Adverse Events In Relation To Dose of Study Medication

Using a systematic approach of examining AE potentially associated with dose of study medication, the events of pneumonia, sepsis, arteriovenous graft site infection, musculoskeletal pain, catheter related complication, chest discomfort, and decubitus ulcer were associated with a high dose of study medication in both the Mircera and reference groups. The infectious complications may be associated with a high dose given in response to a fall in hemoglobin, which often accompanies infection. No association between the dose of Mircera and incidence of AE indicative of toxicity was found.

Overall Incidence of AE in Relation to Dose of Study Medication

Patients were classified into quintiles, based on mean QW dose of study agent administered. In the overall safety population, for Mircera, quintiles were categorized at doses of < 0.18.0, < 29.8, < 37.5, < 56.9, and > 56.9 µg/week. For epoetin, the corresponding cut-offs were < 4266.7, < 6875, 11250, < 18000, and > 18000 IU/week. For darbepoetin alfa, the quintiles were doses of < 18.3, < 29.1, < 40, < 55, and > 55 µg/week. All AE were categorized by dose quintile and tabulated by treatment group (Mircera and reference). As approximately equal numbers (20%) of AE should fall in each of these categories, a large deviation from 20% in a quintile suggests that the particular AE may be associated with a high or low dose of study medication. The evidence for this is stronger if a trend is observed (percentages increasing or decreasing across all categories).

Thus for this analysis, an AE was considered to have a possible association with a high dose of study medication if there was an event rate of either > 25% in the fifth or last dose quintile AND > 20% in the fourth dose quintile or > 30% in the last quintile. This is a conservative assessment, which allows AE to be considered whether there is a trend towards a higher event rate in higher quintiles or just a particularly high rate in the highest quintile.

Since larger differences in the percentages can occur with small numbers, there also had to be a greater than 2 event difference between the number of events in the first quintile and the last quintile for an event to be considered. Since a dose effect was assessed to detect a possible toxicity, associations with low doses are not reported. A relationship to dose in one of the two treatment groups should be associated with a higher AE rate in that treatment group. If this is not the case, then the association may be a chance finding. The exception to this rule is in the case of a trend to a higher dose in both treatment groups; here the AE incidence rates could be the same.

The events of pneumonia, sepsis, arteriovenous graft site infection, musculoskeletal pain, catheter related complication, chest discomfort, and decubitus ulcer were associated with a high dose of study medication in both the Mircera and reference groups, although a biological mechanism for these findings is not apparent. The infectious complications may be associated with a high dose given in response to a fall in hemoglobin, which often accompanies infection.

The same analysis was performed for patients in the anemia correction and hemoglobin maintenance study populations separately, although these smaller exploratory subgroups are subject to random effects. There were no identified concerns regarding the association of AE with a high dose of study medication in either of these subgroups.

Deaths and Serious Adverse Events in Relation to Dose of Study Medication

Overall there was a similar trend seen in both treatment groups for a higher percentage of deaths in the highest dose category. By quintile, the percentages of deaths in each of the five increasing

dose quintiles were 16%, 16%, 22%, 20%, and 26% in the Mircera group, and 10%, 17%, 21%, 16%, and 36% in the reference group. The only two causes of death related to high dose of study medication were cardiac arrest in the Mircera treatment group and cardio-respiratory arrest in the reference group.

For SAE, there was also a trend seen in both treatment groups for a higher percentage of SAE overall in the highest dose category. All SAE were examined to systematically identify a possible trend or association with dose of study medication. An SAE was identified as associated with dose if it met criteria described earlier in this section. Since a dose effect was assessed to detect a possible toxicity, associations with low doses are not reported. The following SAE were seen as associated with a high dose using this rule: sepsis, cellulitis, arteriovenous graft thrombosis, and chest pain in both the Mircera and reference groups.

Adverse Events of Special Interest

Specific AE of interest were defined based on the known safety profile for erythropoietins as well as on the available data for Mircera from phase 1 and II studies and in view of the epidemiological background data for the CRF population. These AE of interest included:

- Thromboembolic events: vascular access thrombosis, myocardial infarction, cerebrovascular accident, deep vein thrombosis or other thrombotic events, pulmonary embolism
- Cardiovascular, neurologic, or infection events: hypertension, arrhythmia, congestive heart failure, cardiac arrest; seizures, hypertensive encephalopathy; sepsis

Individual MEDDRA preferred terms for all reported AE in these categories were examined and, where appropriate, multiple preferred terms referring to related clinical diagnoses were grouped within the overall AE term of interest.

Overall Incidence, Intensity, and Outcome

The incidence of all of the overall terms for AE of special interest was similar between the Mircera and reference treatment groups. Vascular access thrombosis AE (10% in both treatment groups) may be associated with higher hemoglobin values, specifically with values > 13 g/dL in both treatment groups. Congestive heart failure AE (5% in both treatment groups) may be associated with hemoglobin values < 11 g/dL. Cardiac arrest AE may be associated with high doses of study medication in both the Mircera and reference groups.

Overall, 40% of patients in the Mircera group and 39% of patients in the reference group reported at least one AE of special interest during the study (**Table 60**). The most frequently reported AE of special interest (≥ 5% in either treatment group) were hypertension, vascular access thrombosis, arrhythmia, and congestive heart failure and this is characteristic of this patient population.

Table 60: Patients with One or More Adverse Event of Special Interest (Overall Safety Population)

	Mircera N = 1789 n (%)	Reference N = 948 n (%)
All events	715 (40)	365 (39)
Hypertension	306 (17)	145 (15)
Arrhythmia	154 (9)	73 (8)
Congestive heart failure	88 (5)	49 (5)
Sepsis	61 (3)	35 (4)
Myocardial infarction	62 (3)	29 (3)
Cerebrovascular accident	49 (3)	24 (3)
Cardiac arrest Sudden death	42 (2) 9 (<1)	19 (2) 0 (0)
Seizures	15 (<1)	8 (<1)
Thromboembolic events Vascular access thrombosis Deep vein thrombosis Pulmonary embolism	198 (11) 170 (10) 11 (<1) 6 (<1)	109 (11) 98 (10) 9 (<1) 0 (0)
Hypertensive encephalopathy	2 (<1)	1 (<1)

Total number of AE = 1030 in 715 patients (both groups). Percentages are based on N.
Multiple occurrences of the same adverse event in one individual counted only once.

Multiple Logistic Regression Analysis

A multivariate logistic regression analysis identified a statistical association of baseline risk factors with an increased probability of AE of special interest, but no effect of erythropoietin treatment.

A multivariate logistic regression analysis was used to examine the effect of baseline disease characteristics on the probability of experiencing an AE of special interest. Baseline disease characteristics examined in the analysis included diabetes, ischemic heart disease, peripheral vascular disease, arterial hypertension, cerebral vascular disease, congestive heart failure, hemorrhage, hyperlipidemia, and venous thrombosis. The analysis was performed in all patients in the phase 3 population (N = 2383), as several of the baseline parameters were not collected in the phase 2 studies.

For AE of special interest potentially associated with hemoglobin changes in the overall safety population, the quintiles indicating a potential association with a change in hemoglobin (either an increase or decrease) are highlighted in bold and italic font in this table. Although there are several AE that appear to be associated with a change in hemoglobin in either the Mircera or reference groups, the results are inconsistent as no event is associated with a change in both

treatment groups. These data suggest that none of the AE terms of special interest, which include several MEDDRA preferred terms, are associated with changes in hemoglobin.

The same analysis was performed for patients in the anemia correction and hemoglobin maintenance study populations separately, although these smaller exploratory subgroups are subject to random effects. There were no identified concerns regarding the association of AE of interest with hemoglobin changes in either of these subgroups.

7.1.5 Common Adverse Events

Adverse Events in the Phase 3 Population

Separate analyses of AE for patients in the Phase 3 population were also included because these six pivotal studies include similar doses of Mircera and a reference comparator, and include large numbers of patients per treatment group. As in the overall safety population, the proportion of patients with one or more AE was similar between groups, as was the frequency of AE in each body system in the Phase 3 population, and the average number of AE per patient (5 in each group). The most frequently occurring AE in the phase 3 population were the same as those seen in the overall safety population: hypertension, diarrhea, nasopharyngitis, headache, and upper respiratory tract infection (**Table 61**). These AE occurred in a similar proportion of patients in both treatment groups.

Adverse events that occurred in at least 2% of patients and with a higher frequency in the Mircera group compared with the reference group were similar to those seen in the overall population including GI hemorrhage (2 vs < 1%) and tachycardia (2 vs < 1%), but in addition included atrial fibrillation (3 vs 1%), arteriovenous fistula site hemorrhage (5 vs 3%), procedural hypertension (3 vs 1%), and post procedural vomiting (2 vs < 1%). None of these events was associated with hemoglobin increases; GI hemorrhage was associated with hemoglobin decreases.

Peripheral edema was higher in the reference group (5%) than in the Mircera group (2%), as was syncope in this population of Phase 3 studies (2 vs < 1%).

Table 61: Adverse Events ≥ 5% in Either Treatment Group (Phase 3 Population)

Body System/ Adverse Event	RO0503821 N = 1435 No. (%)	Reference N = 948 No. (%)
ALL BODY SYSTEMS		
Total Pts with at Least one AE	1294 (90)	862 (91)
Total Number of AEs	7127	4804
INFECTIONS AND INFESTATIONS		
Total Pts With at Least one AE	759 (53)	512 (54)
NASOPHARYNGITIS	162 (11)	93 (10)
UPPER RESPIRATORY TRACT INFECTION	132 (9)	76 (8)
URINARY TRACT INFECTION	72 (5)	55 (6)
INFLUENZA	68 (5)	43 (5)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS		
Total Pts With at Least one AE	608 (42)	379 (40)
PROCEDURAL HYPOTENSION	124 (9)	53 (6)
ARTERIOVENOUS FISTULA THROMBOSIS	76 (5)	50 (5)
ARTERIOVENOUS GRAFT THROMBOSIS	71 (5)	49 (5)
ARTERIOVENOUS FISTULA SITE COMPLICATION	69 (5)	48 (5)
ARTERIOVENOUS FISTULA SITE HAEMORRHAGE	70 (5)	26 (3)
GASTROINTESTINAL DISORDERS		
Total Pts With at Least one AE	529 (37)	350 (37)
DIARRHOEA	164 (11)	106 (11)
VOMITING	72 (5)	60 (6)
CONSTIPATION	62 (4)	50 (5)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS		
Total Pts With at Least one AE	445 (31)	305 (32)
MUSCLE SPASMS	102 (7)	70 (7)
PAIN IN EXTREMITY	76 (5)	55 (6)
BACK PAIN	76 (5)	47 (5)
VASCULAR DISORDERS		
Total Pts With at Least one AE	385 (27)	234 (25)
HYPERTENSION	204 (14)	131 (14)
HYPOTENSION	70 (5)	38 (4)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS		
Total Pts With at Least one AE	330 (23)	230 (24)
PYREXIA	53 (4)	43 (5)
OEDEMA PERIPHERAL	32 (2)	48 (5)
NERVOUS SYSTEM DISORDERS		
Total Pts With at Least one AE	328 (23)	219 (23)
HEADACHE	131 (9)	85 (9)
METABOLISM AND NUTRITION DISORDERS		
Total Pts With at Least one AE	306 (21)	226 (24)
FLUID OVERLOAD	103 (7)	62 (7)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS		
Total Pts With at Least one AE	271 (19)	174 (18)
COUGH	83 (6)	51 (5)

7.1.6 Less Common Adverse Events

Incidence of Adverse Events in Both Treatment Groups Adverse events that occurred in at least 2% of patients and at a higher frequency in the Mircera group compared with the reference group, were procedural hypotension (8.2 vs 5.6%), gastrointestinal hemorrhage (2.0 vs 0.7%), and tachycardia (2.1 vs 1.0%) **(Table 62).**

Although procedural hypotension was reported more frequently in the Mircera group, the true incidence of hypotension could not be confirmed by blood pressure measurements, despite follow-up regarding these events.

