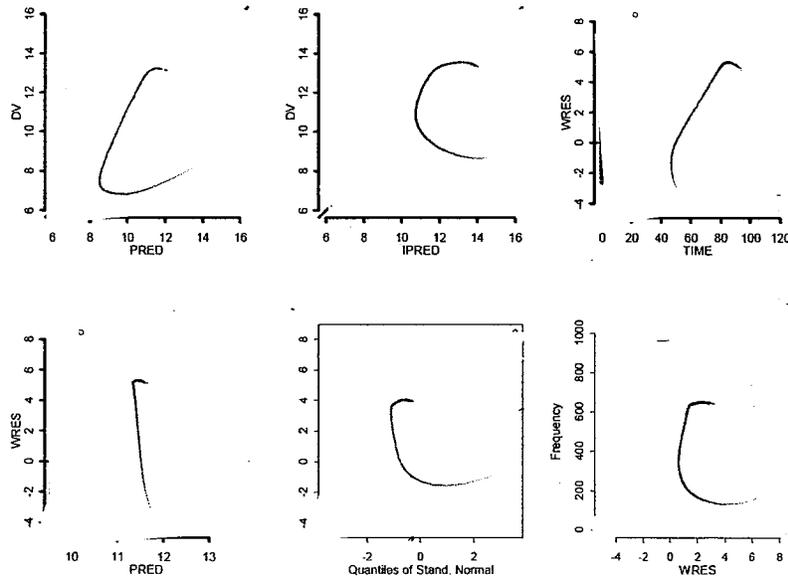
Individual drug concentrations $C(t)$ for the PKPD model were calculated from individual posthoc PK parameters based on the final population PK model. Inter-individual variability in fixed effects model parameters LS, Hb_0 , S_{max} , and SC_{50} was modeled assuming a log-normal distribution for the parameters. The difference between model-predicted and observed Hb values was modeled according to an additive error model. For more modeling details, refer Population PK/PD analyses of mircera of combined Phase II studies BA16260 and BA16528 in chronic kidney disease (1013569.pdf). Figure 11 and Figure 12 represent the individual fits and good of fit plots for the final population PKPD model. Table 2 illustrates parameter Values for the Final PK/PD Model that retains the effect of dialysis status on both life-span and Hb_0 . The corresponding covariate model equation were LS = 81.9 days for patients not on dialysis and 61.3 days for patients on dialysis and Hb_0 = 9.94 g/dL for patients not on dialysis and 9.57 g/dL for patients on dialysis. However, using simulations it was shown that there is no clinically significant impact of dialysis type on the hemoglobin time course.

Figure 11: Individual Fits of the Final Population PK/PD Model (dose finding trials)



Upper panel – study BA16280, lower panel – study BA16528. Left panel: 1x/wk dosing, middle panel: 1x/2 wks dosing, right panel: 1x/3wks dosing

Figure 12: Goodness of Fit Plots for the Final PK/PD Model (dose finding trials)



DV – Observed Hb concentrations [g/dL], PRED (IPRED) – NONMEM predicted Hb concentrations [g/dL] based on population (individual) PK/PD parameters, TIME – time after first drug intake [days], WRES – weighed residual values

Table 2: Parameter Values for the Final PK/PD Model (dose finding trials)

Parameter	Unit	Estimate	Precision of Estimate (CV [%])	IIV (CV [%])
S_{max}	1	0.522	12	-
SC_{50}	ng/mL	2.57	23	100
LS	d	81.9	0.3	25
Hb_0	g/dL	9.94	0.9	9
σ^2	1	0.226		
Effect of Dialysis on LS	1	0.749	0.8	
Effect of Dialysis on Hb_0	1	0.963	2	

RUNID: CRA31206, OFV: -269.584

S_{max} – maximum increase from baseline Hb production, SC_{50} – drug concentration producing half-maximum increase in Hb production, LS – apparent life-span of Hb, Hb_0 – Hb at baseline, σ^2 – error variance, CRP – C-reactive protein, IIV – inter-individual variability

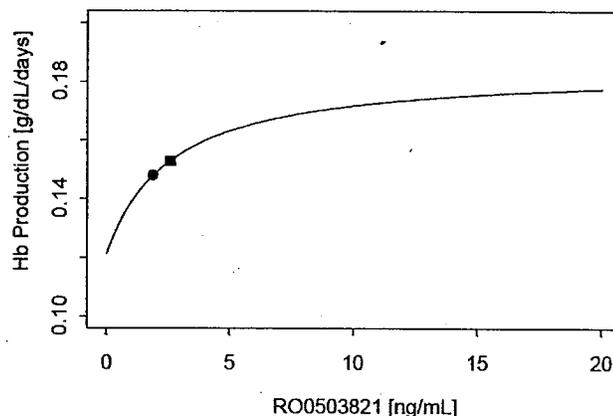
Based on the population PK/PD model, S_{max} - the maximum, drug-induced percentage increase from the baseline hemoglobin production rate - was estimated at 52%. Because of the high correlation of S_{max} with SC_{50} no inter-individual variability was estimated for S_{max} . The mircera concentration that would elicit half of this maximum effect, SC_{50} , was estimated at around 2.6 ng/mL, with a very large inter-individual variability (CV=100%).

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Figure 13 demonstrates the relationship between mircera concentrations and Hb production together with an indication of expected mean mircera concentrations following 0.6 $\mu\text{g}/\text{kg}$ mircera given every two weeks to a 70-kg pre-dialysis patient. Figure 14 shows a simulation of the expected hemoglobin values when a starting dose of 0.6 $\mu\text{g}/\text{kg}$ mircera is given every two weeks to an ESA naïve pre-dialysis 70-kg patient to correct and maintain hemoglobin levels. Interindividual variability and dose adjustments were not considered in this simulation. The simulation shows that hemoglobin, on average, will reach stable levels around 12 g/dL after about 12 weeks of treatment, thus confirming the appropriateness of the starting dose of 0.6 $\mu\text{g}/\text{kg}$ mircera. As drug concentrations of mircera stayed below the population SC50 value most of the time, stimulation of Hb production was less than 50% of its maximum value.

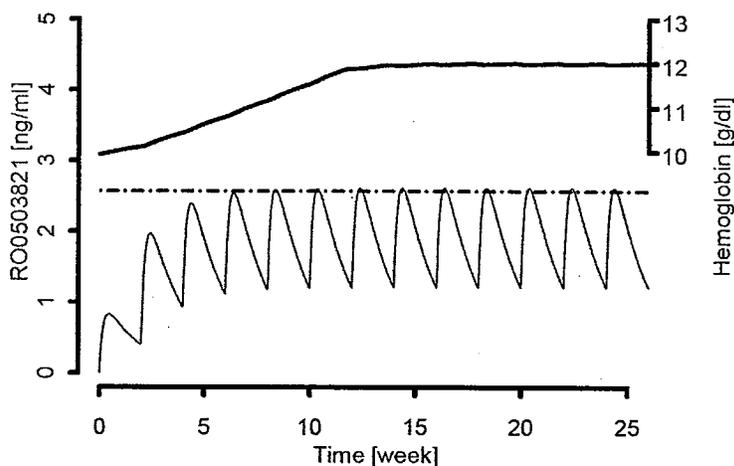
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Figure 13: Expected mircera Concentration vs. Hb Production Relationship following 0.6µg/kg mircera given every two Weeks to a 70-kg Pre-Dialysis Patient (Predictions are based on Population PK and PK/PD Parameters from Final PK and PK/PD Models).



Square: SC50 value (=half-maximum stimulation of RBC-production), Dot: Mean RO0503821 concentration at steady state

Figure 14: Predicted Time Course of Hemoglobin and mircera Plasma Concentrations following 0.6µg/kg mircera given every two Weeks to a 70-kg Pre-Dialysis Patient (Predictions are based on Population PK and PK/PD Parameters from Final PK and PK/PD Models).



Solid line (thin): RO0503821 plasma concentrations, Dashed line: SC50 value (=half-maximum stimulation of RBC-production), Solid line (bold): Hemoglobin level

PKPD modeling of Phase III studies BA16736, BA16739, and BA16740 in chronic kidney disease:

The Hb response model described above was amended to take into account the ceased contribution on Hb of previous epoetin treatment under maintenance treatment conditions (studies BA16739 and BA16740).

$$Hb'(t) = S(t) - S(t - LS) + S_{ESA}$$

$$S(t) = Hb_0 / LS * (1 + E(C(t)))$$

$$S_{ESA} = (Hb_0 - Hb_{sw}) / LS \quad \text{if } 0 \leq t \leq LS \quad \text{otherwise } S_{ESA} = 0$$

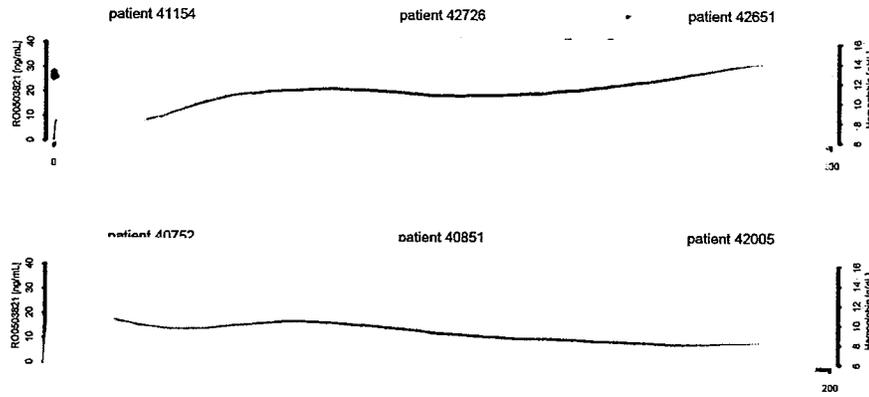
$$E(C(t)) = S_{max} * C(t) / (SC_{50} + C(t))$$

A new term, S_{ESA} , was introduced which accounts for the maintenance treatment condition. S_{ESA} corresponds to the Hb loss rate due to the interruption of former epoetin/ESA treatment after switch to mircera. The S_{ESA} term is only valid during one LS after the switch. Thereafter, previous epoetin treatment has no impact on Hb which then can only be affected by mircera in a way similar to the anemia correction conditions. Hb_{sw} [g/dL] is the hemoglobin concentration at switch from previous epoetin treatment to mircera. Hb_0 is still the Hb value at baseline (i.e., before any epoetin treatment), which was not known in maintenance studies BA16739 and BA16740.

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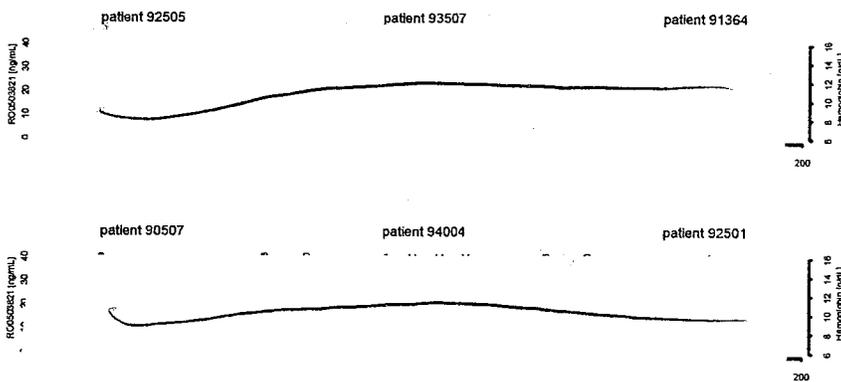
Figure 15: Individual Fits of the Final Population PD Model (a. Study BA16740, b. BA16739 and c. BA16736)

a.



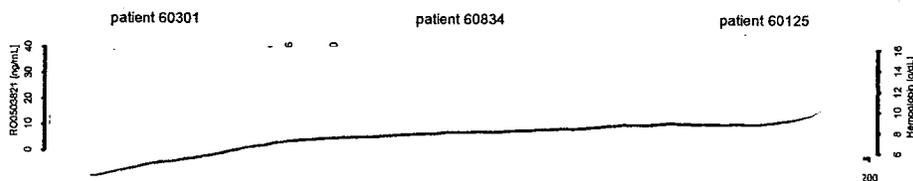
Upper panel – RO0503821 SC 1x/2 weeks, lower panel – RO0503821 SC 1x/4 weeks
Left panel: stable Hb concentrations, Middle panel: initial decline in Hb concentrations,
Right panel: initial increase in Hb concentrations

b.