When tachycardia was examined more appropriately in the context of all arrhythmia AE, the incidence between groups was similar (9% Mircera, 8% reference).

When all of these AE were examined for trends with hemoglobin rate of rise or fall, only GI hemorrhage showed a trend toward a hemoglobin rate of decrease of $\geq$ 0.423 g/dL/week.

Adverse events that occurred in $\geq$ 2% of patients and at a higher frequency in the reference group compared with the Mircera group were peripheral edema (5.1 vs 2.7%), hypoglycemia (3.5 vs 2.2%), skin ulcer (2.9 vs 1.6%), and procedural pain (2.5 vs. 1.5%).

Hematuria was the only adverse events that occurred in < 2% of patients in both groups and at a higher frequency in the Mircera group (1.2%) than in the reference group (0.4%). This AE did not appear to be associated with a hemoglobin rate of rise or fall, hemoglobin level, or dose of study medication. Among patients with hematuria, concomitant medication affecting coagulation or mucosal integrity were given in 21/22 of patients receiving Mircera and in 5/5 of patients receiving a reference agent.

An inspection of possible etiologies of hematuria showed that 7 out of 22 patients in the Mircera group and 3 of 5 patients with comparator treatments had an etiology of CRF compatible with a finding of hematuria. These included glomerulonephritis, polycystic kidney disease, interstitial nephritis, and pyelonephritis. Other possible causes of hematuria were prostate cancer, chronic cystitis, benign prostatic hypertrophy, use of oral anticoagulants in 6 of 22 patients in the Mircera group and none of 5 patients with comparator treatments.

Uncommon AE that occurred at a higher incidence in the reference group than in the Mircera group included: hypercalcemia (1.6 vs 0.3%), lower respiratory infection (1.8 vs 0.7%), atrial flutter (0.8 vs 0.2%), tinea pedis (0.8 vs 0.1%), weight decreased (0.8 vs 0.1%), night sweats (0.7 vs 0.1%), subcutaneous abscess (0.7 vs 0.2%) conjunctivitis allergic (0.6 vs 0.1%), diabetes mellitus inadequate control (0.6 vs 0.1%), liver function test abnormal (0.5 vs 0%), polyneuropathy (0.5 vs 0.1%), crepitations (0.3 vs 0%), vulvovaginal mycotic infection (0.3 vs 0%), and thrombosis (0.3 vs 0%).

Although these differences were seen using Fisher's exact test, they occurred with very low numbers of patients and the results should be interpreted with caution, since imbalances may be identified where none exist and since there is no biologically plausible association between most of these events and erythropoietin product administration.

Table 62: Adverse Events ≥ 2% in Either Treatment Group (Safety Population)

Body System/ Adverse Event	RO0503821 N = 1789 No. (%)	Reference N = 948 No. (%)
ALL BODY SYSTEMS		
Total Pts with at Least one AE	1589 (89)	862 (91)
Total Number of AEs	8928	4804
INFECTIONS AND INFESTATIONS		
Total Pts With at Least one AE	909 (51)	512 (54)
NASOPHARYNGITIS	194 (11)	93 (10)
UPPER RESPIRATORY TRACT INFECTION	154 (9)	76 (8)
URINARY TRACT INFECTION	93 (5)	55 (6)
INFLUENZA	79 (4)	43 (5)
BRONCHITIS	74 (4)	41 (4)
PNEUMONIA	66 (4)	42 (4)
GASTROENTERITIS	58 (3)	29 (3)
CELLULITIS	38 (2)	27 (3)
SEPSIS	30 (2)	17 (2)
SINUSITIS	27 (2)	19 (2)
BRONCHITIS ACUTE	28 (2)	11 (1)
CATHETER SITE INFECTION	18 (1)	18 (2)
GASTROENTERITIS VIRAL	19 (1)	17 (2)
PHARYNGITIS	23 (1)	9 (<1)
ARTERIOVENOUS GRAFT SITE INFECTION	15 (<1)	15 (2)
LOWER RESPIRATORY TRACT INFECTION	12 (<1)	17 (2)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS		
Total Pts With at Least one AE	718 (40)	379 (40)
PROCEDURAL HYPOTENSION	147 (8)	53 (6)
ARTERIOVENOUS FISTULA THROMBOSIS	89 (5)	50 (5)
ARTERIOVENOUS FISTULA SITE COMPLICATION	81 (5)	48 (5)
ARTERIOVENOUS GRAFT THROMBOSIS	79 (4)	49 (5)
ARTERIOVENOUS FISTULA SITE HAEMORRHAGE	71 (4)	26 (3)
FALL	48 (3)	24 (3)
CONTUSION	38 (2)	29 (3)
VASCULAR GRAFT COMPLICATION	42 (2)	24 (3)
PROCEDURAL HYPERTENSION	44 (2)	13 (1)
PROCEDURAL PAIN	26 (1)	24 (3)
GASTROINTESTINAL DISORDERS		
Total Pts With at Least one AE	656 (37)	350 (37)
DIARRHOEA	189 (11)	106 (11)
VOMITING	98 (5)	60 (6)
CONSTIPATION	80 (4)	50 (5)
NAUSEA	78 (4)	39 (4)
ABDOMINAL PAIN UPPER	59 (3)	21 (2)
ABDOMINAL PAIN	48 (3)	24 (3)
DYSPEPSIA	48 (3)	22 (2)
GASTRITIS	37 (2)	14 (1)
GASTROINTESTINAL HAEMORRHAGE	35 (2)	7 (<1)
GASTROOESOPHAGEAL REFLUX DISEASE	19 (1)	16 (2)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS		
Total Pts With at Least one AE	546 (31)	305 (32)
MUSCLE SPASMS	135 (8)	70 (7)
BACK PAIN	100 (6)	47 (5)
PAIN IN EXTREMITY	92 (5)	55 (6)
ARTHRALGIA	77 (4)	39 (4)
SHOULDER PAIN	40 (2)	24 (3)
OSTEOARTHRITIS	28 (2)	19 (2)
MYALGIA	26 (1)	16 (2)
NECK PAIN	19 (1)	15 (2)
VASCULAR DISORDERS		
Total Pts With at Least one AE	466 (26)	234 (25)
HYPERTENSION	239 (13)	131 (14)
HYPOTENSION	96 (5)	38 (4)
HAEMATOMA	34 (2)	18 (2)

Table 62 (cont'd): Adverse Events ≥ 2% in Either Treatment Group

Body System/Adverse Event	RO0503821 N = 1789 No. (%)	Reference N = 948 No. (%)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS		
Total Pts With at Least one AE	426 (24)	230 (24)
PYREXIA	77 (4)	43 (5)
OEDEMA PERIPHERAL	48 (3)	48 (5)
ASTHENIA	67 (4)	27 (3)
FATIGUE	63 (4)	21 (2)
CHEST PAIN	44 (2)	24 (3)
INFLUENZA LIKE ILLNESS	31 (2)	18 (2)
NERVOUS SYSTEM DISORDERS		
Total Pts With at Least one AE	422 (24)	219 (23)
HEADACHE	167 (9)	85 (9)
DIZZINESS	77 (4)	32 (3)
SYNCOPE	19 (1)	15 (2)
METABOLISM AND NUTRITION DISORDERS		
Total Pts With at Least one AE	370 (21)	226 (24)
FLUID OVERLOAD	120 (7)	62 (7)
HYPERKALAEMIA	50 (3)	28 (3)
HYPOGLYCAEMIA	39 (2)	33 (3)
HYPERPHOSPHATAEMIA	30 (2)	17 (2)
ANOREXIA	26 (1)	19 (2)
HYPERCALCAEMIA	6 (<1)	15 (2)
CARDIAC DISORDERS		
Total Pts With at Least one AE	349 (20)	188 (20)
ANGINA PECTORIS	64 (4)	26 (3)
CARDIAC FAILURE CONGESTIVE	45 (3)	26 (3)
ATRIAL FIBRILLATION	46 (3)	14 (1)
MYOCARDIAL INFARCTION	32 (2)	18 (2)
TACHYCARDIA	37 (2)	9 (<1)
BRADYCARDIA	28 (2)	12 (1)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS		
Total Pts With at Least one AE	357 (20)	174 (18)
COUGH	110 (6)	51 (5)
DYSPNOEA	67 (4)	38 (4)
EPISTAXIS	49 (3)	18 (2)
PHARYNGOLARYNGEAL PAIN	37 (2)	16 (2)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS		
Total Pts With at Least one AE	250 (14)	168 (18)
PRURITUS	64 (4)	36 (4)
SKIN ULCER	28 (2)	27 (3)
PSYCHIATRIC DISORDERS		
Total Pts With at Least one AE	171 (10)	90 (9)
INSOMNIA	72 (4)	34 (4)
DEPRESSION	34 (2)	17 (2)
ANXIETY	25 (1)	15 (2)
RENAL AND URINARY DISORDERS		
Total Pts With at Least one AE	148 (8)	62 (7)
RENAL FAILURE CHRONIC	32 (2)	19 (2)
EYE DISORDERS		
Total Pts With at Least one AE	124 (7)	63 (7)
BLOOD AND LYMPHATIC SYSTEM DISORDERS		
Total Pts With at Least one AE	78 (4)	39 (4)
ANAEMIA	56 (3)	21 (2)
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)		
Total Pts With at Least one AE	67 (4)	41 (4)
ENDOCRINE DISORDERS		
Total Pts With at Least one AE	66 (4)	38 (4)
HYPERPARATHYROIDISM SECONDARY	29 (2)	17 (2)

7.1.7 Laboratory Findings

Iron Parameters

Iron parameters (iron, ferritin, and TSAT) were well maintained in both the Mircera and reference groups. Median values were similar between the two groups and did not change appreciably over time. Descriptive statistics for the iron parameters (iron, ferritin, and TSAT) at baseline and after one year are shown in **Table 63**.

Table 63: Iron Parameters (Safety Population)

Treatment	Month of Treatment	N	Mean	Std	Minimum	Q1	Median	Q3	Maximum
IRON									
RO0503821	Baseline	1784	13.11	5.09	0.54	9.85	12.26	15.30	79.18
	12 Months (day 336-369)	865	13.66	5.65	2.15	9.85	12.90	16.40	55.00
Reference	Baseline	941	13.53	5.85	3.94	10.00	12.35	15.75	80.50
	12 Months (day 336-369)	515	12.84	7.79	2.15	8.95	11.65	15.00	132.60
FERRITIN									
RO0503821	Baseline	1782	480.61	355.62	12.00	228.33	401.67	642.50	3831.00
	12 Months (day 336-369)	858	574.75	403.43	11.00	310.40	486.00	750.00	4746.00
Reference	Baseline	941	463.17	344.83	18.00	203.00	406.00	626.00	2945.50
	12 Months (day 336-369)	513	556.72	432.02	12.00	283.00	502.00	737.00	5160.00
TSAT									
RO0503821	Baseline	1762	30.38	11.85	1.00	22.90	28.00	35.17	160.00
	12 Months (day 336-369)	851	33.02	17.74	7.47	23.00	30.00	39.00	233.71
Reference	Baseline	932	30.79	13.23	9.85	22.32	28.50	36.47	160.50
	12 Months (day 336-369)	510	32.72	41.82	6.30	21.00	28.00	36.00	904.10

Review Comments:

- Although the sponsor claims that iron parameters were not appreciably different at baseline or during study between Mircera and the reference groups, an examination of the data presented in **Table 63** show that the mean iron level increased during the study in the Mircera group and decreased during the study in the reference groups. These changes in the mean iron levels suggest that iron was supplemented more aggressively for Mircera than for the reference agents in the open-label studies.
- The clinical experience with iron supplementation indicates that aggressive iron supplementation may increase the incidence of adverse events, including deaths. The suggestive trend towards a higher mortality with Mircera than with reference agents may be a reflection of more aggressive open-label iron supplementation as concomitant therapy with the administration of the study medication.

- The suggestive trend towards a higher mortality with Mircera than with reference agents is most notable with high (0.6 vs 0.4 ug/kg) SC dosing for anemia correction in non-dialysis patients. This observation suggests that aggressive iron supplementation contributes to the higher mortality, rather than being the sole cause for the potentially increased mortality rate.

Platelet Counts

During 12 months of treatment (pooled safety population), the mean and median values for platelets, while within the standard reference range, were lower in the Mircera group than in the reference group, as shown in **Table 64**. In the Mircera group, the mean and median levels of platelets fell immediately at beginning of treatment (mean decrease of 16 x 10^9/L or about 7%) and then remained stable (within normal range in most patients). The proportion of patients with markedly low counts was greater in the Mircera group than in the reference group. The empirical cumulative distribution function of platelet counts are shown in **Figure 16**.

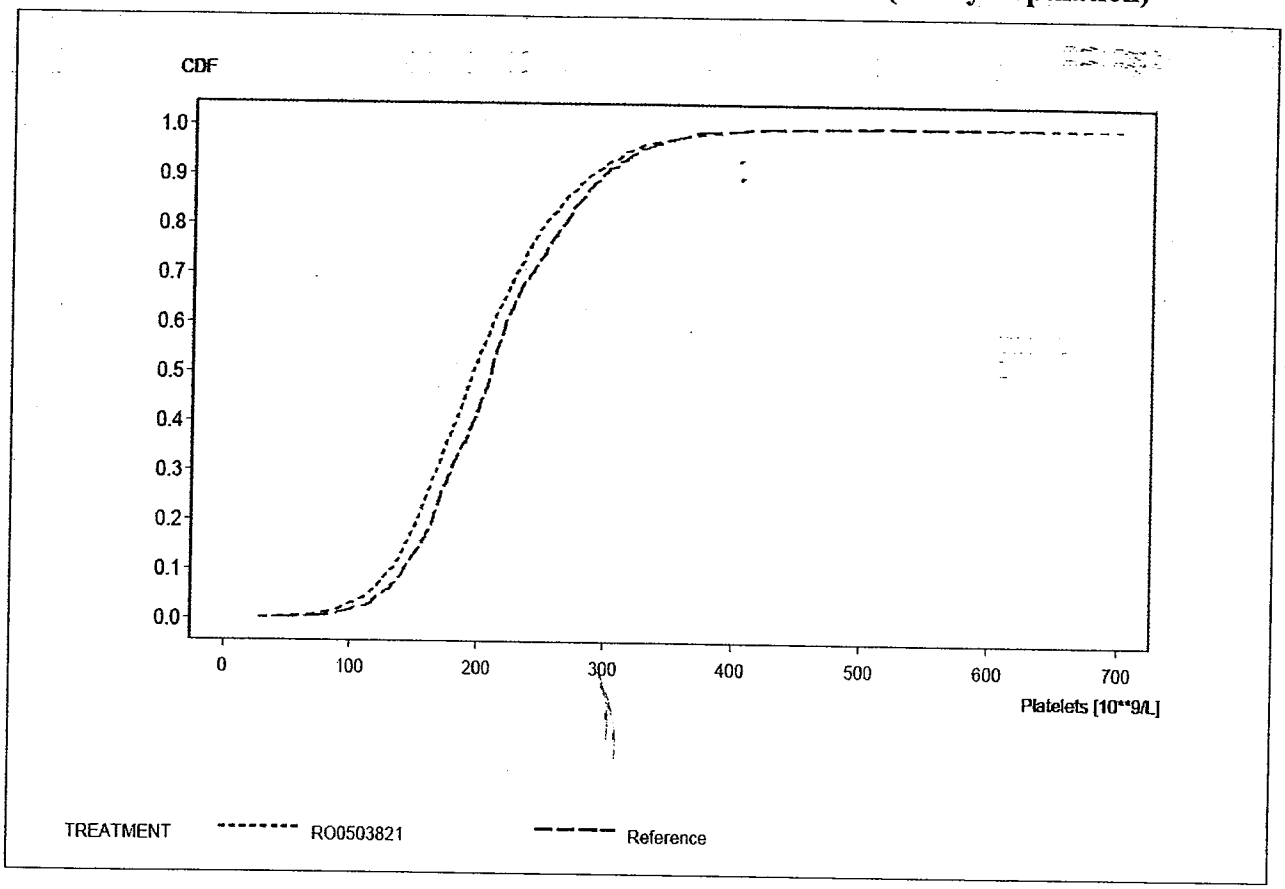
Table 64: Platelet Counts (Safety Population)

EPO	Treatment Month	N*	Platelet Count	Mean Change from Baseline	Maximum Decrease
Mircera	0	1755	218	NA	NA
	1	1474	199	-16	-188
	7	1353	206	-11	-212
	12	864	202	-11	-197
Reference	0	926	214	NA	NA
	1	301	219	4	-205
	7	848	219	6	-265
	12	518	215	6	-167

*N applies to the number of patients contributing to calculating mean platelet counts; the numbers of patients contributing to determining the mean decrease from baseline differ slightly from N shown.

EPO = erythropoietin product; N = number of patients contributing to determining mean platelet counts; NA = not applicable; Treatment Month = beginning of treatment month shown

Figure 16: Cumulative Distribution of Platelet Counts (Safety Population)



CDF = empirical cumulative distribution function; RO0503821 = Mircera

Review Comments:

- The pooled data indicate that a significant and early (within first month of therapy) decrease in the platelet count occurs with Mircera therapy. A similar treatment effect, although not seen with reference agents, may be associated also with the reference agents. Over three-fourths (78%) of the analysis population were enrolled in a hemoglobin maintenance study in which the patients had already been receiving a reference agent at beginning of study; an analysis in patients receiving a reference agent in anemia correction studies may reveal a treatment effect consistent with that observed with Mircera.
- The decrease in the platelet count may be the result of peripheral platelet utilization (as opposed to decreased production, peripheral destruction, or sequestration) and may be associated with an increase in thromboembolic risk that may be difficult to detect as a clinically significant risk. The risk may be increased with the use the reference agents (versus no treatment), and the risk may be increased further with the use of Mircera (versus reference agents).
- The observed decrease in the platelet count may be "spurious." The rheologic properties of blood cells are such that platelets marginalize towards the blood vessel wall with increased red cell mass (by RBC transfusion, and probably also by erythropoietin therapy). Given the same platelet concentration, a blood specimen collected from a non-anemic patient will likely be lower than that from an anemic patient, since the phlebotomy needle tends to be located near the center of the blood vessel where the "local" (blood vessel center versus circumference) platelet

concentration is lower. Platelet marginalization is functionally significant since more platelets are available to interact with endothelial cells to effect hemostasis, including thrombosis. Anemia of renal failure is often associated also with thrombocytopenia, and both anemia and thrombocytopenia may be protective against cardiovascular complications of chronic uremia.

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- The decrease in platelet counts is consistent with (but not supportive of) an increase in thromboembolic risk and serious thromboembolic complications, including acute myocardial infarction, malignant cardiac arrhythmia, and sudden death.

Other Laboratory Parameters

The mean and median values for WBC were all within the standard reference range and were similar throughout the study and between treatment groups. The same was true for the following parameters: AST, ALT, albumin, ALP, and fasting glucose (non-diabetic patients only). Mean and median values for electrolytes (potassium and phosphate) were similar throughout the study and between treatment groups. Mean values were high for these parameters in both groups, but this is characteristic of this patient population.

Marked Laboratory Abnormalities

The types of marked laboratory abnormalities that occurred in the Mircera and reference groups were generally similar (**Table 65**). The most common were low RBC, high phosphate, and high potassium. A similar proportion of patients in the Mircera and reference groups had high phosphate (39% and 36%, respectively) and high potassium (15% in each group), while the proportion of patients with markedly low RBC was higher in the reference group (55%) than in the Mircera group (36%). A total of 5% of the patients in the Mircera group and 2% in the reference group had markedly low platelets. Marked laboratory abnormalities seen during clinical development of Mircera are shown in **Table 65** (CRF patients) and in **Table 66** (health volunteers).