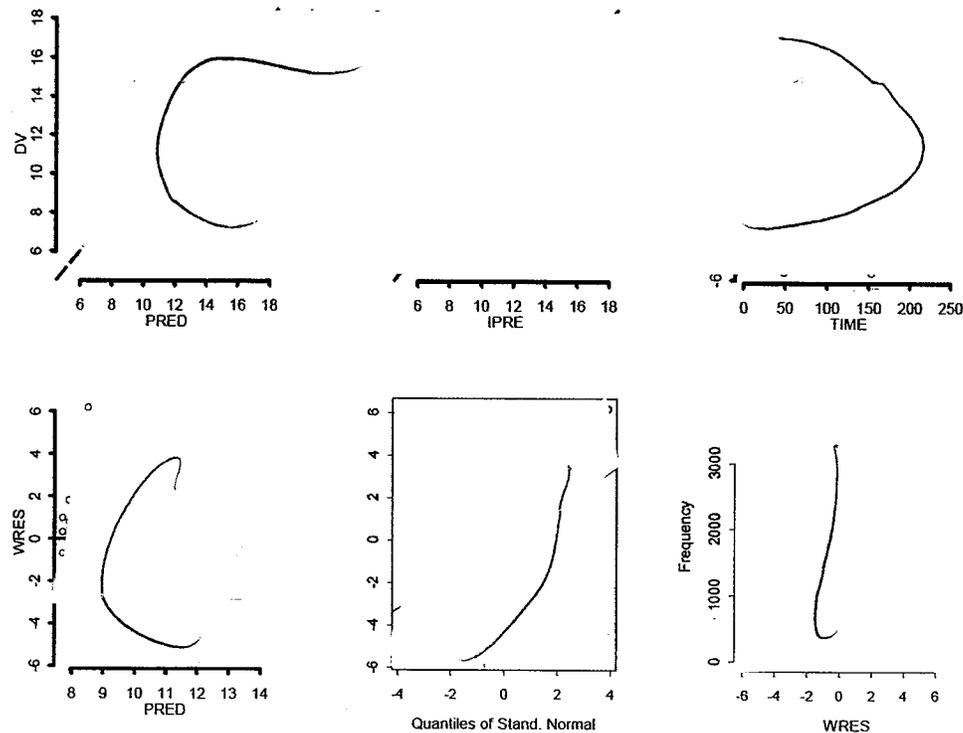
Upper panel – RO0503821 SC 1x/2 weeks, lower panel – RO0503821 SC 1x/4 weeks
Left panel: stable Hb concentrations, Middle panel: initial decline in Hb concentrations,
Right panel: initial increase in Hb concentrations

c.



Left panel: 'regular' Hb concentration time course, Middle panel: delayed increase in Hb concentrations, Right panel: significant increase in Hb concentrations

Figure 16: Goodness of Fit Plots for the Final PD Model



DV – Observed Hb concentrations [g/dL], PRED (IPRED) – NONMEM predicted Hb concentrations [g/dL] based on population (individual) PK/PD parameters, TIME – time after first drug intake [days], WRES – weighted residual values

To illustrate the performance of the final PD model, Figure 15 and Figure 16 show observed and predicted Hb concentrations in individual patients selected from each regimen in studies BA16740, BA16739, and BA16736 and goodness of fits plots for diagnostics purposes. For more modeling details, refer Population PK/PD analyses of mircera of combined Phase III studies BA16736, BA16739, and BA16740 in chronic kidney disease (1020445.pdf)

Table 3: Parameter Values for the Final PD Model

Parameter	Unit	Estimate	RSE (%)
Fixed Effects			
S_{max}	1	0.425	13
SC_{50}	ng/mL	0.898	34
LS	d	61.3*	-
Hb_0	g/dL	9.30*	-
Random Effects IIV			
S_{max}	CV%	142	40
SC_{50}	CV%	559	34
LS	CV%	32	45
Hb_0	CV%	25	53
Covariate Effects			
Effect of CRP on SC_{50}	1	0.319	52
Effect of DEPO on SC_{50}	1	0.303	36
Error Model			
σ^2	1	0.357	4

RUNID: CRA50805; OFV: 2823.755

S_{max} – maximum increase from baseline Hb production, SC_{50} – drug concentration producing half-maximum increase in Hb production, LS – apparent life-span of Hb, Hb_0 – Hb at baseline, IIV – inter-individual variability, CRP – C-reactive protein, DEPO – previous weekly EPO dose, σ^2 – error variance, RSE: Relative standard error of estimate, OFV: NONMEM Objective Function Value, *: fixed

The univariate analyses show that no strong effects exist between dosing schedule, route of administration, and study type and drug related PD parameters S_{max} and SC_{50} .

Table 3 shows parameters for the final PD model that retained the effect of CRP and previous EPO dose (DEPO) on SC_{50} . The corresponding covariate model equation was

$$SC_{50} = 0.898 \cdot (CRP/5)^{0.319} \cdot (DEPO/4000)^{0.303} \text{ [ng/mL]}$$

Time-varying CRP values ranged from 0 to 308 mg/L. In the patient population studied, 1 patient had values above 200 mg/L, 8 patients values above 100 mg/L, and 34 patients values above 50 mg/L. Baseline CRP values ranged 0 to 79.9 mg/L with a median of 5.2 mg/L.

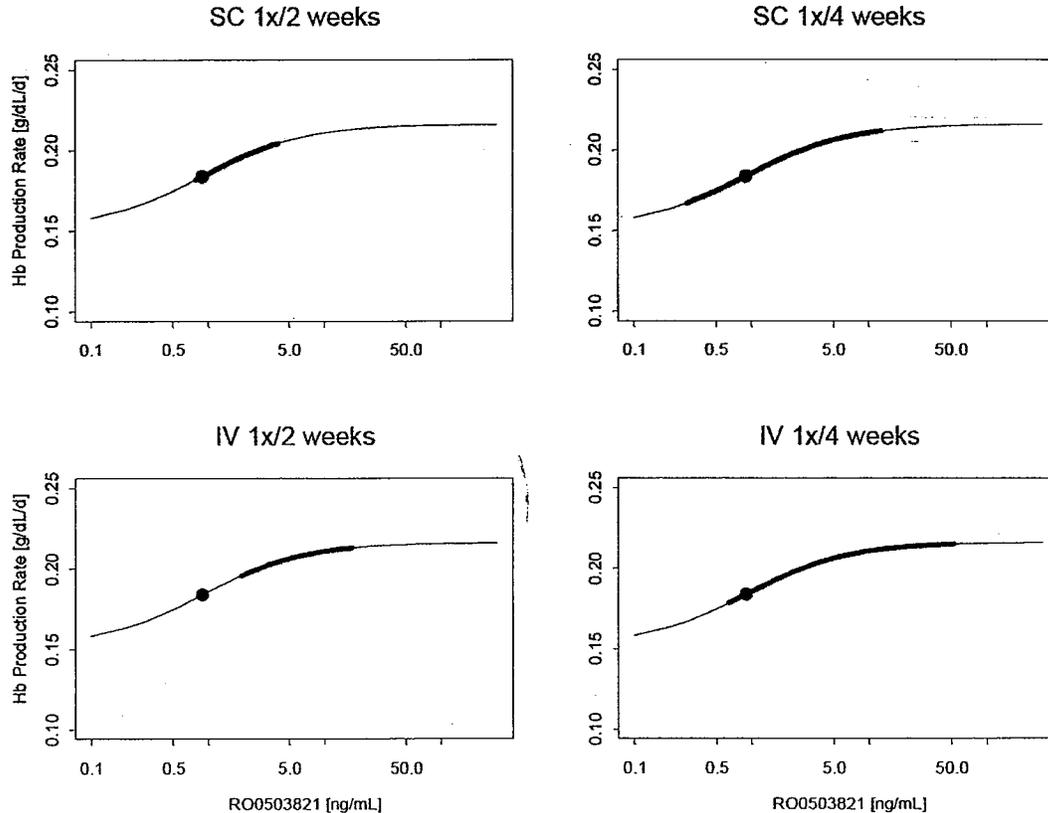
Table 4: Predicted Covariate Effects on SC_{50}

Covariate	Reference Value	Change in Covariate from Reference	Effect on SC_{50} *
CRP	5 mg/L	CRP · 5	67% increase
		CRP · 10	108% increase
		CRP · 50	248% increase
DEPO	4000 IU	EPO · 5	63% increase
		EPO · 10	100% increase
		EPO · 20	148% increase

* Typical values of SC_{50} at reference covariate values: 0.898 ng/mL

Table 4 quantifies these relationships for specified increases in covariates. For example, a 5 times increase in CRP predicts a 67% increase in SC50, independent of initial CRP value.

Figure 17: Model Based Relationship between mircera Concentrations at Steady-State and Hb Production Rate for SC and IV Administration and 1x/2 Weeks and 1x/4 Weeks Dosing



Closed Circle: SC₅₀ value (=half-maximum stimulation of Hb production rate), Bold Line: Concentration range at steady-state in a typical patient. Median dose from evaluation phase of studies BA16739 and BA16740 used for calculation of concentration range.

Based on the population PD model, S_{max} - the maximum, drug-induced percentage increase from the baseline Hb production rate - was estimated at 43%. The mircera concentration that would elicit half of this maximum effect, SC₅₀, was estimated at around 0.9 ng/mL, with a very large inter-individual variability (CV=559%). Figure 17 demonstrates this relationship for both routes of administration (IV, SC) and for both treatment schedules (1x/2 weeks and 1x/4 weeks) at steady state of mircera treatment. Median doses from the evaluation phase of studies BA16739 and BA16740 were used to calculate the mircera concentration range at steady state.

In conclusion, the results of the analysis are as follows:

- In the PD model, the covariates gender, age, body weight (BW), race, transferrin saturation (TSAT), ferritin, albumin, platelets, dialysis and dialysis adequacy measurement, Kt/V, had no effect on the PD parameters of mircera.

- The PD parameter SC_{50} increased with time-varying C-reactive protein (CRP) and previous epoetin dose. These findings support the use of previous epoetin dose to adjust the starting dose of mircera in patients currently treated with an ESA.
- The high variability in PD parameters, especially SC_{50} (with a CV% of 559%), is consistent with the current clinical practice, namely individual monitoring of Hb and adjustment of the dose based on measured Hb concentrations.

Reviewer's analysis

The effectiveness of mircera was well established in 6 clinical studies. All studies show consistent success in correction/maintaining Hb levels within the defined threshold.

The sponsor's modeling results were replicated for the base as well as the final model. Overall, the model fits well and does have mechanistic basis. Mircera shows exposure dependent effect on Hb in the correction as well as maintenance setting. From the base to the final model, CRP and the use of epoetin was found to be statistically significant covariates, however, it did not lead to appreciable improvement in the fit. The covariates were allowed in the model as the mechanistic basis is available. The literature reports indicate that CRP levels correlate with anemia parameters, higher levels being associated with an increased comorbidity burden, lower hemoglobin (Hb) levels, and higher ESA dose requirements.[‡] Thus, an increase in SC_{50} as a function of CRP (see Table 4) confirms that higher dose might be needed for patients with high CRP level. Given the titration setting and safety concerns (see 6.1), it might be appropriate not to adjust the starting dose of mircera based on the above covariates. Individualized dosing approach will essentially compensate for the above differences in SC_{50} .

No dose adjustments other than those established in registration trials were investigated, therefore, no additional analyses or model refinement was attempted.

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[‡] Nephrol Nurs J. 2006 Sep-Oct;33(5):555-8

6.2. Are there any exposure-safety concerns that could justify upper dose limit for mircera?

Reviewer's analysis

The safety of ESAs has been thoroughly questioned in literature.[§] Anemia develops in most patients with CRF, historically often requiring blood transfusion, with obvious risks. With the advent of recombinant erythropoietin in the late 1980s, it became possible to treat anemia without blood transfusion. It is also understood that additional considerations are important, such as ensuring adequate iron stores, providing sufficient folate and vitamin B12, and identifying other conditions affecting the hemoglobin level. Yet, there are unresolved controversies related to the hemoglobin levels at which this therapy should be initiated, as well as its target hemoglobin level.

According to current standards, anemia resulting from CRF is treated when the hemoglobin value falls below 9.0 g/dL, however, many patients are not treated before they need renal replacement therapy. Recently, the National Kidney Foundation Kidney Disease Outcomes Quality Initiative (K/DOQI) panel on anemia suggested that the target hemoglobin level should be 11.0 g/dL or greater, with caution urged if a hemoglobin value of more than 13.0 g per deciliter is intentionally maintained.

Two trials (CREATE** and CHOIR^{††}) were recently published that addressed the optimal target level for hemoglobin in patients with CRF who do not yet need renal-replacement therapy. Neither of these studies of CRF had the anticipated results. One would have expected that normalization of the hemoglobin level would be beneficial. Theoretically, a higher hematocrit level should improve oxygen delivery to tissues. However, there seems a concern that complete correction of anemia might increase both blood pressure and the risk of thrombosis and accentuate vasoconstriction.

In the CREATE study, early complete correction of anemia (to a target hemoglobin value in the normal range, 13.0 to 15.0 g per deciliter) did not seem to decrease the incidence of cardiovascular events, as compared with partial correction of anemia (to a target hemoglobin value of 10.5 to 11.5 g per deciliter). In the CHOIR study, a higher target hemoglobin value (13.5 g per deciliter, as compared with 11.3 g per deciliter) was associated with increased risks of death, myocardial infarction, hospitalization for congestive heart failure (without renal-replacement therapy), and stroke without improvement in the quality of life.

On these lines, the exposure safety analyses of mircera presented a challenging scenario. Table 5 illustrates summary of number of deaths on mircera and its comparison with the control arm. Overall, the proportions look similar across the

[§] Remuzzi, G., and Ingelfinger, J.; Correction of anemia- payoffs and problems. N Engl J Med 2006;355:2144-46

Levin A. Understanding recent haemoglobin trials in CKD: methods and lesson learned from CREATE and CHOIR. Nephrol Dial Transplant 2007; 22: Editorial Comments

** Drüeke TB, Locatelli F, Clyne N, et al. Normalization of hemo-globin level in patients with chronic kidney disease and anemia. N Engl J Med 2006;355:2071-84.

†† Singh AK, Szczech L, Tang KL, et al. Correction of anemia with epoetin alfa in chronic kidney disease. N Engl J Med 2006; 355:2085-98.

treatment arms. The review question was raised based on discrepancy observed in the number of fatal events which mapped to the MedDRA preferred term of 'sudden death' occurred in the mircera group (nine) and none in the reference arm. However, 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%]), the overall incidence of events of this nature is similar between the treatment arms.