Table 65: Marked Laboratory Abnormalities (Safety Population)

Parameter Abnormality	Value	RO0503821 N = 1789	Reference N = 948
HEMATOLOGY			
PLATELETS (10**9/L) - HIGH	n	1774	938
	single not last	2 (<1%)	7 (<1%)
	last or replicated	2 (<1%)	6 (<1%)
	any	4 (<1%)	13 (1%)
PLATELETS (10**9/L) - LOW	n	1774	938
	single not last	44 (2%)	10 (1%)
	last or replicated	39 (2%)	9 (<1%)
	any	83 (5%)	19 (2%)
RBC (10**12/L) - HIGH	n	618	229
	single not last	3 (<1%)	1 (<1%)
	last or replicated	2 (<1%)	0
	any	5 (<1%)	1 (<1%)
RBC (10**12/L) - LOW	n	618	229
	single not last	56 (9%)	22 (10%)
	last or replicated	164 (27%)	105 (46%)
	any	220 (36%)	127 (55%)
WBC (10**9/L) - HIGH	n	1772	938
	single not last	7 (<1%)	11 (1%)
	last or replicated	11 (<1%)	3 (<1%)
	any	18 (1%)	14 (1%)
WBC (10**9/L) - LOW	n	1772	938
	single not last	31 (2%)	13 (1%)
	last or replicated	10 (<1%)	2 (<1%)
	any	41 (2%)	15 (2%)
LIVER FUNCTION			
ALAT (SGPT) (U/L) - HIGH	n	1767	940
	single not last	24 (1%)	11 (1%)
	last or replicated	17 (<1%)	8 (<1%)
	any	41 (2%)	19 (2%)
ALK. PHOS. (U/L) - HIGH	n	1769	940
	single not last	32 (2%)	15 (2%)
	last or replicated	38 (2%)	36 (4%)
	any	70 (4%)	51 (5%)
ASAT (SGOT) (U/L) - HIGH	n	1761	934
	single not last	22 (1%)	10 (1%)
	last or replicated	17 (<1%)	5 (<1%)
	any	39 (2%)	15 (2%)
PROTEIN			
ALBUMIN (g/L) - LOW	n	1748	924
	single not last	52 (3%)	29 (3%)
	last or replicated	74 (4%)	47 (5%)
	any	126 (7%)	76 (8%)
ELECTROLYTES			
PHOSPHATE (mmol/L) - HIGH	n	1770	939
	single not last	294 (17%)	149 (16%)
	last or replicated	404 (23%)	190 (20%)
	any	698 (39%)	339 (36%)
PHOSPHATE (mmol/L) - LOW	n	1770	939
	single not last	70 (4%)	45 (5%)
	last or replicated	45 (3%)	23 (2%)
	any	115 (6%)	68 (7%)
POTASSIUM (mmol/L) - HIGH	n	1768	939
	single not last	160 (9%)	93 (10%)
	last or replicated	113 (6%)	50 (5%)
	any	273 (15%)	143 (15%)
POTASSIUM (mmol/L) - LOW	n	1768	939
	single not last	15 (<1%)	7 (<1%)
	last or replicated	8 (<1%)	0
	any	23 (1%)	7 (<1%)
MISCELLANEOUS			
Parameter Abnormality	Value	RO0503821 N = 1113	Reference N = 538
GLUCOSE FASTING (mmol/L) - HIGH	n	1097	525
	single not last	7 (<1%)	1 (<1%)
	last or replicated	3 (<1%)	3 (<1%)
	any	10 (<1%)	4 (<1%)
GLUCOSE FASTING (mmol/L) - LOW	n	1097	525
	single not last	2 (<1%)	0
	last or replicated	0	0
	any	2 (<1%)	0

Table 66: Marked Laboratory Abnormalities in Healthy Volunteers (Pooled Phase 1 Studies)

Parameter Abnormality	Value	All Periods Placebo N = 77	All Periods RO 50-3821 N = 461
PLATELETS (10**9/L) - LOW	n	77	461
	single not last	0	2 (<1%)
	last or replicated	0	0
	any	0	2 (<1%)
RBC (10**12/L) - HIGH	n	77	461
	single not last	5 (6%)	36 (8%)
	last or replicated	2 (3%)	58 (13%)
	any	7 (9%)	94 (20%)
WBC (10**9/L) - HIGH	n	77	461
	single not last	0	1 (<1%)
	last or replicated	0	0
	any	0	1 (<1%)
WBC (10**9/L) - LOW	n	77	461
	single not last	0	2 (<1%)
	last or replicated	0	1 (<1%)
	any	0	3 (<1%)
EOSINOPHILS (10**9/L) - HIGH	n	77	461
	single not last	0	1 (<1%)
	last or replicated	0	1 (<1%)
	any	0	2 (<1%)
LYMPHOCYTES (10**9/L) - LOW	n	77	461
	single not last	4 (5%)	14 (3%)
	last or replicated	0	3 (<1%)
	any	4 (5%)	17 (4%)
NEUTROPHILS (10**9/L) - LOW	n	77	461
	single not last	3 (4%)	8 (2%)
	last or replicated	0	9 (2%)
	any	3 (4%)	17 (4%)
ALAT (SGPT) (U/L) - HIGH	n	77	461
	single not last	1 (1%)	2 (<1%)
	last or replicated	1 (1%)	3 (<1%)
	any	2 (3%)	5 (1%)
ASAT (SGOT) (U/L) - HIGH	n	77	461
	single not last	0	15 (3%)
	last or replicated	1 (1%)	6 (1%)
	any	1 (1%)	21 (5%)
TOTAL BILIRUBIN (umol/L) - HIGH	n	77	461
	single not last	1 (1%)	5 (1%)
	last or replicated	0	1 (<1%)
	any	1 (1%)	6 (1%)
POTASSIUM (mmol/L) - HIGH	n	77	371
	single not last	1 (1%)	2 (<1%)
	last or replicated	0	1 (<1%)
	any	1 (1%)	3 (<1%)
GLYCOSURIA (0 to 4+) - HIGH	n	77	419
	single not last	0	8 (2%)
	last or replicated	0	2 (<1%)
	any	0	10 (2%)
HEMATURIA (0 to 4+) - HIGH	n	77	419
	single not last	9 (12%)	26 (6%)
	last or replicated	4 (5%)	10 (2%)
	any	13 (17%)	36 (9%)
PROTEINURIA (0 to 4+) - HIGH	n	77	419
	single not last	1 (1%)	2 (<1%)
	last or replicated	0	1 (<1%)
	any	1 (1%)	3 (<1%)

Review Comments:

As might be expected, the pattern of marked abnormalities seen in CRF patients receiving erythropoietin differs from that seen in healthy volunteers receiving erythropoietin. Electrolyte imbalances (particularly hyperkalemia), expected in CRF, may decrease the threshold for a serious cardiac arrhythmia and sudden death, particularly when superimposed on acute coronary thrombosis and cardiac ischemia.

7.1.8 Vital Signs

In the overall safety population, the mean and median values of diastolic and systolic blood pressure were generally stable over time and similar between treatment groups. Median diastolic blood pressure was 78 mm Hg in both groups at baseline, and 77 mm Hg after one year. Similarly, median systolic blood pressure was 140 mm Hg and 141 mm Hg at baseline in the Mircera and reference groups, respectively, and 140 mm Hg in both groups after one year. Similar results were seen for the correction and maintenance study populations.

Since there is a possible relationship between hemoglobin and blood pressure, blood pressure findings for the correction and maintenance studies are provided separately. In the correction studies there was a slight increase in median diastolic blood pressure between months 2 to 4 and between months 8 and 10 in the reference group only, although the number of patients between months 8 and 10 is small (**Figure 6**). Median systolic blood pressure was relatively constant over time in the Mircera group, and fluctuated slightly in the reference group. In the maintenance studies, median systolic and diastolic blood pressure was constant over time in the Mircera (Q2W and Q4W) and reference groups.

7.1.9 Electrocardiograms (ECG)

For the pooled phase 3 studies, summary statistics over time for ECG intervals, HR, PR, RR, QRS, QT, QTcB, QTcF, and QTcR were unrevealing and showed similar mean values at each time point between treatment groups. The percentage of patients with QTcR changes from baseline $\geq$ 60 msec was greater in the reference group (5.7%) than in the Mircera group (3.8%). The percentage of patients with QTcR intervals > 480 msec was similar in the Mircera group (11.8%) and the reference group (11.0%). There were very few cases of a temporal association between these finding and clinical events. Overall the data suggest that there is no clinical evidence of QTc prolongation or associated clinical events.

The central tendency analysis on time-matched change from baseline values of QTcS at population tmax after the last dose showed no statistically significant difference between Mircera treatment and placebo (0.860 msec, 95% CI -4.80 to 6.60; ANOVA, F-value = 0.06, p = 0.80). Furthermore, there were no differences between Mircera treatment and placebo in time-matched change from baseline values or absolute values of QT/QTc measured at numerous time points during the study. The results obtained after the first, second and third dose were consistent and independent of the correction method used to calculate QTc intervals.

The categorical analysis on time-matched change from baseline and absolute values of QT and/or QTc showed no trend for a difference between Mircera and placebo. There was no subject with an absolute value of QT and/or QTc > 500 msec or a time-matched change from baseline QTc interval > 60 msec. Two male subjects had a maximum value of QTcB > 450 msec, one after Mircera treatment and one after placebo. One female subject had a maximum value of QTcB >

470 msec after Mircera treatment. However, with the Fridericia and the study-specific correction, no subject had a maximum value of QTc > 450 msec either after Mircera or placebo treatment.

Mircera had no effect on the other ECG parameters measured (PR, QRS, T and U wave morphology, and HR). The results show that Mircera has no effect on QT interval and other ECG parameters after multiple intravenous doses of 3.2 ug/kg in healthy volunteers. (See consult)

7.1.10 Immunogenicity

To date, no patients treated with Mircera had newly developed detectable anti- Mircera or anti-erythropoietin antibodies in any of the clinical trials. No cases of PRCA with Mircera were reported in clinical trials.

Antibody determinations were performed in all phase 2 and phase 3 studies. In case of a positive result, a functional assay was to be performed to detect the presence of neutralizing antibodies. However, for patients with antibody levels around the limit of detection of the assay, the neutralizing antibody test was not done. This is because the sensitivity of the neutralizing antibody test would not result in a meaningful outcome for these patients. Importantly, patients with these low levels did not show any clinical symptoms of a loss or lack of treatment effect regarding their anemia and continued treatment with either Mircera or a reference comparator.

One patient who received Mircera Q2W had detectable levels of anti-erythropoietin antibody (above the limit of quantification of 5 ng/ml) at baseline, day 90, and day 365 (range of 6.09 to 6.99 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 antibody before treatment with study medication, and the antibody titer did not increase as the patient continued treatment with Mircera. This patient completed the 52-week treatment period.

One patient receiving a reference agent (epoetin beta) tested positive for anti-erythropoietin antibody (detectable levels of anti-erythropoietin at days 89, 142, 201, 257, 285, 313, and 369; range 10.6 to 14300 ng/mL). These antibody findings were associated with a drop in hemoglobin to a minimum of 6.2 g/dL, which was treated with 14 RBC transfusions (between week 19 and week 43). A test for neutralizing anti-erythropoietin antibodies produced no valid results.

7.1.11 Human Carcinogenicity

Mircera is a new molecular entity (NME) built from two well-characterized biotechnology products: methoxy polyethylene glycol and epoetin beta. Epoetin beta is used widely in Europe, and methoxy polyethylene glycol is a structural component of many widely used biotechnology products. The potential for Mircera to cause cancer in humans has not been studied directly but may be considered to be sufficiently low to permit product approval without direct studies. The potential for erythropoietin products as a class to promote tumor progression in patients with cancer continues to receive attention (ref).

7.1.12 Special Safety Studies

Of compelling interest is the potential for Mircera and other erythropoietin products to increase morbidity and mortality when used "inappropriately" to treat anemia of CRF, as suggested by recent literature (ref). The approval of erythropoietin products over the last three decades had been supported by scientific and regulatory thinking which accepted the alleviation of CRF-associated anemia to be clinically beneficial and unlikely to be associated with an adverse clinical outcome. Roche has patterned Mircera development after the development of Amgen's

darbepoetin alfa, with guidance from FDA, and Mircera development did not include a rigorous investigation of potential "inappropriate" treatment of anemia in CRF. Whether or not new clinical studies are necessary to further define the CRF treatment indication, for Mircera as well as previously approved erythropoietin products, remains an important regulatory concern for all erythropoietin products as a class. The apparent imbalance in sudden deaths (see above) may indicate "inappropriate" erythropoietin therapy, and the potential for "inappropriate" therapy may be greater with long-acting erythropoietin products.

Additional Safety Data: BA16736 and BA16738

In addition to data from the two phase 3 correction studies (BA16736 and BA16738) that are included in this integrated safety summary, separate patient listings of deaths, SAE, and withdrawals are provided for these two studies using the final data for the 141 Mircera-treated patients and 126 reference-treated patients who had not completed the extension period of the study at the time of database closure (November 2005) for these studies and hence were not included in the original integrated safety data.

BA16736

Five out of 14 patients in the Mircera Q2W group and one out of 16 patients in the Mircera Q4W group had one or more SAE. Two out of 11 patients in the epoetin reference group had one or more SAE. None of the SAE were considered related to study treatment. Two patients died: one in the Mircera Q2W group (unevaluable event, SAE of sudden death) and one in the reference group (aortic dissection). There were no additional withdrawals due to AE in this phase of the study.

BA16738

Nine out of 56 patients in the Mircera Q2W group had one or more SAE (total of 12 SAE); 11 out of 55 patients in the Mircera Q4W group had one or more SAE (total of 16 SAE); and 24 out of 115 patients in the darbepoetin alfa reference group had one or more SAE (total of 37 SAE). None of the SAE were considered related to study treatment.

Three patients receiving Mircera died, two in the Mircera Q2W group (deaths due to acute cardiac failure and pulmonary edema) and one in the Mircera Q4W group (death due to myocardial infarction). Five patients died in the reference group. There were three additional withdrawals due to AE (2 events of dementia and myocardial infarction in the Mircera Q4W group, and an event of lower GI hemorrhage in the reference group) in this phase of the study.

Safety Data from Phase I Studies in Healthy Subjects (Pooled Population)

A total of 499 healthy subjects participated in the Phase I studies and are included in the pooled Phase I safety population. Of these subjects, 77 received placebo and 461 received Mircera. The majority of these subjects were male and Caucasian. Except for a higher percentage of male subjects in the Mircera group, the demographic characteristics were similar between the placebo and Mircera groups. Marked laboratory abnormalities seen with Mircera administration in healthy volunteers are presented above in discussing laboratory abnormalities seen in CRF patients.

Clinical and Pre-Clinical (Toxicology) Data

In the preclinical toxicity studies performed in normocythemic animals, a fixed dosing regimen caused many adverse changes including mortality and serious pathogenesis secondary to

exaggerated pharmacological effects. The serious pathological findings in preclinical toxicity studies with Mircera were associated with uncontrolled polycythemia in affected animals.

Mortality

One male rat receiving once weekly dose of 0.3 µg/kg/dose (sc), two female rats receiving 1 µg/kg/dose (sc), one male and one female rats receiving 3 µg/kg/dose (sc) were sacrificed for humane reasons following 9-16 weeks of treatment based on hematology data that indicated marked decreases in erythrocyte counts, hemoglobin, and hematocrit (4.0 - 12.2%) . These rats were described as having pale appendages in-life, a sign of anemia, and various organs were also described as pale at necropsy. These necropsy observations were associated with either polycythemia or anemia.

Polycythemia-Related Toxicities

Treatment of rats and dogs with Mircera once weekly at 0.3-3 ug/kg/dose for 26 weeks (rats only), at 1-10 µg/kg/dose for 13 weeks, or at 1-30 ug/kg/dose for 4 weeks resulted in various histopathological findings including vascular congestion, hemorrhage, thrombosis, necrosis, and/or inflammation in various organs and tissues including brain, heart, kidney, liver, spleen, stomach, and thymus and were associated with uncontrolled polycythemia in affected animals. Vascular congestion was characterized by excessive accumulation of blood in the affected organ and accounted for the dilatation of the lumen of the blood vessels of that organ. The markedly increased total erythrocyte mass and the corresponding increase in blood viscosity that predisposes animals to vascular congestion, thrombosis and hemorrhage is believed to be the cause of these pathological findings. Although the profile of histopathological findings in each study was not completely identical, the key findings generally overlapped across the studies. No distinctive pattern related to dose, species, gender, or route of administration could be established. Instead, these findings were generally associated with the polycythemic condition of individual animals. There were no increases in platelet counts in rats and dogs treated with Mircera. The coagulation parameters PT and APTT increased when RBC counts increased following treatment with Mircera. The effects on coagulation parameters were likely artifactual changes due to relatively higher plasma concentrations of the anticoagulant, sodium citrate, in the whole blood samples that had increased red blood cell mass and therefore decreased plasma volume, and were not considered to be the direct effects of Mircera on hemostasis.

These findings seen in normal animals with uncontrolled stimulation of erythropoiesis are unlikely to be encountered in clinical practice, where the dose can be carefully adjusted on the basis of measured hemoglobin, which is regularly monitored, to maintain the hemoglobin level in the target range.

Development of Anti-Erythropoietin Antibodies and Anemia

As expected when heterologous human protein is introduced to animal species, some rats and dogs developed anti-erythropoietin antibodies following repeated administrations of Mircera, and at the same time developed resistance in responding to once-weekly administration of Mircera, resulting in anemia. Resistance to Mircera following repeated treatment observed in animal studies is considered a reflection of the presence of neutralizing antibodies to Mircera, and endogenous erythropoietin in these animals. The presence of antibodies to a human-derived biotechnology product in dogs and rats was not unexpected and may not be relevant for humans.

Genotoxicity and Carcinogenicity

Standard mutagenicity studies were not performed with Mircera. For biotechnology products, in particular high-molecular-weight recombinant human proteins, genotoxicity tests routinely conducted for traditional pharmaceuticals are not applicable as direct interaction of these products with DNA or other chromosomal material is not expected. Furthermore, based on the inert nature of the attached PEG moiety, pegylation is not expected to lead to a product with substantially altered chemical reactivity to DNA. Standard carcinogenicity studies are also generally inappropriate for biotechnology products such as Mircera due to the development of antibodies against human proteins in test animals. Therefore, carcinogenicity studies were not performed.

Chronic administration of Mircera to Wistar rats for up to 26 weeks did not induce pre-neoplastic changes or hyperplasia in any tissues other than hematopoietic target organs. In addition, Mircera did not stimulate proliferation of various human tumor cell lines in vitro other than in a cell line (UT-7) which is known to require erythropoietin for its growth and survival in the culture. The results from these studies suggested that it is unlikely that Mircera has the potential to stimulate growth of normal or malignant human cells other than the erythroid progenitor cells in the bone marrow.

In tissue binding studies, Mircera bound only the hematological progenitor cells in the bone marrow, the intended target cells for Mircera. Overall, the tissue binding profile of Mircera was comparable to that of epoetin beta.

The above data do not suggest that Mircera is likely to pose a greater risk than other erythropoietin products. The clinical data from this program did not indicate an excess of malignancy with Mircera vs the comparator treatments.

7.1.13 Withdrawal Phenomena and/or Abuse Potential

Withdrawal phenomena or abuse potential have not been observed to date with Mircera or other erythropoietin products. The use of Mircera to treat anemia of CRF (including indefinite use) is expected to be not associated with significant withdrawal phenomena or abuse potential.

7.1.14 Human Reproduction and Pregnancy Data

As for other erythropoietin products, adequate data regarding human reproduction and pregnancy is lacking for Mircera (Pregnancy Category C) (ref).

7.1.15 Assessment of Effect on Growth

The effect of Mircera treatment on growth has not been studied.

7.1.16 Overdose Experience

The clinical consequences of Mircera overdose have not been adequately studied. In the studies performed to date, overdose (defined by excessive hemoglobin rate of rise or hemoglobin overshoot; see above) was clinically managed by holding or decreasing the dose of Mircera with hemoglobin monitoring. A clear temporal association between overdose and adverse clinical events has not been observed. However, the clinical experience to date indicates that any dose that raises the hemoglobin to a level above 13.5 g/dL may be viewed as an overdose (ref). The maximum "safe" dose or hemoglobin level is not known, but the complex concept of overdose in erythropoietin therapy in CRF is receiving increasing attention (ref).

7.1.17 Post-Marketing Experience

As an NME, Mircera has not been approved and there is no post-marketing experience to date.

7.2 Adequacy of Patient Exposure and Safety Assessments

7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

Patients enrolled in the phase 2 and phase 3 clinical studies received a range of Mircera doses by IV or SC, at administration schedules of 1x/week to once every 4 weeks. All were combined in the overall safety population. In this overall population, for the first 12 months, the median weekly dose of study medication was 30 µg Mircera/week for each time point, with a maximum of 1282 ug/week.

- In the overall population, at 6 months 1422 patients were receiving Mircera; at 12 months 1011 patients were receiving Mircera; and 95 patients completed 24 months of treatment with Mircera. In the maintenance population, 1127 patients were receiving Mircera at 6 months, 856 at 12 months, and 58 at 24 months. In the correction population, exposure to Mircera was less: 295 patients were receiving Mircera at 6 months, 155 at 12 months, and 37 at 24 months.
- Cumulative patient exposure in the Mircera group was 1532 patient exposure years (PEY) for 1789 patients, or 0.86 PEY per patient. In the reference group, the cumulative patient exposure was 778 PEY for 948 patients or 0.82 PEY per patient. Hence, the PEY per patient was slightly higher in the Mircera group than in the reference group.
- By subgroups of study design, route of administration, mode of dialysis, dose schedule, among others, patient exposure differed between subgroups, but was generally consistent with the sample size in the subgroup.

Safety Population

In the overall population, 1422 and 1011 patients were receiving Mircera at 6 months and 12 months, respectively, and 95 patients completed 24 months of treatment with Mircera. As there were no comparators in the three phase 2 studies that continued beyond 12 months, the patient exposure was less for the comparators: 584 patients were receiving epoetin at 6 months and 356 at 12 months. For darbepoetin alfa, 300 patients were receiving darbepoetin alfa at 6 months and 157 at 12 months. Therefore, the "reference group" had a total exposure of 884 patients receiving treatment at 6 months and 513 at 12 months.

For the first 12 months, the median weekly dose of study medication was stable at 30 ug Mircera/week for each time point, with a maximum of 1282 ug/week (**Table 67**). After 12 months, the median weekly Mircera dose fluctuated between 19 and 25 ug/week between months 13 and 29. The median weekly epoetin dose fluctuated between 6900 and 8000 IU/week over the 12 months of study. The median weekly darbepoetin alfa dose fluctuated between 20 and 30 µg/week, similar to that seen for Mircera. The median cumulative total dose of Mircera and darbepoetin alfa at 12 months was similar (22 - 23 ug/kg).

For the overall population, the cumulative patient exposure in the Mircera group was 1532 patient exposure years (PEY) for 1789 patients, or 0.86 PEY per patient. In the reference group, the cumulative patient exposure was 778 PEY for 948 patients or 0.82 PEY per patient. Hence, the PEY per patient was slightly higher in the Mircera group than in the reference group. This is

largely a result of the fact that there was no reference arm in any of the phase 2 studies, three of which included 2-year optional long-term extensions (see **Figure 1**). As seen in **Table 67**, the phase 2 studies include 354 patients with a cumulative patient exposure of 354.6 PEY, i.e., an average of about one year per patient for the phase 2 studies alone, none of which included a reference group. When patient years were examined for the Phase 3 studies only, the PEY per patient was the same in both treatment groups (0.82).