Table 5: Summary of number of deaths in phase II (p2) and III (p3) clinical trials comparing mircera and active control

Patient-Years		Mircera N = 1244	Control N = 836	Odds Ratio
Sudden Deaths	P3	9 (0.72%)	0 (0%)	NA
	P2+P3	10 (0.80%)	0 (0%)	
Cardiac Mortality	P3	54 (4.3%)	30 (3.6%)	1.21
	P2+P3	71 (4.4%)	30 (3.6%)	1.24
Overall Mortality	P3	100 (8.0%)	64 (7.7%)	1.05
	P2+P3	130 (8.1%)	64 (7.7%)	1.06

The sponsor attempted to reconcile the above differences in the safety update (major amendment 015, extending the PDUFA clock by 3 months). According to the sponsor, when the adjudicated diagnosis of sudden death was assigned in a blinded manner the outcome was a nearly equal distribution between mircera (1.96%) and reference (1.90%) treatments. These results further support the sponsor's position that there is no association of sudden death to treatment with mircera and that the safety profile of mircera is similar to other ESA therapies. In addition, the sponsor claimed that the safety update finds the imbalance in the reports of 'sudden death' between the mircera and reference groups less marked with the longer duration of treatment, and the data continue to support that the imbalance is attributable to the ambiguous use of this MedDRA preferred term.

However, the review team did not find the explanation satisfactory and decided to continue the analyses on the original submission keeping the new results in the context.

In addition to the concerns noted above, potential dose dependent effect of ESAs on patients' safety has been noted at several instances. Currently, these guidelines do not have any upper dose limit for ESAs, however, do caution the use of a low ESA dose for maintenance purposes. According to the current dosing guidelines, the recommended starting dose of Aranesp® for the correction of anemia in adult CRF patients is 0.45 mcg/kg body weight, administered as a single IV or SC injection once weekly. Because of individual variability, doses should be titrated to not exceed a target hemoglobin concentration of 12 g/dL. Further, it is noted that for many patients the appropriate maintenance dose will be lower than this starting dose. Predialysis patients, in particular, may require lower maintenance doses.

Therefore, a dose-event relationship was investigated to assess if there is any upper limit on mircera dose. The dose was used a predictor variable as mircera concentration data were collected in only subset of patients enrolled in the registration trials. Table 6 illustrates the number of patients used in the following analyses.

Table 6: Number patients (number of deaths) used in the analyses by study and ESAs in maintenance studies.

	BA16739	BA16740	BA17283	BA17284	Total
Darbepoetin	0	0	156(12)	0	156
Epoetin	225 (17)	191 (12)	0	168 (10)	584
Mircera	442 (34)	381 (31)	153 (13)	165 (7)	1141
Total	667 (51)	572 (43)	309 (25)	333 (17)	1881

Figure 18 illustrates the relationship between the last observed median dose per week and % deaths by treatment groups in the maintenance studies. The current representation should be viewed with caution as

1. Due to the maintenance setting, the dose is not constant over the study duration. The last observed value before the event/last observation was noted, however, the dose does remain constant for considerable duration if the patients are in the maintenance setting.
2. The dose of the mircera in the maintenance setting was calculated based on the dose of the previous ESA for a given patient. Therefore, the dose of mircera will be higher if the dose of the previous ESA was also higher. This becomes especially important for patients with early events. It might be difficult to attribute these events to mircera or even to the previous ESA.
3. Lastly, the dose of the previous or current ESAs will be higher for non-responders with severe disease status. Due to the patients' disease status, these patients would have been at higher risk and what seems like a dose effect could be confounded by the disease severity.
4. The dosing regimens for patients within and between groups vary from 1-3x/wks to 1/4wks (as shown in Table 7). The dose was normalized per week irrespective of the dosing regimen.

Table 7: Number of patient on each ESAs by dosing regimens in maintenance studies

	Darbepoetin	Epoetin	Mircera
BA16739			
1*/1-3wks	0	225	0
1*/2wks	0	0	221
1*/4wks	0	0	221
BA16740			
1*/1-3wks	0	191	0
1*/2wks	0	0	190
1*/4wks	0	0	191
BA17283			
1*/1-2wks	156	0	0
1*/2wks	0	0	153
BA17284			
1*/2wks	0	0	165
1-3*/wks	0	168	0

In spite of these limitations, the dose dependent increase in proportion of death is still concerning and the trend is consistent across ESAs as shown in Figure 18. Additionally, Figure 19 and Figure 20 illustrate time to death on mircera and epoetin stratified by last dose per week. The median dose per week was used to stratify these groups. Due to

low incidence of events the statistical significance was not achieved, however, a trend towards high doses accelerating the time to death was noticeable for mircera as well as epoetin.

Further, Figure 21 illustrates comparison of time to death on mircera and the respective respective reference in the study. Figure 22 illustrates comparison of time to death on mircera and epoetin by combining data from three studies. Overall, mircera seem to aggravate time to death compared to the reference treatment, however, the differences were not statistically significant. The trend does pose some concern in assessing risk – benefit profile of mircera alone as well as relative to the existing reference agents. As outlined in the previous section, the effectiveness of mircera was established using the non-inferiority tests. The assessment is further complicated due to lack of knowledge on the baseline risk of not treating anemia caused due to CRF.

Further analyses were focused on time to first serious adverse event (SAE^{‡‡}) or first drug related AE^{§§} (Figure 23 and Figure 24). The notion was, a trend for death due to dose effect or ESA agent would be similar for SAE and other AEs. However, the evidence was not consistent. There was little or no difference for time to first SAE between mircera and the reference treatment. For time to first drug related AE the trend pointed in the direction consistent with a trend seen for time to death. These analyses were considered inconclusive due to potential noise gathered in definitions of SAE and first drug related AE.

Sponsor analysis

After a meeting with the sponsor, the sponsor voluntarily replicated our analyses (see amendment 025 reports- Individual Study Kaplan _2_.pdf and Pooled Analyses.pdf). According to the sponsor, the results of these additional pooled analyses of Kaplan-Meier plots and the summary statistics confirm that the overall mortality rate of mircera is similar to that of darbepoetin and epoetin. Furthermore, the individual study analyses also show the same trend for mortality with mircera compared to darbepoetin and epoetin despite the variability associated with small numbers.

Overall, the risk-benefit of mircera and overall ESA agents is questionable. At this time, it is not possible to optimize the treatment given uncertainties in dose effect, Hb target (partial or complete correction), Hb minimum to start ESA treatment (baseline risk) or any other predictors (such as, slope of Hb response) that would maximize overall benefit.

^{‡‡} The definition and reporting requirements of ICH Guidelines for Clinical Safety Data Management, Definitions and Standards for Expedited Reporting, Topic E2 were adhered to.

^{§§} As identified in the CRF- defined as the event with a reasonable suspected causal relationship to the drug, or causality is unknown.

Figure 18: Dose response analysis for % deaths by treatment groups from all maintenance studies (BA16739, BA16740, BA17283 and BA17284)

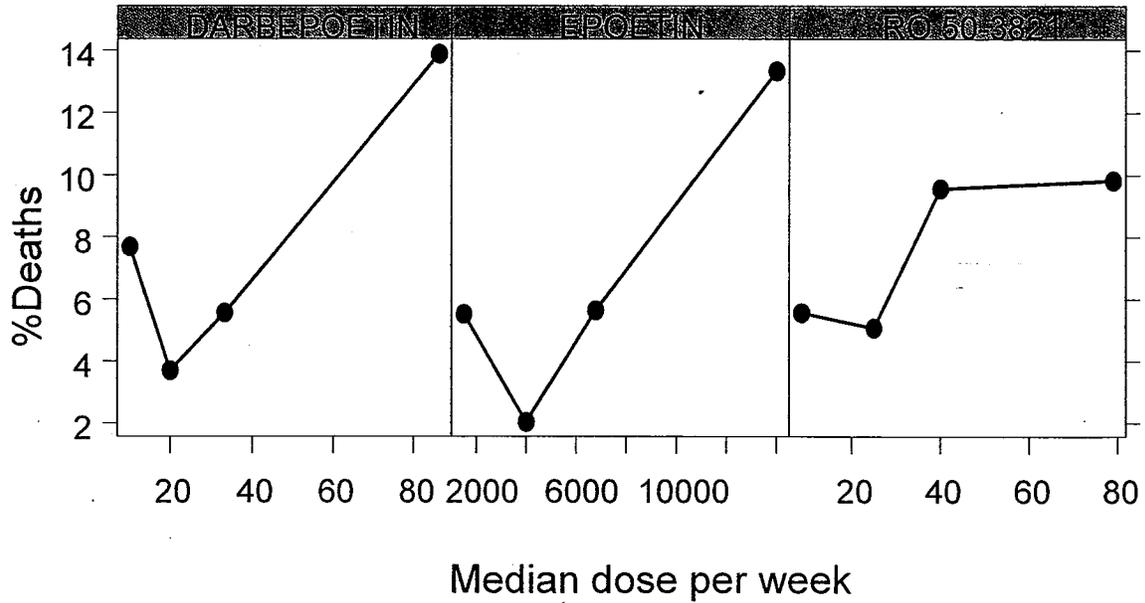


Figure 19: Survival curve assessing mircera dose effect from all maintenance studies (BA16739, BA16740, BA17283 and BA17284)

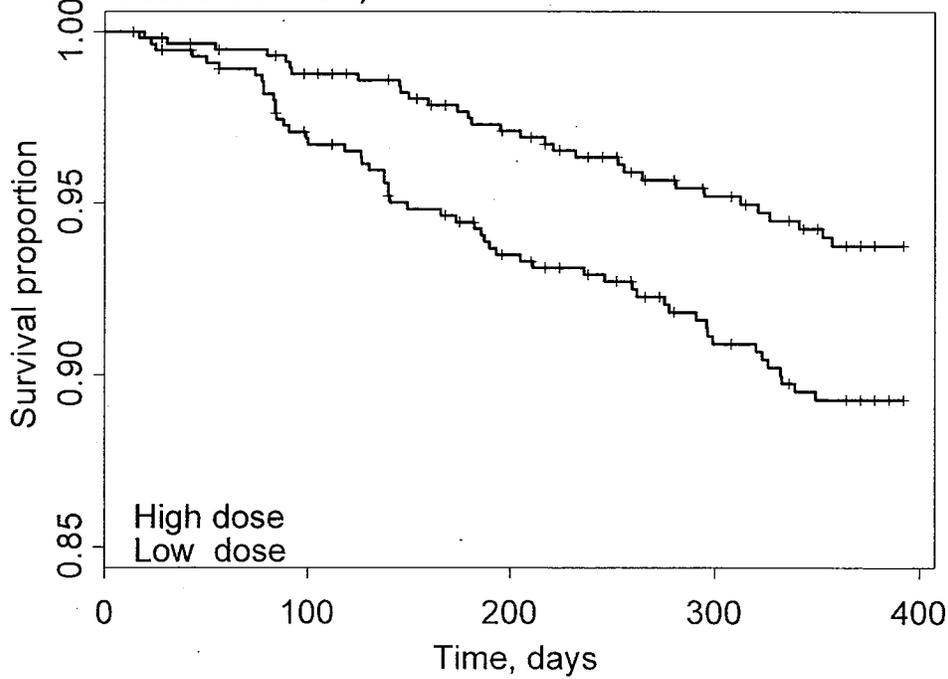


Figure 20: Survival curve assessing epoetin dose effect from maintenance studies (BA16739, BA16740 and BA17284)

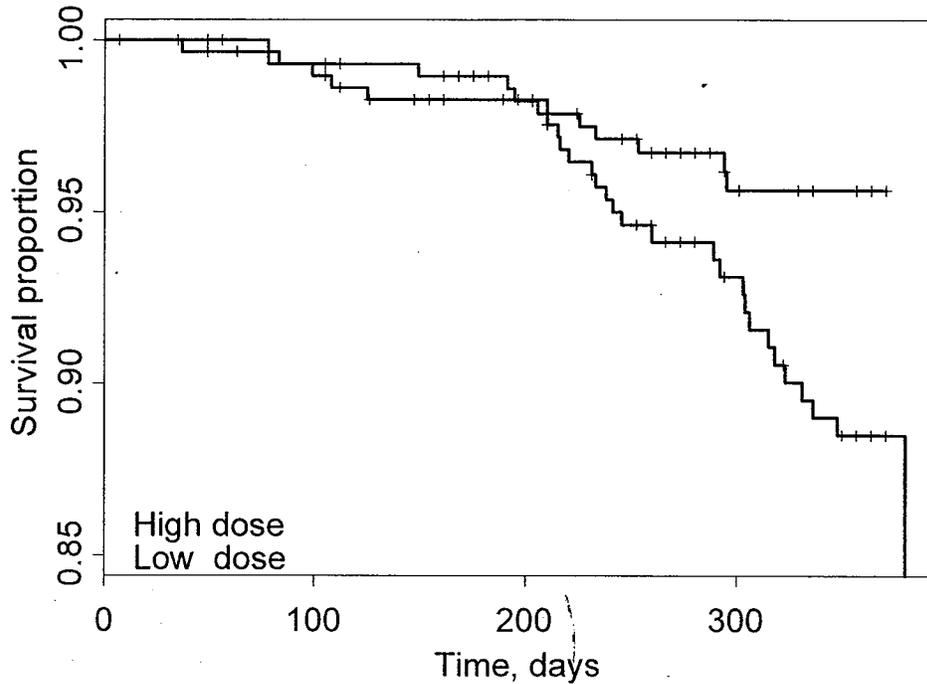


Figure 21: Mortality rate on mircera versus control for all maintenance studies (BA16739, BA16740, BA17283 and BA17284)