Table 67: Patient Exposure Years (Safety Population)

	RO0503821 (N = 1789)		Reference (N = 948)	
	N	PEY	N	PEY
Total	1789	1531.98	948	777.98
Study Design				
Correction	422	324.42	208	135.63
Maintenance	1367	1207.56	740	642.36
Study Type				
Phase II	354	354.60		
Phase III	1435	1177.38	948	777.98
Route of Study Drug Administration				
IV	930	798.61	541	461.81
SC	859	733.36	407	316.18
Mode of Current Dialysis				
Hemodialysis	1499	1287.34	755	653.67
Peritoneal Dialysis	64	39.47	31	23.98
Not yet on Dialysis	226	205.16	162	100.33
Schedule of Study Drug Administration				
<=1*/ week	136	130.80	923	755.44
1*/2 weeks	1112	900.07	25	22.54
1*/3 weeks	88	85.70		
1*/4 weeks	453	415.40		
Age				
<65	1009	856.36	527	436.18
65-74	429	372.18	222	180.25
>=75	351	303.44	199	161.56
Weight				
<65	598	515.93	286	241.61
65-<80	651	549.92	336	275.51
>=80	539	465.89	325	260.35
Gender				
Female	755	666.76	398	329.62
Male	1034	865.21	550	448.36
Race				
Black	362	328.84	186	151.31
Caucasian	1298	1096.42	675	557.32
Oriental	85	66.96	60	48.68
Other	44	39.75	27	20.68
Ethnicity				
Hispanic	134	110.82	80	64.68
Non-Hispanic	1301	1066.55	868	713.31
Geographical Region				
US	641	568.37	328	260.47
Non-US	1148	963.61	620	517.51
Diabetes Status				
Diabetic	676	573.52	410	324.52
Non-Diabetic	1113	958.46	538	453.47
Cardiovascular Disease at Baseline				
Yes	1372	1122.58	922	755.28
No	63	54.79	26	22.71

Administrations of Study Treatment

As the overall population included studies where the dose of Mircera was given once every one, two, three, or four weeks, depending on the study, the number of administrations overall varied considerably. Over the course of all 10 studies included in the overall population, the median number of administrations of Mircera was 16; the mean was 19.6, with a maximum of 124 administrations.

Subgroups

In the correction population, the PEY were substantially lower than in the overall or maintenance populations, 324 and 136 cumulative PEY in the Mircera and reference groups, respectively, in the correction studies. The PEY per patient was higher in the Mircera group (0.77) than in the reference group (0.65), due to the phase 2 exposure in the Mircera group only. When the PEY was examined for the Phase 3 correction studies, the PEY per patient was similar between groups (0.69 Mircera, 0.65 reference).

By route of study drug administration (IV/SC), the overall patient exposure was higher in the IV patients (799 and 462 PEY in the Mircera and reference groups, respectively) than in the SC patients (733 and 316 PEY, respectively). The PEY per patient was similar between treatment groups for the IV route (0.85-0.86), but higher in the Mircera group (0.85) than in the reference group (0.77) for the SC route.

For the Phase 3 maintenance studies, which was the population used for analyses of AE by dose schedule of Mircera (Q2W vs Q4W), the overall patient exposure was higher with the Q2W schedule (611 PEY) than with the Q4W schedule (362 PEY), but the PEY per patient was actually higher with the Q4W schedule (0.88) than with Q2W (0.84).

For dialysis modality, the cumulative patient exposure was highest with hemodialysis patients and lowest for peritoneal dialysis patients. The PEY per patient was similar between groups for patients on hemodialysis; higher in the reference group (0.77) than in the Mircera group (0.62) for patients on peritoneal dialysis; and higher in the Mircera group (0.91) than in the reference group (0.62) for patients not on dialysis.

By baseline characteristics the following results were seen for the overall safety population (**Table 32**). It should be noted that most of the differences in total patient exposure seen were the results of differences in sample sizes, as it was total number of patient years and not mean exposure per patient:

- Age: Total patient exposure was greatest for patients < 65 years of age, and lowest for patients 75 years of age or older. Differences between groups in PEY per patient were: higher PEY per patient in the Mircera group for the two higher age categories and a lower PEY per patient in the Mircera group compared with the reference group for the < 65 age category.
- Weight: Within each treatment group, the total patient exposure was similar among the three weight categories. However, the PEY per patient was slightly higher in the Mircera group than in the reference group in each of the three weight categories.
- Gender: The total PEY were higher for male patients than females in both groups. Again, the PEY per patient was slightly higher in the Mircera group than in the reference group in both male and female patients.
- Race: The total PEY were greatest for Caucasians in both treatment groups. PEY per patient was similar between treatment groups for Caucasian and Oriental patients and higher in the Mircera group than in the reference group for Black patients.
- Ethnicity: The total PEY were higher for non-Hispanic patients in both treatment groups. PEY per patient were similar between treatment groups for both Hispanic and non-Hispanic patients.

- Geographic region: The total PEY were higher for non-US patients than for US patients in both treatment groups. PEY per patient were higher in the Mircera group than in the reference group in US patients, but similar between treatment groups for non-US patients.
- Diabetes: The total PEY were higher for non-diabetic patients in both treatment groups. PEY per patient were higher in the Mircera group than in the reference group for diabetic patients, but similar between groups for non-diabetic patients.
- Cardiovascular disease: The total PEY were much greater for patients with cardiovascular disease at baseline than without in both treatment groups. In both patients with cardiovascular disease at baseline and without, the PEY per patient were similar between treatment groups.

7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

The secondary clinical data sources used to evaluate the safety of Mircera include the clinical literature (ref), the data that supported the initial approval of darbepoetin alfa (ref) and its major supplements,

7.2.3 Adequacy of Overall Clinical Experience

The extent of clinical experience with Mircera available to date is comparable to the extent of experience that had been available with other erythropoietin products at their respective time of approval. The overall clinical experience with all erythropoietin products as a class, however, raises concerns about the adequacy of the experience with Mircera as well as with previously approved erythropoietin products (ref). How this "inadequate" experience is to be reconciled for Mircera and for previously approved erythropoietin products remains an important regulatory concern.

7.2.4 Adequacy of Special Animal and/or In Vitro Testing

See Appendix (Toxicology).

7.2.5 Adequacy of Routine Clinical Testing

See Section 7.1.7 above.

7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup

See Appendix (Clinical Pharmacology).

7.2.7 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study

See Section 2 for a discussion of the appropriateness of the hemoglobin level to be targeted in using erythropoietin products to treat anemia associated with CRF.

7.2.8 Assessment of Quality and Completeness of Data

The data submitted in support of this BLA are of adequate quality and completeness to permit an adequate evaluation of product safety and efficacy.

7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

In order to explore the potential relationship between the higher rate of hemorrhage seen with Mircera (than with reference agents) and the mild decrease in platelet count associated with Mircera (but not with reference agents), the agency requested the following additional safety analyses:

- Among the patients who had thrombocytopenia, how many patients had bleeding events (including serious and non-serious events) and what types of bleeding event (e.g., gastrointestinal, intracranial) were in each group?

  Sponsor Response

  In the pooled (phases 2 and 3) population, 7.5% (134/1789) of Mircera treated patients had at least one post baseline platelet value < 100 at any time compared to 4.4% (42/948) among reference treated patients.

- Among the patients who had hemorrhage events (including serious and non-serious events), how many patients had thrombocytopenia in each group? What were the lowest platelet counts for those patients?

  Sponsor Response

  Among the 379 patients in the Mircera group who had at least one hemorrhagic event, 10.3% had platelet counts < 100 at any time in the study. Among the 166 patients in the reference group who had at least one hemorrhagic event, 4.2% had platelet counts < 100 at any time in the study irrespective of the timing of occurrence of low platelet event and hemorrhagic event.

  Among the 93 patients in the Mircera group who had at least one serious hemorrhagic event, 12.9% had platelet counts < 100 at any time in the study. Among the 38 patients in the reference group who had at least one serious hemorrhagic event, 7.9% had platelet counts < 100 at any time in the study irrespective of the timing of occurrence of low platelet event and serious hemorrhagic event.

- For each group (Mircera vs reference), among patients WITHOUT thrombocytopenia, how many had bleeding (serious, non-serious, types) and how do these numbers compare with bleeding in patients WITH thrombocytopenia?

  - Do the data suggest that platelet counts < 100 x 10^9/L on Mircera correlate more closely with bleeding than does platelet counts < 100 x 10^9/L on reference agents?
  - For each group, what is the average platelet count in patients with bleeding?

  Sponsor Response

  As shown in the following table (**Table 68**), out of 1655 patients in the Mircera group without a low platelet value recorded at any time, 340 patients (20.5 %) had a hemorrhagic event. In comparison, out of 906 patients in the reference group without a low platelet value at any time, 159 patients (17.5%) had a hemorrhagic event.

  Out of 134 patients in the Mircera group with a low platelet value (<100) recorded at any time, 39 patients (29.1 %) had a hemorrhagic event. Out of the 42 patients in the reference group with a low platelet value recorded at any time, 7 patients (16.7%) had a hemorrhagic event.

Table 68: Hemorrhagic Events in Platelet Groups (Safety Population)

		Platelet Value <100 [10**9/L]	(%)	No Platelet Value <100 [10**9/L]	(%)	Total
RO0503821 (N=1789)	Hemorrhagic Aes	39	29.1	340	20.5	379
	No Hemorrhagic Aes of Interest	95	70.9	1315	79.5	1410
	Total	134	100.0	1655	100.0	1789
	GI Hemorrhage	13	9.7	76	4.6	89
	Intracranial Hemorrhage	1	0.7	15	0.9	16
	Vascular Hemorrhage	13	9.7	88	5.3	101
	Other	20	14.9	200	12.1	220
Reference (N=948)	Hemorrhagic Aes	7	16.7	159	17.5	166
	No Hemorrhagic Aes of Interest	35	83.3	747	82.5	782
	Total	42	100.0	906	100.0	948
	GI Hemorrhage	2	4.8	30	3.3	32
	Intracranial Hemorrhage	0	0.0	5	0.6	5
	Vascular Hemorrhage	1	2.4	44	4.9	45
	Other	6	14.3	93	10.3	99

Review Comment: These results suggest that the mild decrease in platelet counts is NOT related to the higher rates of hemorrhage with Mircera, since higher rates of hemorrhage were seen also in patients with normal platelet counts. The sponsor claims that the higher rates of hemorrhage seen with Mircera reflect unequal baseline patient characteristics (anticoagulation status). Additional analyses are needed to demonstrate that hemorrhage is not a safety concern for Mircera.

7.4 General Methodology

7.4.1 Pooling Data across Studies to Estimate and Compare Incidence

Pooled data across all studies were used to evaluate the safety of Mircera relative to the reference agents as a single group. In addition to pooled data analyses, individual study analyses may be helpful in evaluating the safety of Mircera relative to each specific reference agent (epoetin alfa, epoetin beta, darbepoetin alfa). Individual study analyses may permit an indirect comparison of the safety of the reference agents, and may reveal new areas of safety concern for erythropoietin products as a class.