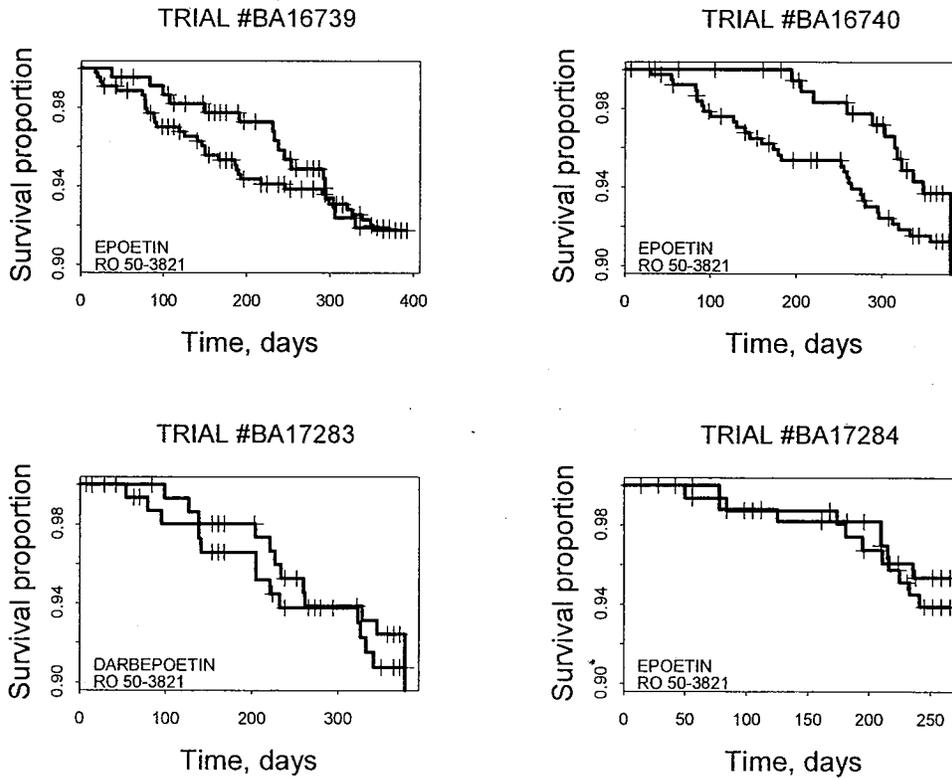


Figure 22: Mortality rate comparing mircera and epoetin from BA16739, BA16740 and BA17284

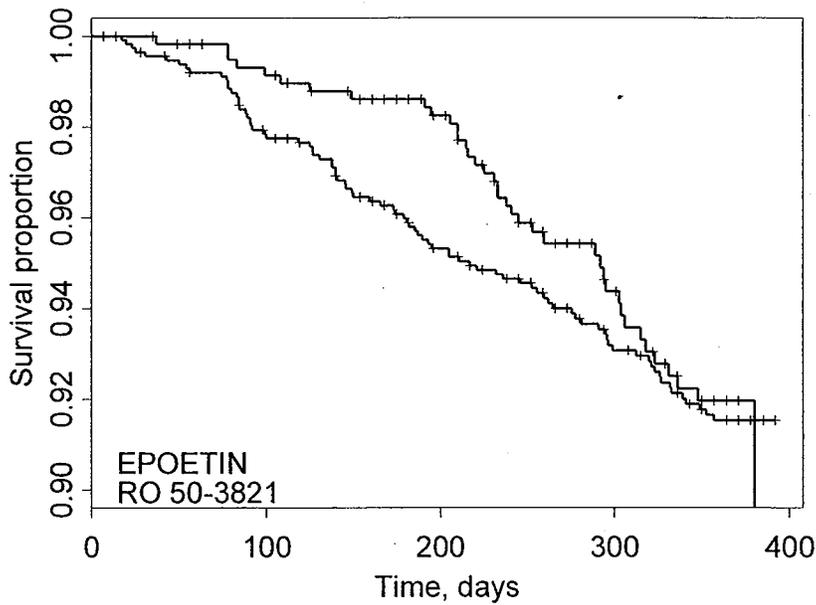


Figure 23: First SAE occurrence rate on mircera versus control for all maintenance studies (BA16739, BA16740, BA17283 and BA17284)

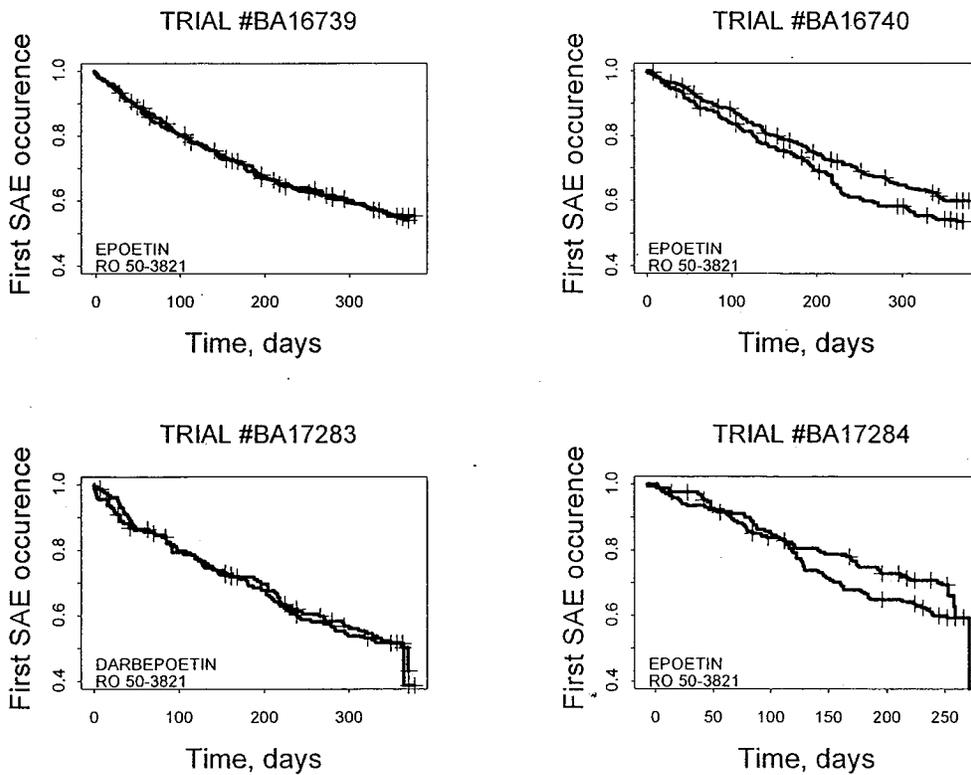
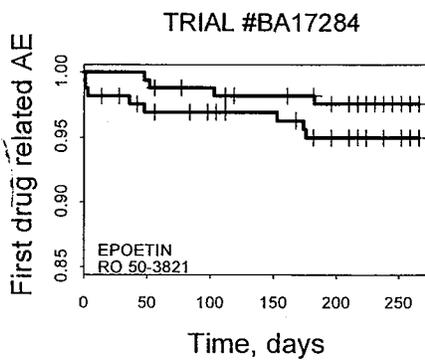
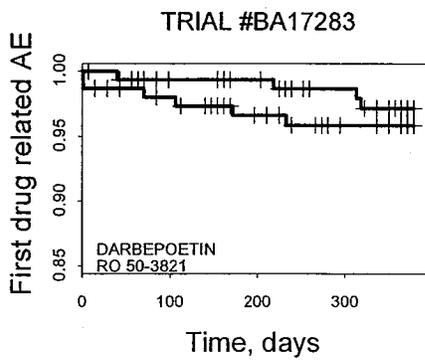
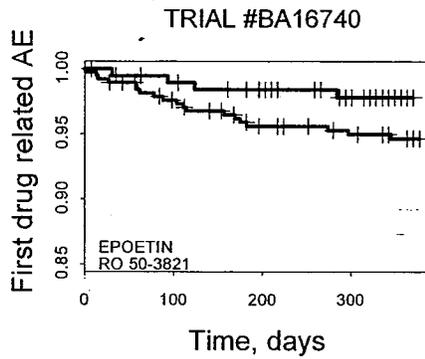
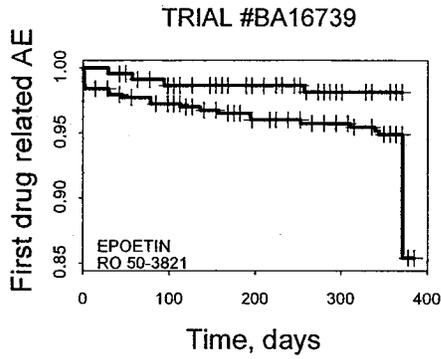


Figure 24: First drug related AE occurrence rate on mircera versus control for all maintenance studies (BA16739, BA16740, BA17283 and BA17284)



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Table 10: Parameter Values for Final PK Model (dose finding trials)

Parameter	Unit	Estimate	Precision of Estimate (CV [%])	IIV (CV [%])	IOV (CV [%])
CL/F	L/d	1.60	6	53	40
V/F	L	20.7	9	67	
ka	1/d	0.825	16	82	
Effect of BW on CL/F	1	1.11	19		
Effect of AGE on V/F	1	0.611	33		
σ^2 (proportional)	1	0.115			
σ^2 (additive)	1	0.0025 FIXED			

RUNID: CRA2CV08, OFV: 976.538

Legend: CL/F – apparent drug clearance, V/F – apparent volume of distribution, ka – absorption rate constant, σ^2 – error variance, IIV – inter-individual variability, IOV – inter-occasion variability

Table 11: Parameter Values for Final PK Model (registration trials)

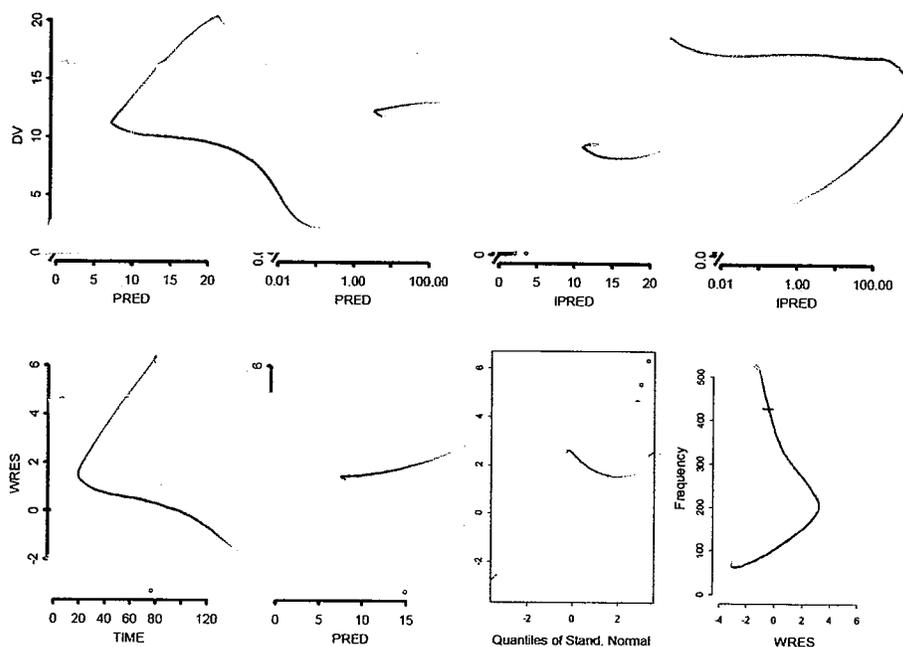
Parameter	Unit	Estimate	RSE (%)
Fixed Effects			
CL	L/d	0.749	2
V	L	4.72	2
ka	1/d	0.825*	-
F	1	0.394	4
Random Effects IIV			
CL	CV%	28	9
V	CV%	27	11
ka	CV%	82*	-
F	CV%	0*	-
Random Effects IOV			
CL	CV%	9	32
Covariate Effects			
Effect of BW on CL	1	0.571	13
Effect of BW on V	1	0.443	17
Effect of Age on V	1	0.267	19
Error Model			
m	ng/mL	0.150*	-
σ_1^2 (proportional)	1	0.141	6
σ_2^2 (additive)	1	0.691	12

RUNID: CRA40717, OFV: 6067.782

CL – drug clearance, V – volume of distribution, ka – absorption rate constant, F – bioavailability, IIV – inter-individual variability, IOV – interoccasion variability, m – error model parameter, σ^2 – error variance, RSE: Relative standard error of estimate, OFV: NONMEM Objective Function Value, *: fixed

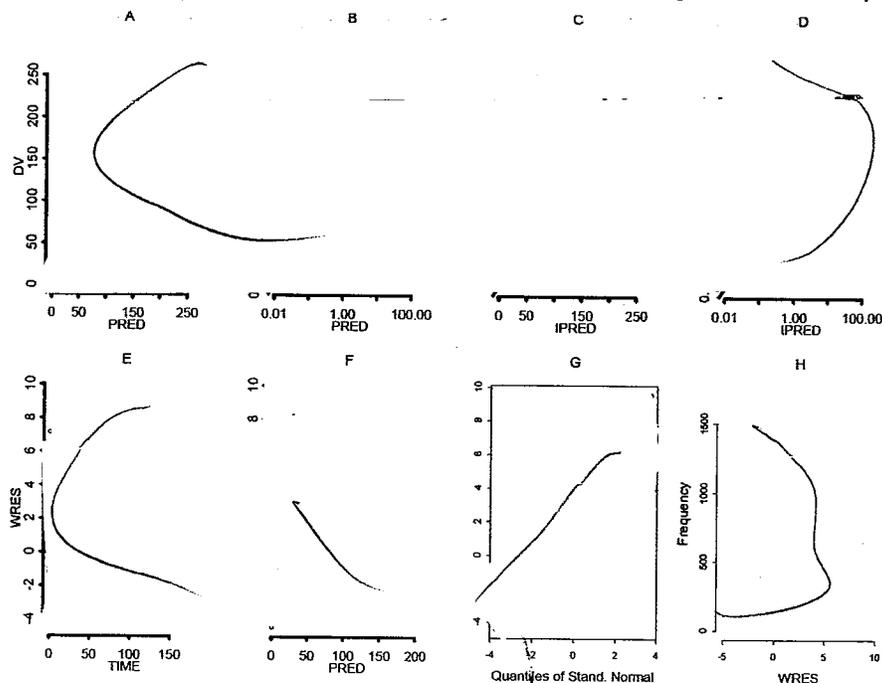
Figure 25 and Figure 26 illustrate the goodness of fits plots for the final models in each of the analyses. The association between the base model parameters and covariates was very weak. The relationship between CL and body weight was characterized by a high variability. There was a small reduction of inter-individual variability for CL (drops of 10% and 2% in analyses II and III, respectively) when comparing the final PK model (with all statistically significant covariates including body weight) with the basic model (without any covariates). A statistically significant increase of V with body weight was found in analysis of the registration trials but not in analysis of the dose finding trials. The addition of covariates, however, resulted in little or no change in IIV on CL and V. There was also little or no improvement in model fits.