7.4.2 Explorations for Predictive Factors

Hemoglobin rate of rise and hemoglobin excursions were explored for their potential association with adverse events and for their potential value in serving as laboratory indicators predictive of clinical adverse events. No associations were noted: the incidence of adverse clinical events was not appreciably different between patients who did or did not experience excessive hemoglobin rates of rise or hemoglobin excursions. The hemoglobin parameters appear not to be useful as predictors of adverse clinical events.

The emerging clinical literature suggests that adverse clinical outcomes may be associated with higher hemoglobin levels, at least for levels that exceed 13.5 g/dL (ref). This apparent association

with the target hemoglobin across prospectively randomized study arms is not inconsistent with the apparent lack of an association with hemoglobin excursions across retrospectively defined patient subgroups; among others, one likely explanations is that patients who were less ill, had higher endogenous (untreated) baseline hemoglobin levels, and were more responsive to erythropoietin treatment were both more likely to experience hemoglobin excursions *and* less likely to experience adverse clinical events. In the retrospective analyses, the exploration of the potential link between the hemoglobin level and adverse clinical event was biased through a pre-existing correlation. A comparison of the incidence of adverse events across study arms prospectively randomized to different hemoglobin levels is necessary to explore the potential for "high" hemoglobin treatment levels ("hemoglobin excursions") to result in adverse clinical events. The CHOIR and the TREAT were two such studies (ref). The association seen in CHOIR was not seen in TREAT, possibly due to insufficient study power given the endpoint used.

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

See Section 7 above.

8.2 Drug-Drug Interactions

Formal drug interaction studies were not performed in the clinical evaluation Mircera.

8.3 Special Populations

No special populations are identified for Mircera.

8.4 Pediatrics

In this BLA, the sponsor requested a waiver for pediatric assessment. To support this request, the sponsor has submitted a pediatric development plan under IND 10158.

8.5 Advisory Committee Meeting

A meeting of the Cardio-Renal Advisory Committee is currently scheduled for September 2007. A briefing document for this meeting is currently under preparation.

9 OVERALL ASSESSMENT

9.1 Conclusions

The submission presents adequate efficacy data. The efficacy data demonstrate the efficacy of Mircera in raising or maintaining the hemoglobin in patients with CRF and anemia, including patients on or not on dialysis.

The submission does not present adequate safety data. The safety data do not permit the writing of adequate directions for using Mircera for the proposed indications as part of the product label. Specifically, the safety data do not permit an evaluation of the risk-benefit ratio associated with the hemoglobin levels used in the study.

9.2 Recommendation on Regulatory Action

The need for additional safety data applies to the entire class of erythropoietin products. The risk-benefit ratio of erythropoietin products will be discussed at the September 2007 meeting of the Cardio-renal Drugs Advisory Committee.

9.3 Recommendation on Post-Marketing Actions

No post-marketing actions are recommended at this time. The outcome of the advisory committee meeting is expected to influence the approvability of this BLA.

9.4 Labeling Review

The format and content of the product label for Mircera are expected to be similar to those for approved erythropoietin products (epoetin alfa and darbepoetin alfa). See Appendix (Label).

9.5 Comments to Applicant

- The submission presents adequate efficacy data. The efficacy data demonstrate the efficacy of Mircera in raising or maintaining the hemoglobin in patients with CRF and anemia, including patients on or not on dialysis.
- The pivotal clinical studies described in your BLA have used a hemoglobin level of up to 13 g/dL as the upper limit of the hemoglobin target range. The incidence of deaths and other serious adverse events observed with Mircera use in your pivotal clinical studies may be related to the targeted hemoglobin level.
  - Based on the results provided in your BLA, it is difficult to specify an appropriate hemoglobin level to be targeted in using Mircera for the indication proposed. The ability to write adequate directions for use as part of the product label is critical to the approvability of a BLA.
  - In addition to patient-specific factors, agent-specific factors may affect the choice of the hemoglobin target for a given patient receiving a specific erythropoietin stimulating agent (ESA). The clinical consequences of potential over-treatment with a longer-acting ESA may more difficult to reverse, and it may be appropriate to use a lower hemoglobin target for a longer-acting ESA.
  - We plan to discuss the risks associated with the use of erythropoietin stimulating agents in chronic kidney failure at the meeting of the FDA Cardio-Renal Advisory Committee in September of 2007. The meeting will not focus on your BLA, but we expect the meeting outcome to have important implications in resolving the concerns identified above for your BLA. Additional comments will be forthcoming from the agency after this meeting.
- The pooled safety data described in your BLA indicate a higher rate of hemorrhage, including serious gastrointestinal and intracranial hemorrhage, in patients treated with Mircera than in patients treated with reference ESAs. Please submit additional data which clearly demonstrate that the observed higher rate of hemorrhage is not specific to Mircera relative to reference ESAs.

10 APPENDICES

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

Memorandum

Sponsor's financial disclosure review: see clinical review section 1.3.4

Memorandum

Safety update review(s) see clinical review section 5.3.5

ACTING DIVISION DIRECTOR'S REVIEW MEMORANDUM

BLA:	125164
DRUG:	Pegzerepoetin alfa
TRADENAME:	Mircera™
FORMULATION:	Single use vials of Mircera (50 to 1000 mcg) in 1 mL phosphate buffer with defined excipients; also single use, prefilled syringes of Mircera (50 to 250 mcg) in 0.3 mL or 0.6 mL , [redacted] with defined excipients
ROUTE:	Intravenous (IV) or subcutaneous (SC)
DOSE:	0.6 mcg/kg IV or SC once every two weeks for patients who are not currently receiving an erythropoiesis stimulating agent (ESA); Defined conversion factor in the label for patients receiving an ESA; label describes the same ESA class dosing guidelines
SPONSOR:	Hoffmann La Roche
SUBMITTED:	April 18, 2006
PDUFA DUE DATE:	May 17, 2007
DD MEMO COMPLETED:	May 15, 2007
DD MEMO PREPARERS:	Dwaine Rieves, MD, Acting Division Director 5-17-07 Division of Medical Imaging and Hematology Products

SPONSOR'S PROPOSED INDICATION:

"Mircera is indicated for the treatment of anemia associated with chronic renal failure including patients on dialysis and patients not on dialysis."

RELATED DRUGS:

Mircera is a member of the class of ESA that includes the FDA-licensed products, Epoetin alfa (Procrit/Epogen) and Aranesp (Darbepoietin alfa).

RELATED REVIEWS:

Clinical:	John Lee, M.D.; Ruyi He, M.D., Ph.D.
Statistics:	Yuan Richard Chen, Ph.D, Jyoti Zalkikar, Ph.D.
Chemistry:	Ingrid Markovic, Ph.D., Dov Pluznik, Ph.D., Lai Xu, Ph.D., Serge Beaucage, Ph. D., Susan Kirshner, Ph.D., Barry Cherney, Ph.D.
Microbiology:	Patricia Hughes, Ph.D., Michelle Clark Stuart, M.S.
Pharm-toxicology:	Yanli Ouyhang, Ph.D., Adebayo Laniyonu, Ph.D.
Clin Pharmacology:	Ike Lee, Ph.D, Hong Zhao, Ph.D.
Pharmacometrics:	Pravin Jadhave, Ph.D., Jogarao Gobburu, Ph.D.
Project Manager:	Florence Moore, RN, MSN, RAC
Advisory Committee:	None

RECOMMENDED REGULATORY ACTIONS:

a. Issuance of Complete Review Letter:

Mircera is a form of epoietin beta (a product marketed in Europe) that has been modified by pegylation to produce a molecule that has a longer serum half-life than the currently

marketed ESAs. This longer half-life allows more convenient (biweekly or monthly) dosing compared to the currently marketed ESAs. Roche submitted this application to support solely an indication for Mircera use in the treatment of the anemia of chronic renal failure and the proposed text for this indication [redacted] marketed ESAs (however, these marketed ESAs also have other indications, including use in the treatment of chemotherapy-induced anemia in some patients with cancer). Convenience in dosing is, from the FDA review team's perspective, the only putative advantage of Mircera over the currently marketed ESAs.

The BLA review cycle was extended by a December 4, 2006 submission of additional clinical safety data that was recorded as a major amendment. During this extended review cycle new published data raised important questions regarding the safety of ESAs, especially with respect to the "targeting" of hemoglobin values in excess of 12 g/dL (specifically, the "CHOIR" study and several studies of ESA use in cancer patients). Together these publications necessitated the development of a boxed warning and additional warning text for the currently marketed ESAs and a plan to address dosing and usage issues at an Advisory Committee on September 11, 2007.

This review cycle has resulted in the identification of several items for the sponsor to address, including clinical, manufacturing and immunogenicity concerns. Additionally, final labeling and final product labeling are contingent upon the sponsor justifying the appropriateness of all components of "class labeling" for Mircera with respect to dosing and usage (including the extensive class labeling regarding use of ESAs in the treatment of chemotherapy anemia, an indication that Mircera will lack). This is especially important since Mircera has much different pharmacokinetics from the currently marketed ESAs and certain clinical data indicate that the hemoglobin response to Mircera may be delayed, compared to other ESAs.

The September 11, 2007 Advisory Committee is not intended to specifically vet the Mircera application's data. Instead, the Committee's input is essential to support the continued marketing of all ESAs with the current version of class labeling. Since the Mircera product label may use some or all of this class labeling, the Committee's discussion may importantly impact the final Mircera product label and post-marketing committments.

Overall, the sponsor has supplied clinical data that appears sufficient to support licensure if the deficiencies within the Complete Review (CR) letter are addressed. The CR letter does not ask specifically for additional pre-licensure data from new clinical studies. Instead, most of requested items pertain to clarifications and additional analyses, especially with respect to justification of the full extent of "class labeling" for Mircera with safety information.

Note: two publications importantly signal safety concerns for excessive targeting of hemoglobin concentrations:

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

b. Requirement of the sponsor to conduct post-marketing studies and to submit additional information:

During the review the following findings were of special note and are applicable to conceptualization of post-marketing clinical studies:

-A need for a randomized, controlled, post-marketing clinical study assessing safety outcomes in patients with serum C-reactive protein concentrations in excess of 30 mg/L.

Roche actively screened and eliminated subjects with C-reactive protein levels in excess of 30 mg/L. This exclusion process eliminated approximately 3% of subjects who, in clinical practice, would be eligible for treatment with an ESA. Analyses of adverse outcomes categorized by C-reactive protein support the sponsor's conclusion that the active screening program did not adversely impact the safety database. Nevertheless, the soundness of this conclusion will be verified by obtaining additional clinical data from patients with elevated C-reactive protein concentrations. In general, the study would compare Mircera to other ESAs although other designs may be reasonable.

-A need for a post-marketing clinical study that compares cardiovascular outcomes when subjects are randomized to specific categories of "target" hemoglobin values under 12 g/dL. The Mircera clinical development program targeted hemoglobin concentrations in excess of 11 g/dL with cessation of dosing for hemoglobin values in excess of 14 g/dL. In light of published data (CHOIR study and Normal Hematocrit study), ESA labels were modified to state that ESAs should be dosed to achieve the lowest hemoglobin value necessary to avoid blood transfusion. Safe usage of Mircera would be optimized by the conduct of a study that provided data pertinent to appropriate "targeting" of hemoglobin values under 12 g/dL.