Figure 25: Goodness of Fit Plots for the Final PK Model (dose finding trials)



DV – Observed RO0503821 concentrations [ng/mL], PRED (IPRED) – NONMEM predicted RO0503821 concentrations [ng/mL] based on population (individual) PK parameters, TIME – time after first drug intake [days], WRES – weighted residual values

Figure 26: Goodness of Fit Plots for the Final PK Model (registration trials)



DV – Observed RO0503821 concentrations [ng/mL], PRED (IPRED) – NONMEM predicted RO0503821 concentrations [ng/mL] based on population (individual) PK parameters, TIME – time after first drug intake [days], WRES – weighted residual values

From the population analyses combined with data from a few early phase studies, several labeling claims were made.

6.3.1. In CRF patients, the pharmacokinetics of mircera were studied after the first dose and after administrations on week 9 and week 19 or 21. Multiple dosing was found to have no effect on clearance, volume of distribution and bioavailability of mircera.

Using the final population PK model, potential effects of time on PK parameters CL, V, and F were investigated. As blood samples were taken after the first dose of mircera, at week 9 and at weeks 19-21 of mircera treatment, population PK parameters were calculated using these time periods as covariates. The results are shown in. Although there was always a statistically significant change in the NONMEM objective function value, the extent of the relative effects on the PK parameters with respect to values after the first dose was minor. Changes in CL, V and F were always below $\pm 15\%$ which indicates that the PK of mircera does not change with time. It also appears that the model for testing time effect on V did not converge fully. This, probably, could be due to lack of information to estimate all these parameters uniquely.

Table 12: Effect of Time on PK Parameters CL, V, and F

	First dose	Week 9	Week 19/21	
No. of Patients	400	392	276	
CL (L/d)	0.798	0.718	0.710	
V (L)	4.40	4.88	4.92	#
F	0.381	0.408	0.419	\$

#: minimization terminated, \$: covariance step aborted

There are little or no differences in PK parameters across the sampling times. On the other hand, there is no reason expect time dependency for any of these parameters, therefore, the claim is acceptable.

In CRF patients, the pharmacokinetics of mircera were studied after the first dose and after administrations on week 9 and week 19 or 21. Multiple dosing was found to have no effect on clearance, volume of distribution and bioavailability of mircera.

6.3.2. After administration every 4 weeks in CRF patients, there was virtually no accumulation of mircera, as demonstrated by a ratio of accumulation of 1.03. After administration every 2 weeks, the ratio of accumulation in serum was 1.12.

Based on the final population PK model, the ratio of accumulation of mircera was calculated for each patient using the post-hoc estimates of CL and V. The results are presented in for each of the two dosing intervals and apply to both IV and SC routes of administration. The results showed that for the 1x/2 weeks schedule serum concentrations of mircera are on average 12% higher at steady-state compared to the first administration. For the 1x/4 weeks schedule, there is virtually no increase in serum concentrations when comparing steady-state with first administration.

Table 13: Accumulation Ratios of mircera (mean \pm SEM) in CRF Patients in Phase III Studies after Administration of RO0503821 1x/2 Weeks and 1x/4 Weeks

	1x/2 weeks	1x/4 weeks
Number of patients	263	137
Ratio of Accumulation	1.12 \pm 0.01	1.03 \pm 0.002

However, there was discrepancy between accumulation found in CRF patients (population PK analysis) and healthy volunteers (two early phase studies).

Table 14: Accumulation Ratios (Mean \pm SEM) of mircera in Healthy Subjects (Studies BP16346 and WP16422)

Dose ($\mu\text{g}/\text{kg}$)	R_{acc} , day 43/day 1 Study BP16346 1x/3 weeks	R_{acc} , day 43/day 1 Study WP16422 1x/2 weeks
0.4	1.38 \pm 0.11 (N = 10)	1.78 \pm 0.14 (N = 7)
0.8	1.05 \pm 0.08 (N = 7)	1.35 \pm 0.06 (N = 7)
1.6	1.40 \pm 0.14 (N = 8)	1.84 \pm 0.31 (N = 7)
3.2	1.29 \pm 0.13 (N = 9)	2.17 \pm 0.19 (N = 8)

According to the sponsor, these results showed that after multiple administrations 1x/4 weeks in CRF patients, there was no meaningful accumulation of mircera. After multiple administrations 1x/2 weeks, mean R_{acc} was higher, as expected from the $t_{1/2}$ and the dosing interval, but still considered a low value. There was an apparent difference in the ratios of accumulation when comparing healthy volunteers and patients, for which there is no explanation. As the number of subjects included in these calculations was much higher for CRF patients ($n = 400$) than for healthy volunteers ($n = 63$), a greater weight should be given to the data from CRF patients.

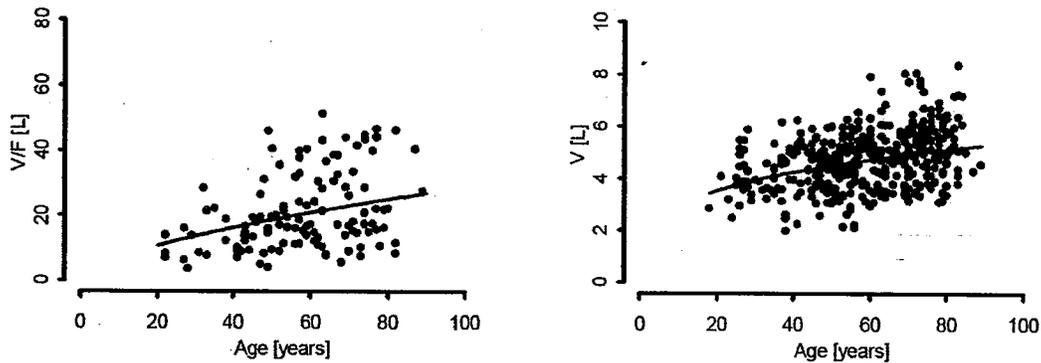
In reviewer's opinion, the analyses approach and methodology are acceptable. The labeling should reflect these discrepancies, therefore, the following changes are proposed to the labeling statement.

6.3.3. Population analyses evaluated the potential effects of demographic characteristics on the pharmacokinetics of mircera. Results of these analyses showed that no dose adjustments are necessary for age, gender, or race.

Age: The population analyses showed a statistically significant increase of V of mircera with age. The magnitude of the effect of age on V was different in the two analyses and was less pronounced in analysis of registration trials. The small magnitude of the effect and the remaining high variability after inclusion of age in the model indicate that this finding (effect of age on V) is not clinically relevant (Figure 27).

Using the regulatory definition of elderly patients (> 65 years), the PK of mircera was compared in adult and elderly patients. Post-hoc estimates of these parameters were calculated using the data from analysis III in a total of 400 CRF patients (Table 15). The results showed that PK parameters are comparable in adult and elderly patients.

Figure 27: Relationship between Volume of Distribution and Age in Analysis of dose finding trials (Left Panel) and Analysis of registration trials (Right Panel)



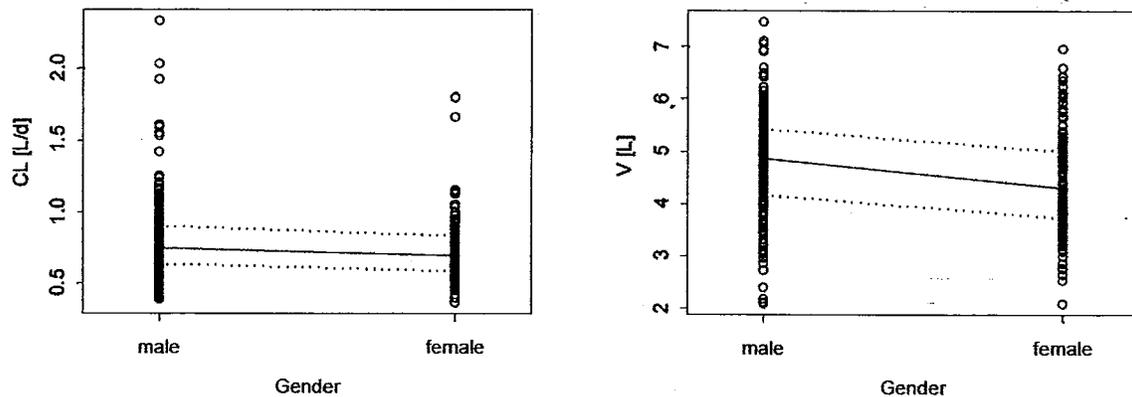
The dots represent the individual values and the line represents the model-estimated regression curve.

Table 15: Pharmacokinetic Parameters (Mean \pm SEM) in Adult and Elderly CRF Patients (registration trials)

Parameter (Mean \pm SEM)	Age 18 - 65 Years N = 246 (61%)	Age \geq 65 Years N = 154 (39%)
Age (year)	48.2 \pm 0.7	74.5 \pm 0.4
V (L)	4.42 \pm 0.06	5.13 \pm 0.09
CL (L/day)	0.823 \pm 0.018	0.782 \pm 0.019
F	39%	39%

Gender: Four different analyses were done to assess effect of gender on mircera PK. The first analysis used data derived from a model independent evaluation in study BP16964. Using ANOVA and data from 35 healthy volunteers (19 males and 16 females), no statistically significant effect of gender on AUC_{last} ($p = 0.315$) and C_{max} ($p = 0.067$) was found. The second analysis used data derived from study BP18035. Using ANOVA and data from 42 healthy volunteers (25 males and 17 females), no statistically significant effect of gender on AUC_{last} ($p = 0.370$) and C_{max} ($p = 0.593$) was found. The third and fourth analyses used a non-linear mixed effect modeling approach with gender tested as a covariate. The third analysis used data from Phase II studies in CRF patients (55 males and 69 females) and showed no gender effect on PK parameters (CL/F, V/F and k_a). The fourth analysis used data from Phase III studies in CRF patients (238 males and 162 females) and provided results similar to the third analysis with no effect of gender on the PK of mircera.

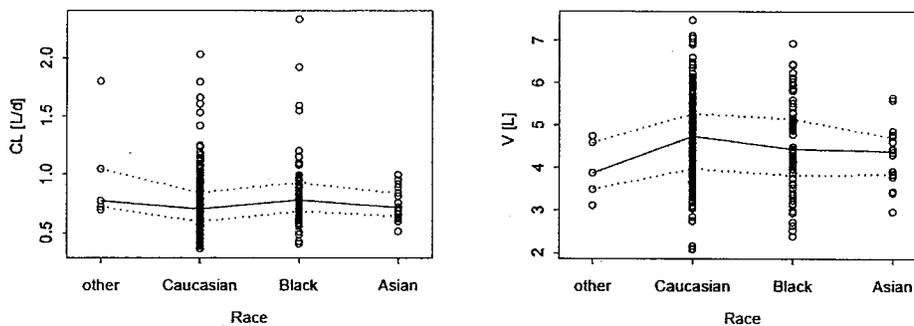
Figure 28: Relationship between Gender and PK Parameters from the Basic PK Model



Race:

This analysis included 306 Caucasian patients (77%), 71 Black patients (18%), 18 Asian patients (4.5%) and 5 patients with race categorized as "other". There were no statistically significant differences in the PK parameters of mircera in Black patients compared with Caucasian patients. Although the number of Asian patients was too small to draw any firm conclusions regarding this race, the analysis suggested no difference in the PK of RO0503821 in this subgroup of patients compared with Caucasian or Black patients. No conclusions regarding the race group "other" could be drawn from this analysis due to the small number of patients involved.

Figure 29: Relationship between Race and PK Parameters from the Basic PK Model



CL – drug clearance, V – volume of distribution, solid line – median, dotted lines – 1st and 3rd quartile.

In addition, the Study JP16690 aimed to assess the PK, PD and safety of RO0503821 following IV administration was used to support the claim. An additional objective was to demonstrate PK and PD comparability of RO0503821 between Japanese and Caucasian subjects. Single ascending doses of 0.8, 1.6 and 3.2 $\mu\text{g}/\text{kg}$ were administered to 72 healthy male volunteers, 36 of Japanese and 36 of Caucasian origin. The primary PK parameter, AUC_{last} , was comparable between Japanese and Caucasian subjects for all doses tested. The ratio Japanese/Caucasian of means for all doses combined was 1.10 (90% CI 0.86-1.42). There were no major differences between Japanese and Caucasian subjects for other PK parameters. Mean values of $t_{1/2}$ ranged

6.3.5. No formal drug-drug interaction studies have been performed. The effect of other drugs on the pharmacokinetics and pharmacodynamics of mircera was explored using a population analysis approach. There was no indication of an effect of concomitant medications on the pharmacokinetics and pharmacodynamics of mircera.

According to the sponsor, no drug-drug interaction studies have been performed. The clinical results do not indicate any interaction of mircera with other medicinal products. The effect of other drugs on the PK and PD of mircera was explored using a population analysis approach. There was no indication of an effect of concomitant medications on the PK or PD of mircera. Review of the literature on currently marketed ESAs (epoetin alfa and beta and darbepoetin alfa) did not identify any publication that would suggest that epoetin/darbepoetin alfa has the potential to alter the PK of other drugs. Historically, concerns have been raised about the possible worsening of anemia when angiotensin-converting enzyme (ACE) inhibitors are administered and the possible blunting of the effect of rhuEPO. However, a clinical study to address this potential interaction concluded that ACE inhibitors do not increase rhuEPO dose requirements or reduce Hct levels in these patients.

To assess whether a drug-drug interaction could be expected from the polyethylene glycol (PEG) moiety of RO0503821, a search was carried out for this in published studies and in the label of drugs consisting of pegylated proteins (Adagen, Oncaspar, Intron/Peg- Intron, Roferon-A/Pegasys, Neupogen/Neulasta). This search revealed no drug-drug interactions that could be related to the PEG moiety.

To date, during the conduct of the clinical studies with mircera, there was no case report indicating a possible drug-drug interaction or an adverse event that could have been caused by a drug-drug interaction. Review of the labels of epoetin alfa, epoetin beta and darbepoetin alfa did not indicate any alteration in the PK of other drugs. There is a potential for a drug-drug interaction with drugs that bind or penetrate into RBCs (eg, cyclosporin and tacrolimus), and on this basis, levels of these drugs were to be monitored in all Phase III studies as indicated in their labels.

On the basis of information from the literature and the labels of marketed ESAs of no specific drug-drug interaction, the drug-drug interaction potential of mircera was investigated using a population PK approach. In analysis of registration trials, an evaluation was performed to assess whether some concomitant medications could have an effect on the PK and PD of RO0503821. Concomitant medications in the 30 patients with the lowest and highest individual values of CL, V, Smax and SC50 were examined. If a concomitant medication was present in more than 15 out of these 30 patients, the frequency distribution of the PK and PD parameters in patients with and without the concomitant medication was compared graphically with regards to central tendency and variability. Heparin sodium, iron sucrose, calcium carbonate, folic acid and paracetamol were found to be satisfying the above criterion of 15 out of these 30 patients at the extremes of distribution. The results of this analysis did not reveal any concomitant medication with an effect on the PK or PD parameters of mircera.

Additional analysis was performed identify mostly commonly administered medications in CRF patients. Concomitant medications from studies BA16736, BA16739 and

BA16740 were documented. Figure 31 shows the list of most commonly administered and proportion of patient receiving concomitant medications with at least one instance of administration (cut off 30%). Figure 32 shows the list of most commonly administered and proportion of patient receiving concomitant medications as a part of ongoing therapy.

Figure 31: Proportion of patients with at least one instance with the concomitant medication (dosage regimen for concomitant medications are not fully documented)

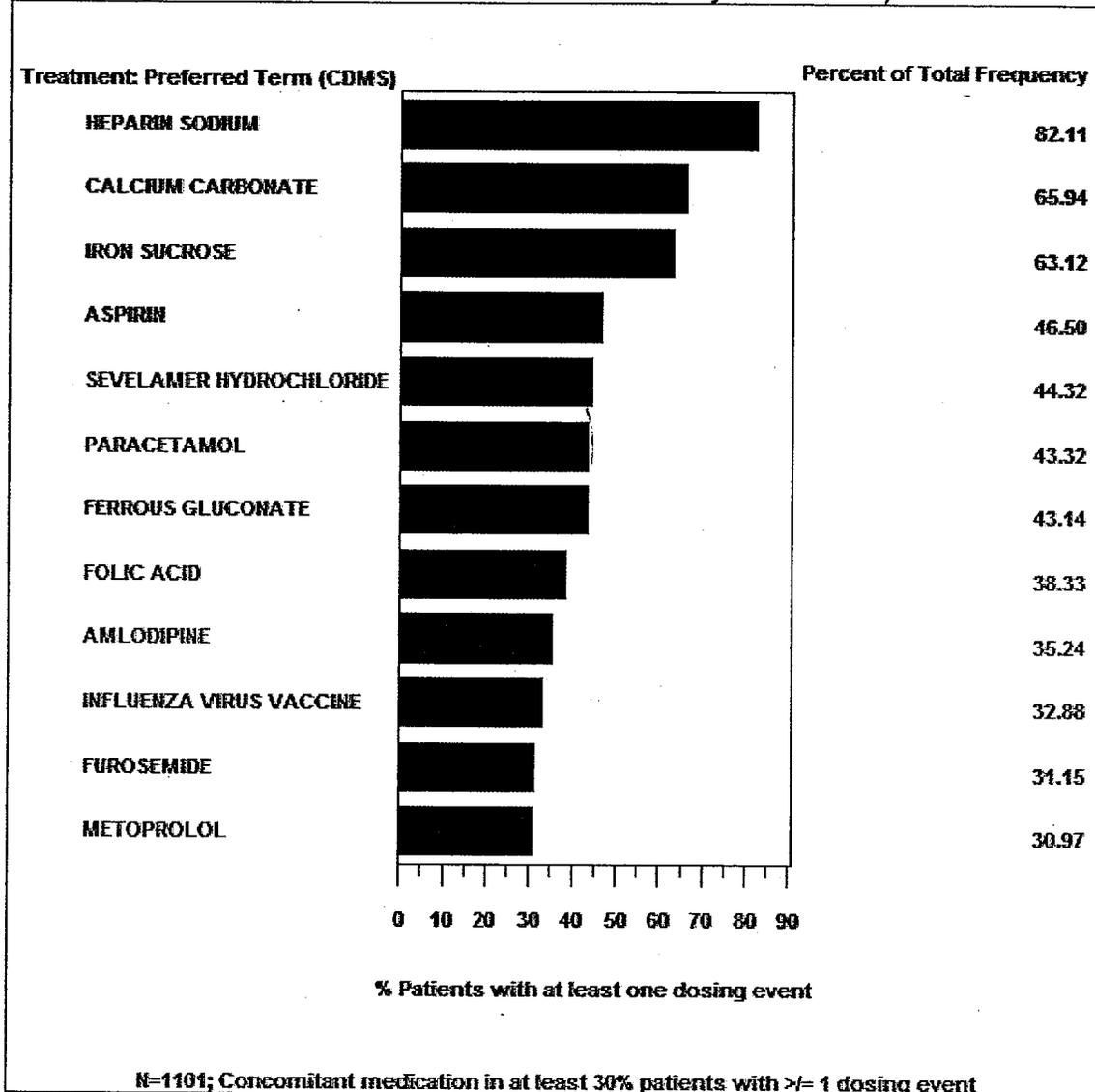
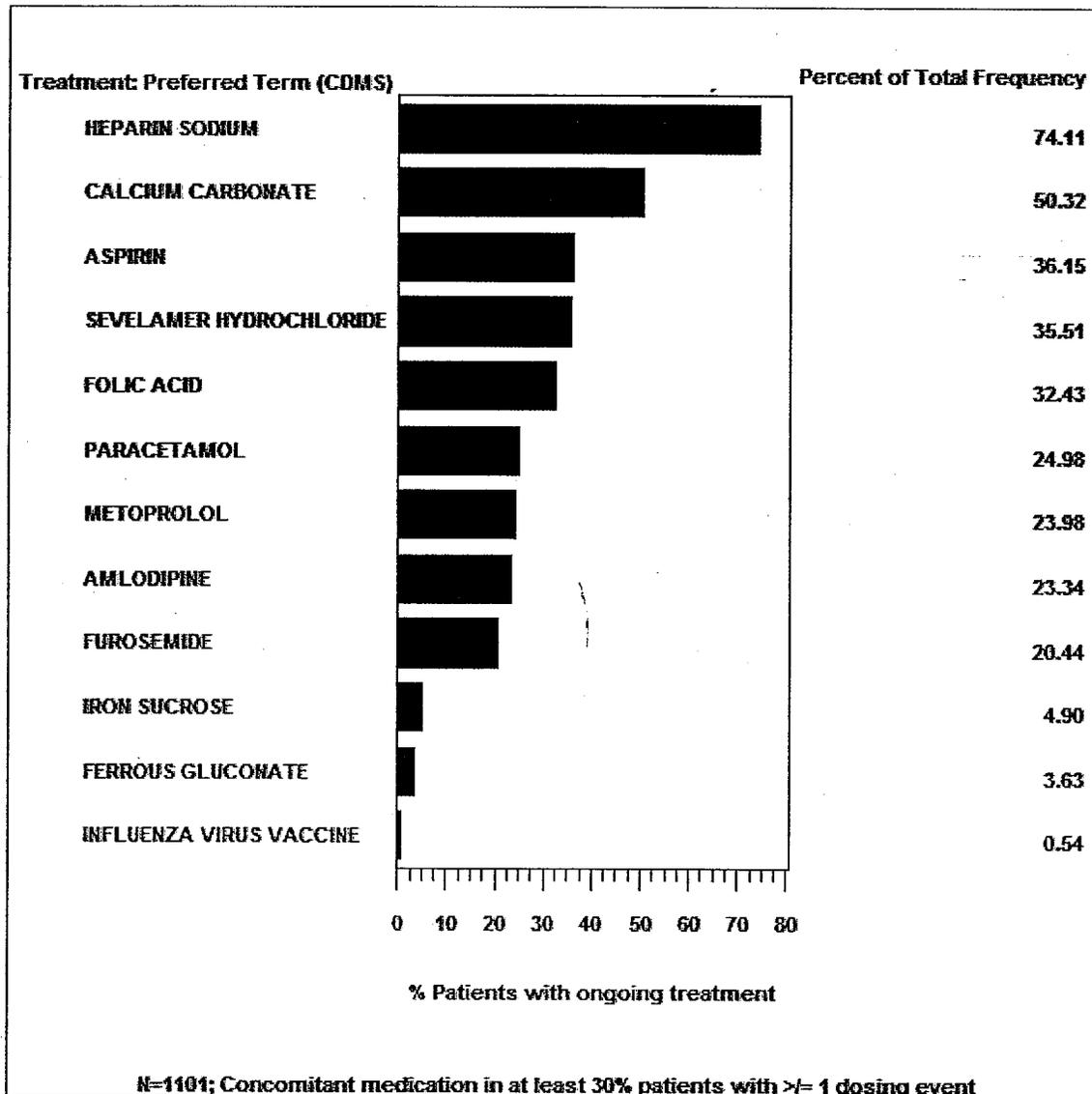


Figure 32: Proportion of patients with ongoing therapy of concomitant medication (dosage regimen for concomitant medications are not fully documented)



Given the list of medications used in the patient population, it is impractical to search for covariates in the population PK analysis. There are two major limitations of such studies to assess drug interactions.

1. These medications were not prospectively planned to be administered with mircera. Medications have been included on patient need basis.
2. The dosing regimen for concomitant medications is not fully documented. However, given the in-patient setting for these trials, it is safe to assume that standard therapeutic doses of concomitant medications have been administered.

The sponsor has made good case for not having to conduct dedicated drug-drug interaction studies based on mechanistic pharmacokinetic understanding. Other ESA agents (Aransep, Procrit) are similarly labeled without conducting any drug drug interaction studies. The effect on pharmacodynamics is rather complicated to evaluate using

population PKPD approach. Although, the sponsor's methodology seems reasonable, no conclusive inference can be drawn for the design limitations and theoretical concerns mentioned above. Overall, the claim is acceptable with minor modifications.

No formal drug-drug interaction studies have been performed. There was no indication in clinical studies of an effect of concomitant medications on the pharmacokinetics of mircera.

6.4. Is titration scheme proposed by the sponsor acceptable?

Hemoglobin values over time in studies BA16736 and BA16738 are depicted graphically in Figure 1 (ITT population). In both studies, median Hb concentrations reached levels \geq 11 g/dL during the correction period in all treatment groups. 11 g/dL is considered to be the lower limit of clinically acceptable Hb concentrations for this patient population. In both studies, the rate of increase was slower in the mircera group than in the reference group.

According to the medical reviewer, the time to reach steady state effect is not a major issue. Given the controversies associated with the Hb correction (complete vs partial correction), in the clinical setting, the preference would be to use less aggressive correction methods. In addition, steady state kinetics of Hb are driven by the pharmacodynamic half life, hence, the reversal of over correction could be an issue. Therefore, the current titration seems reasonable.

6.5. Given that body weight was not identified as a major covariate, is $\mu\text{g}/\text{kg}$ dosing supported?

Sponsor's analysis

The sponsor's analyses suggest that starting dose adjustment according to body weight would decrease the inter-patient variability in systemic exposure (AUC and possibly C_{max}). However, this reduction in inter-patient variability in systemic exposure would be small. On the other hand, the Phase III results showed high inter-patient variability in PD parameters that is not linked to body weight. Therefore, the small reduction in the PK variability resulting from using a body weight-adjusted starting dose would not substantially reduce the overall variability in the dose-effect relationship. This makes adjustment of the starting dose using body weight unwarranted. However, adjustment of the starting dose using body weight would not have a negative impact on the efficacy/safety of mircera in CRF patients not previously treated with an ESA.

In the Phase III maintenance studies in CRF patients on dialysis, the starting dose of mircera was selected on the basis of the previous ESA dose (expressed in IU) without taking body weight into account. The dose of the previous ESA was a relatively good predictor of the mircera dose (fixed dose expressed in μg) that was needed to bring Hb within the target range. In the Phase III correction studies, the starting dose of mircera was based on body weight (expressed in $\mu\text{g}/\text{kg}$) and the gradual increase in Hb allowed the achievement of a high response rate in CRF patients on dialysis and not on dialysis. The results from all Phase III studies with mircera show that both a body weight-adjusted dose (in $\mu\text{g}/\text{kg}$) and a fixed dose (in μg) can be used with mircera.

Reviewer's analysis

The impact was further evaluated using data from two studies (BA16736 and BA16738) were used to create the following graphs. The data were further stratified by high and low body weight, based on median body weight. Two important patient related outcomes, time to first overshoot (defined as Hb level > 13 g/dL) and time to response defined as an increase in Hb = 1.0 g/dL from baseline and a single Hb concentration = 11.0 g/dL, without RBC transfusion, during the first 24 weeks after first dose (until day 173, end of correction period)), were used. The expectation was if the dose other than the optimum dose is given to patients who are on the opposite side of the distribution, the overshoot will be earlier in patients with higher than optimum dose and the time response will be late for patients with lower than optimum dose.

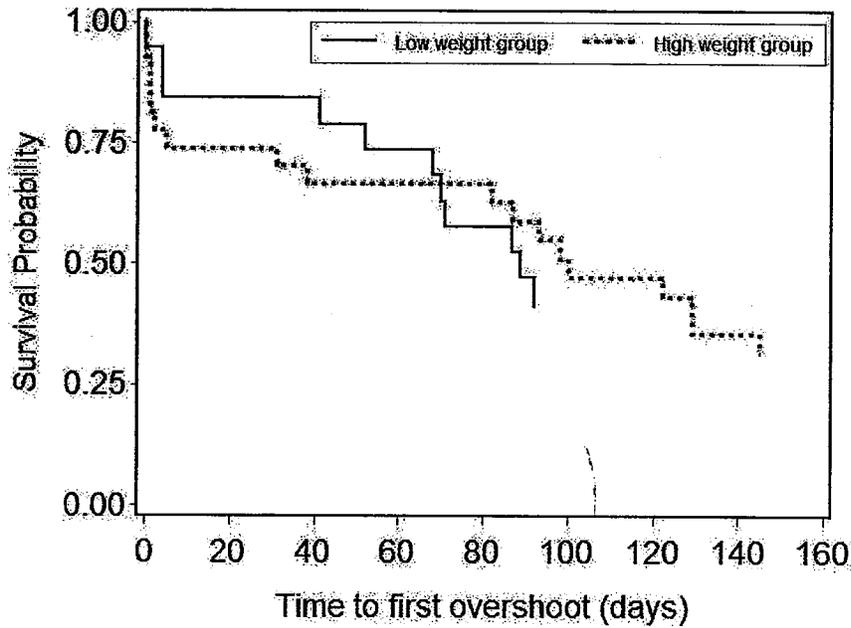
Figure 33 and Figure 34 illustrate time to first overshoot by body weight groups in BA16736 and BA16738 studies. Figure 35 and Figure 36 illustrate time to response by body weight groups in BA16736 and BA16738 studies. Overall, there were no significant differences for either endpoints between high and low body weight groups. In conclusion, no clinically relevant differences are expected between body weight based dosing versus fixed dosing in selecting the starting dose.

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Figure 33: Survival function assessing time to first overshoot (defined as Hb level > 13 g/dL)
BA16736

Time to first overshoot in BA167136

Randomized treatment group=EPOETIN REFERENCE ARM



Time to first overshoot in BA167136

Randomized treatment group=ONCE EVERY TWO WEEKS ON R0050382.1

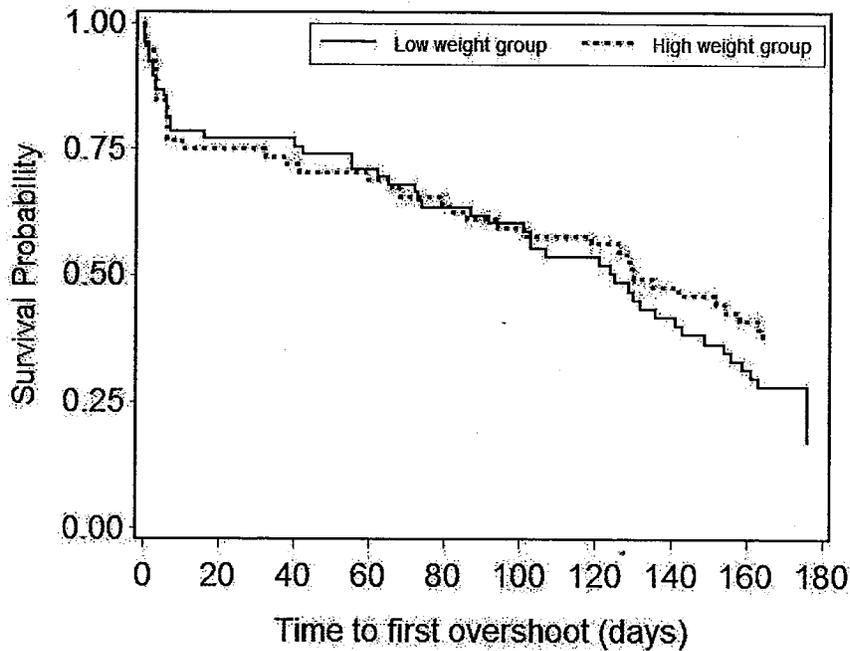
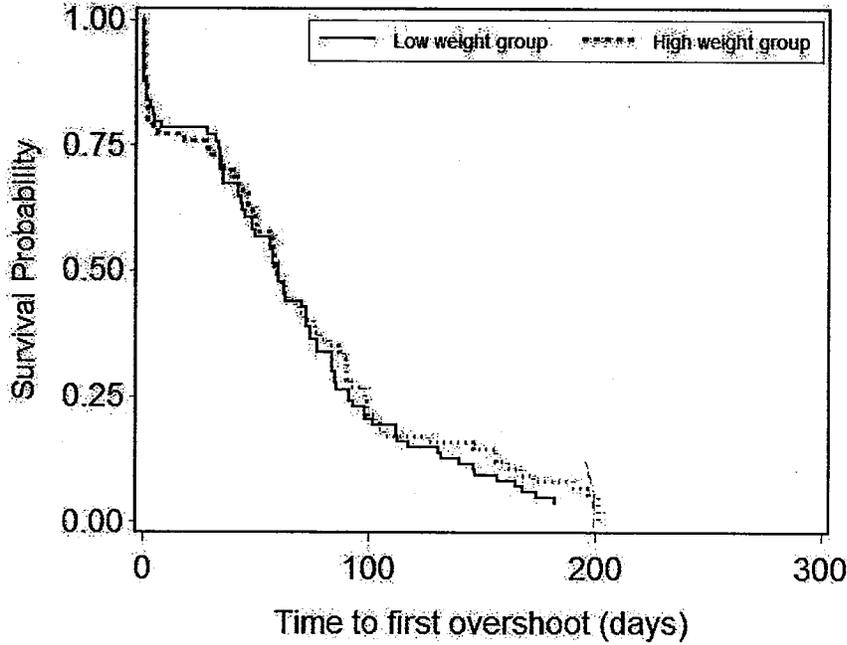


Figure 34: Survival function assessing time to first overshoot (defined as Hb level > 13 g/dL)
BA16738

Time to first overshoot in BA167138

Randomized treatment group=ONCE EVERY TWO WEEKS ON SUBCUTANEOUS R00503821



Time to first overshoot in BA167138

Randomized treatment group=ONCE EVERY WEEK ON SUBCUTANEOUS DARBEPOETIN ALFA

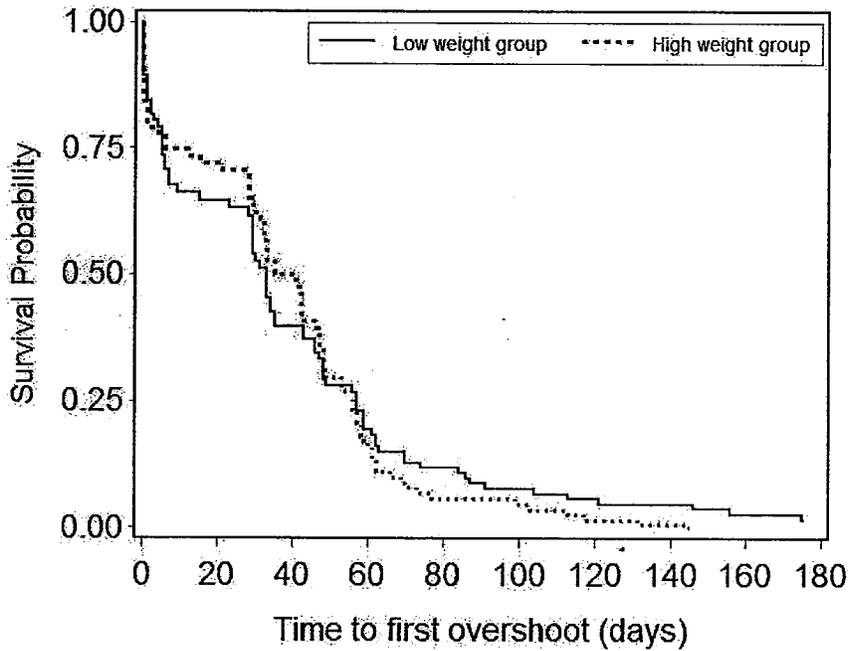
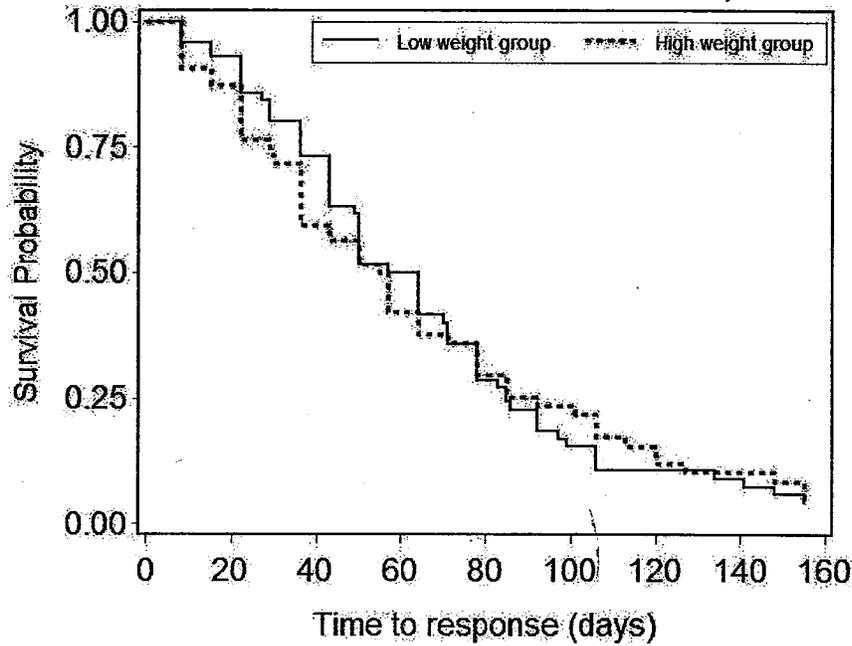


Figure 35: Survival function assessing time to response (protocol defined) BA167136

Time to response in BA167136

Randomized treatment group=ONCE EVERY TWO WEEKS ON R0050382.1



Time to response in BA167136

Randomized treatment group=EPOETIN REFERENCE ARM

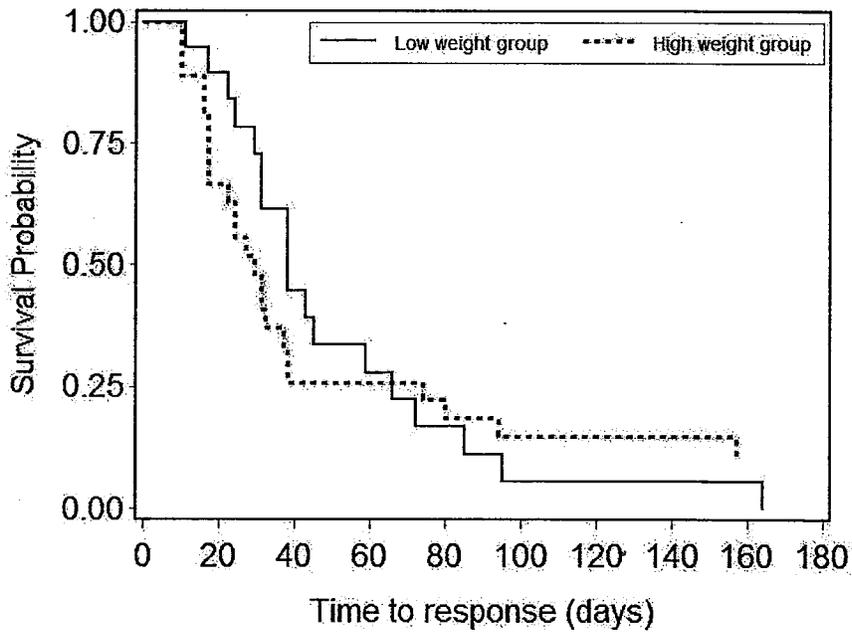
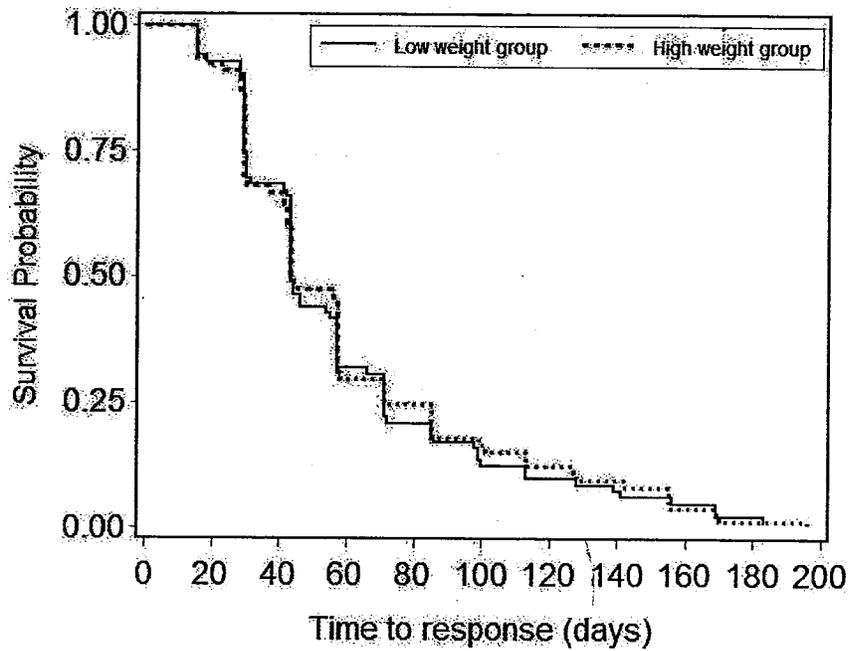


Figure 36: Survival function assessing time to response (protocol defined) BA167138

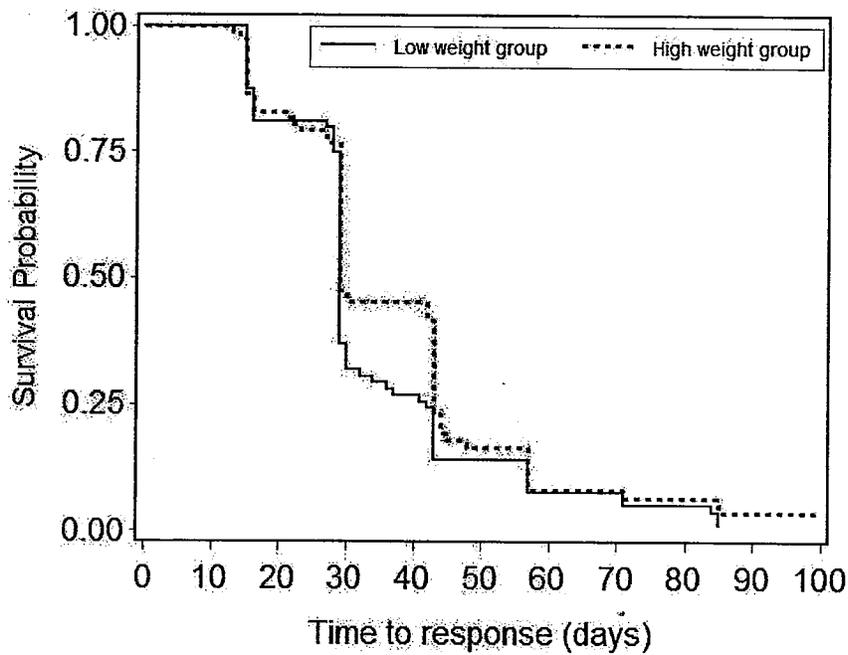
Time to response in BA167138

Randomized treatment group=ONCE EVERY TWO WEEKS ON SUBCUTANEOUS ROO503821



Time to response in BA167138

Randomized treatment group=ONCE EVERY WEEK ON SUBCUTANEOUS DARBEPOETIN ALFA



Pharmacometrics components in Clinical Pharmacology QBR

Summary of clinical pharmacology findings

Exposure-Response Relationships

The effectiveness of mircera was well established in 6 clinical studies. All studies show consistent success in correction/maintaining Hb levels within the defined threshold. The patients are treated by periodic monitoring of Hb levels and assessing the change from previous measurement to adjust the dose. For example, if the rate of rise in Hb is greater than 2 g/dL over a month, the dose is to be reduced by approximately —

However, the risk-benefit of mircera and overall ESA agents is questionable. At this time, it is not possible to optimize the treatment given uncertainties in dose effect, Hb target (partial or complete correction), Hb minimum to start ESA treatment (baseline risk) or any other predictors (such as, slope of Hb response) that would maximize overall benefit.

Effect of Intrinsic Factors: age (elderly, pediatrics), gender, race, renal/hepatic impairment

Based on population analyses, the pharmacokinetics of mircera are not significantly altered due to common demographic characteristics. Results of these analyses showed that no dose adjustments are necessary for age, gender and race. The safety and efficacy of mircera therapy has not been established in patients with hemoglobinopathies, severe liver disease, seizures or with platelet level greater than $500 \times 10^9/L$. Therefore, caution should be used in these patients.

Effect of Extrinsic Factors: if any

No formal drug-drug interaction studies have been performed. There was no indication in clinical studies of an effect of concomitant medications on the pharmacokinetics of mircera.

Question based review

Dose selection

What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?

See pharmacometrics review section 5 for the details on study design aspects of dose finding and registration trials.

What is the basis for selecting the response endpoints or biomarkers and how are they measured in clinical pharmacology and clinical studies?

Erythropoietin, a hormone produced primarily in the kidneys, stimulates the production of red blood cells (RBCs) in bone marrow and is essential for the maintenance of normal RBC count. Anemia, caused by erythropoietin deficiency, is a hallmark of

chronic kidney disease (CRF). Although the pathogenesis of renal anemia is multifactorial, decreased production of erythropoietin is considered the main etiologic factor. Anemia is also a common disease symptom in cancer patients. Exogenous replacement of erythropoietin by the recombinant hormone, epoetin, is a well-accepted therapy for treatment of anemia in patients with CRF and in cancer patients undergoing chemotherapy. As Hb is mainly carried by RBCs, the life span of RBCs determines the duration of Hb elevations due to stimulation of erythropoiesis. Therefore, Hb levels are monitored in the clinical studies to assess effectiveness.

Exposure-Response

What are the characteristics of the exposure-response relationships for efficacy? If relevant, indicate the time to the onset and offset of the desirable pharmacological response or clinical endpoint.

The effectiveness of mircera was well established in 6 clinical studies. All studies show consistent success in correction/maintaining Hb levels within the defined threshold.

See pharmacometrics review section 4.1 and 6.1 for the details on exposure response relationship in dose finding and registration trials.

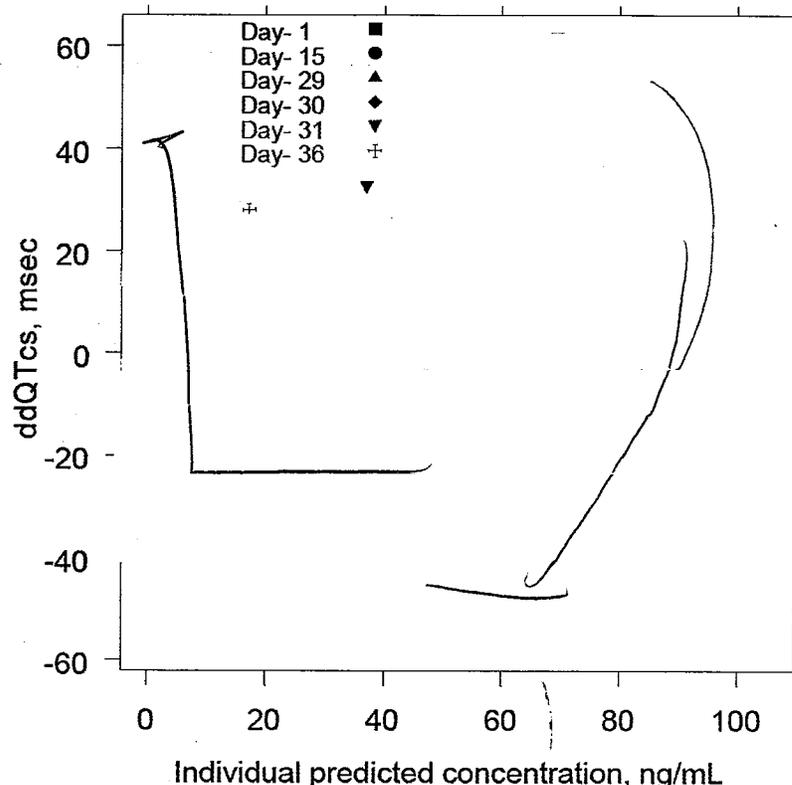
What are the characteristics of the exposure-response relationships for safety?

The exposure safety analyses of mircera presented a challenging scenario. Overall, the proportion of deaths seemed similar across the treatment arms. The review question was raised based on discrepancy observed in the number of fatal events which mapped to the MedDRA preferred term of 'sudden death' occurred in the mircera group (nine) and none in the reference arm. However, 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%]), the overall incidence of events of this nature is similar between the treatment arms. There was some trend towards the dose effect of ESAs on mortality, however, the effect is confounded by disease severity status. In other words, there is an indication that proportion of deaths increases with dose. At the same time, severely ill patients need higher doses of mircera for maintaining Hb levels.

Hence, the risk-benefit of mircera and overall ESA agents is questionable. At this time, it is not possible to optimize the treatment given uncertainties in dose effect, Hb target (partial or complete correction), Hb minimum to start ESA treatment (baseline risk) or any other predictors (such as, slope of Hb response) that would maximize overall benefit. See pharmacometrics review sections 4.2 and 6.2 for the details on exposure response relationship in dose finding and registration trials.

Does this drug prolong the QT or QTc interval?

The QT review was done as a part of a joint review process of IRT-QT team. There were no apparent signal of QT prolongation, based on concentration-QT analyses. Figure 37 compares QTcS time course (normalized for day of the treatment) for baseline, placebo and RO 050-3821. There are no apparent differences other than a spike observed in the baseline measurement at day -1. Figure 38 compares time-matched baseline adjusted QTcS (dQTcS) time course placebo and RO 050-3821 at day 1, 15 and 29 (period 2 was also normalized for ease of comparison). There are no



The following limitations to the Sponsor's QT study were noted in the report:

- The study lacks a positive control arm; therefore, assay sensitivity cannot be determined.
- There are conflicting results between the ICH E14 endpoint, where the upper 90% bound of the confidence interval crosses 10 msec and the concentration-QT analysis, which does not show a concentration-QTc relationship. It is possible that the E14 endpoint might represent a "false positive" in this circumstance as this endpoint may be sensitive to variability in the data.
- From the mean QTc results, we note a large standard deviation, implying a sizable degree of variability in .QTc. A large variability in the QT/QTc data is also suggested in Figures 10 and 11 (see review).
- It is not clear which ECG leads was chosen for QT measurement, or how many readers were involved in interpreting ECGs for a given subject.
- Since ECGs were not available to us in the ECG warehouse, we are unable to verify that the QT measurements were made appropriately.

See full QT review submitted by the IRT-QT team for more details.

Is the dose and dosing regimen selected by the Sponsor consistent with the known relationship between dose-concentration-response, and are there any unresolved dosing or administration issues?

Yes, dose and dosing regimen are consistent with the known relationship between dose and concentration response for effectiveness. The dose titration scheme, frequency of

monitoring of Hb response was found to be appropriate. Although, the weight based dosing is not supported by the data, there was no counter evidence to suggest that the dosing strategy tested in clinical trials is not appropriate. For more details, see pharmacometrics review sections 4.4, 4.5, 6.4, and 6.4.

At this time, the dosing is unresolved from safety viewpoint. As noted above, due to non-inferiority testing and titration setting, the dose effect on mortality is confounded by disease severity status. In other words, there is an indication that proportion of deaths increases with dose. At the same time, severely ill patients need higher doses of mircera for maintaining Hb levels. The issue seems consistent across all ESA agents used in this therapeutic area. For more details, see pharmacometrics review sections 4.2 and 1.1.

Intrinsic Factors

What intrinsic factors influence exposure and/or response, and what is the impact of any differences in exposure on efficacy or safety responses?

Based upon what is known about exposure-response relationships and their variability and the groups studied, healthy volunteers vs. patients vs. specific populations, what dosage regimen adjustments, if any, are recommended for each of these groups? If dosage regimen adjustments are not based upon exposure-response relationships, describe the alternative basis for the recommendation.

Elderly

Based on population analyses, the pharmacokinetics of mircera are not significantly altered due to common demographic characteristics. Results of these analyses showed that no dose adjustments are necessary for age. For more details refer pharmacometrics review section 4.3.3 on effect of intrinsic factors.

Pediatric Patients

The safety and efficacy of mircera in pediatric patients have not been established.

Gender

Based on population analyses, the pharmacokinetics of mircera are not significantly altered due to common demographic characteristics. Results of these analyses showed that no dose adjustments are necessary for gender. For more details refer pharmacometrics review section 4.3.3 on effect of intrinsic factors.

Race

Based on population analyses, the pharmacokinetics of mircera are not significantly altered due to common demographic characteristics. Results of these analyses showed that no dose adjustments are necessary for race. For more details refer pharmacometrics review section 4.3.3 on effect of intrinsic factors.

Renal impairment

The drug is intended in chronic kidney disease population (target population).

Hepatic impairment

The safety and efficacy of mircera therapy has not been established in patients with hemoglobinopathies, severe liver disease, seizures or with platelet level greater than $500 \times 10^9/L$. Therefore, caution should be used in these patients.

Extrinsic factors

What extrinsic factors (drugs, herbal products, diet, smoking, and alcohol use) influence dose-exposure and/or -response and what is the impact of any differences in exposure on response?

The effect on mircera from herbal products, diet, smoking and alcohol has not been established. See next topic for drug interactions.

Drug-drug interactions

No formal drug-drug interaction studies have been performed. There was no indication in clinical studies of an effect of concomitant medications on the pharmacokinetics of mircera. For more details refer pharmacometrics review section 6.3.5 on drug drug interactions.

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On Original*