In addition to these items, Roche will be requested to provide a summary of the proposed pediatric clinical study of Mircera (submitted to the IND) and a time line for initiation, completion and submission of the study results.

Importantly, discussions at the September 11, 2007 Advisory Committee may impact the extent and nature of the post-marketing clinical studies and the sponsor is encouraged to request a meeting to discuss the impact of the Committee's discussions upon the post-marketing commitments.

c. Tentative approval of the trade name, Mircera

This recommendation is consistent with that of the FDA Office of Drug Safety/Division of Medication Errors and Technical Support finding of July 19, 2006.

d. Pediatric Research Equity Act (PREA) of 2003 expectations:

In a February 21, 2006 letter, FDA informed Roche that clinical studies of Mircera usage among pediatric patients aged 5 to 18 years were deferred and that clinical studies were waived for pediatric patients aged 0 to 5 years. Within the original BLA application, Roche noted, "Based on the FDA recommendations, Roche intends to revise the pediatric development plan and submit protocols for FDA review to IND 10158 by November, 2006. In accordance with the PREA of 2003, Roche commits that the pediatric development plan and any agreed pediatric study will be developed and conducted with due diligence at the earliest time possible."

REVIEW COMPONENTS:

Background

Mircera is a modified form of epoetin beta, a product marketed in Europe. The modification mainly consists of additional of a polyethylene glycol-like congener to the molecule which greatly increases the molecular weight of the compound and prolongs the *in vivo* serum half-life. Roche targeted usage of Mircera in the treatment of anemia of chronic renal failure for the first clinical indication under a biological license application. Indeed, the clinical development program was strikingly similar to that for darbepoetin alfa and differed predominantly in that Roche provides considerably more long term (1 year) clinical exposure data.

Roche has also performed clinical studies of Mircera usage in the treatment of anemia due to cancer chemotherapy. However, that indication (common to all marketed ESAs) is not sought by Roche. Importantly, a clinical study of Mircera usage among approximately 150 patients with non-small cell lung cancer showed a marked increase in the number of deaths among patients receiving Mircera, compared to patients receiving another ESA. The sponsor's exploratory analyses of this study do not suggest that apparent mortality disadvantage was due to imbalances in baseline characteristics and no other analyses (outside of a drug effect) could account for the mortality finding. Instead, the study provides an important safety signal for Mircera usage among cancer patients. The sponsor has not clarified whether additional clinical studies will be pursued in cancer patients.

Brief Regulatory Timeline

- April 18, 2006 - submission of BLA
- June 1, 2006 Filing action, BLA was assigned a standard review
- October 16, 2006 Mid-cycle meeting
- December 4, 2006 Submission of major amendment
- March 16, 2007 Regulatory briefing
- May 17, 2007 PDUFA due date

Clinical Review

The clinical review was performed by Dr. John Lee. Dr. Ruyi He provided Team Leader expertise to the review and a secondary review. I have examined the clinical review and I concur with the major findings and the important comments regarding recommendation for licensure, if the sponsor sufficiently addresses the items described in the FDA complete review letter. Some components of the review are clarified and highlighted below.

Substantial evidence of safety and effectiveness for Mircera was obtained from six confirmatory clinical studies. The primary endpoints in all these studies were assessments of the extent to which Mircera could elevate or maintain blood hemoglobin concentrations, a surrogate marker for the actual clinical benefit of "avoidance of blood transfusion."

a. Efficacy:

As summarized below, Roche provides persuasive evidence of Mircera efficacy both in the "initiation" setting and the "maintenance" setting for the treatment of anemia due to chronic renal failure. All primary endpoints were achieved in a statistically and clinically meaningful manner.

The "initiation" setting refers to clinical studies that assess Mircera effects in anemic patients with chronic renal failure who have never previously been treated with and ESA. Studies 16736 (dialysis patients) and 16738 (patients not receiving dialysis). These are probably the most informative clinical studies in the entire clinical development program since the study databases include patients who are potentially intolerant of ESAs. The primary endpoints in these studies were not comparisons between study groups but statistical tests that the proportion of "responders" to Mircera exceeded 60%. "Responders" were assessed as patients who achieved a 1 g/dL increase in hemoglobin concentration with the achieved hemoglobin > 11 g/dL and avoidance of blood transfusion. Multiple secondary endpoints explored various permutations of changes in blood hemoglobin concentration.

The "maintenance" setting refers to clinical studies that assess Mircera effects in anemic patients with chronic renal failure who are currently receiving an ESA. Hence, the database from these studies is limited to patients who, at study enrollment, are known to be tolerant of ESAs. Since ESAs are so widely used in clinical practice and often initiated early in the development of anemia, recruitment of subjects for maintenance studies is much easier than the recruitment for initiation studies. Hence, maintenance studies account for the vast majority of clinical data in the Mircera database. As summarized below, four studies assessed Mircera effficacy in the hemoglobin maintenance setting. The primary endpoints in these studies was a comparison of the changes (various end of study periods - baseline) in hemoglobin concentration between the study groups using a non-inferiority margin of - 0.75 g/dL for the lower limit of the two-sided 95% confidence interval (this is a reasonable margin since clinical data show that a 0.5 g/dL change in hemoglobin concentration may result from diurnal variation alone).

Table 1. Confirmatory Studies of Mircera Safety and Efficacy

Study	Design Features	Results
"Initiation"		
16736	Mircera vs Epoetin alfa or beta in 181 dialysis patients over 24 week period, IV	Mircera responders: 93% Epoetin responders: 91%
16738	Mircera vs Darbepoetin alfa in 324 non-dialysis patients over 28 week period, SC	Mircera responders: 98% Darbepoetin responders: 96%
"Maintenance"		
16739	Mircera vs Epoetin alfa or beta in 540 dialysis patients over 1 year; IV	Average change in hemoglobin values for Mircera were all < 0.1 g/dL; all comparator p values < 0.001
16740	Mircera vs Epoetin alfa or beta in 474 dialysis patients over 1 year; SC	
17283	Mircera vs Darbepoetin alfa in 249 dialysis patients over 1 year; IV	
17284	Mircera prefilled syringes vs Epoetin alfa or beta in 256 dialysis patients over 36 weeks	

Of special note from the efficacy analyses was that, in the correction studies, the increase in hemoglobin concentration was delayed for Mircera patients, compared to patients receiving other ESAs (median time to response was 57 and 43 days in the Mircera groups and 31 days in the Epoetin group and 29 days in the Darbepoetin group).

b. Safety:

Overall, 1789 patients received Mircera in phase 2 or 3 clinical studies, including 1144 patients who received Mircera for at least one year and 95 patients who received Mircera for at least two years. This safety database is consistent with prior expectations for ESAs. For example, the safety database for Darbepoetin included 1598 patients with 185 exposed for at least one year.

Comparisons between Mircera and other ESAs are based upon a database of 1789 Mircera patients (84% on hemodialysis) and 948 reference ESA patients (80% on hemodialysis). Since hemodialysis patients are generally regarded as clinically more vulnerable to medical problems, the slight imbalance in hemodialysis representation (more hemodialysis patients receiving Mircera) may have impacted some of the imbalances detected in safety analyses.

The most notable findings from the Mircera safety database review were the following:

-Sudden deaths:

Overall, mortality rates were similar between patients receiving Mircera (10%) and other ESAs (11%), based upon cumulative safety information supplied in the major amendment. However, the sponsor reported in the original submission that deaths recorded as "sudden death" were different between study group with 9 sudden deaths in the Mircera group but none in the comparator ESA groups. Information supplied in the major amendment included "extended follow-up" from extension studies (in which subjects were continued on randomized/assigned treatment regimens). In this "extended follow-up, the cumulative total number of sudden deaths was 14 (Mircera) vs 5 (reference ESA).

As Dr. Lee noted in his review, no unique features appear to implicate Mircera in the occurrence of sudden deaths and it is notable that no sudden deaths were reported in the two "initiation" studies (the studies perhaps most important to assessing safety).

Notably, preclinical studies did not suggest QT abnormalities in animals and the sponsor's clinical QT study also did not disclose abnormalities although the study lacked the "positive control" and was regarded as not fulfilling the expectation of a "thorough" QT clinical study. However, it is important to note that a "thorough" QT clinical study performed among healthy subjects is generally intended to assess the effects of small molecular weight products (not biologic products like Mircera) and may have very little applicability to subjects in renal failure.

Together, the long term follow-up data, nonclinical data and overall mortality findings sufficiently resolve the initial concerns regarding an possible increase in sudden deaths among Mircera patients, compared to patients receiving other ESAs.

-C-reactive protein concern:

As previously noted, Roche excluded approximately 3% of potentially eligible subjects solely because of elevated C-reactive protein (CRP) concentrations. This is an important consideration since patients with elevated CRP (> 10 mg/L) have been identified as especially vulnerable to toxicity from ESAs. This concern was discussed at an internal FDA regulatory briefing where the consensus was that active CRP screening did not importantly compromise the Mircera safety database since:

-the upper limit (30 mg/L) was relatively high
-a small number of subjects were excluded (~ 3%)

The sponsor also supplied additional exploratory analyses that showed that, when the entire database is subdivided into quartiles according to baseline CRP values, all risk ratios (Mircera compared to ESA) for important safety outcomes within all quartiles either favored Mircera or included 1 (showing similar risks for Mircera to ESA).

Together, the exploratory analyses and supportive data support the reasonableness of the submitted safety database. Nevertheless, a post-marketing commitment is proposed to address this subject.

-Hemorrhage:

Overall, the rate of serious adverse events was numerically lower for Mircera patients (37%) compared to reference ESAs (40%). However, serious gastrointestinal hemorrhage rates were higher for Mircera patients (1.2% versus 0.2%). Overall serious bleeding events were also slightly higher for Mircera patients (5.2% versus 4%). As Dr. He notes in his review, co-medications did not appear to account for the slightly higher hemorrhage rate among Mircera patients.

The hemorrhage findings will be noted in the product label to suggest a possible risk for Mircera but given the multiplicity of safety endpoint assessments and the slight imbalance in the proportion of hemodialysis patients as well as no preclinical data to support a hemorrhage risk for Mircera, the actual risk for hemorrhage with Mircera appears only slightly increased or similar to that for other ESAs.

-Thrombocytopenia

The laboratory data show that most patients exposed to Mircera experience a small decrease in platelet counts, with the lowered count still within the range of "normal." Additionally, 7.5% of Mircera patients but only 4.4% of reference ESA patients have a platelet count at any time of less than 100 x 109/L. It is notable that this imbalance also mirrors the imbalance in the baseline distribution of hemodialysis patients between the two study groups (Mircera versus ESA). Of note also is that, with respect to the two "initiation" clinical studies and comparisons between Mircera and another ESA, decreases in platelet counts following Mircera exposure were seen only in the patients on hemodialysis (Study 16738), not in the non-hemodialysis clinical study (study 16736). In the non-hemodialysis study, both Mircera and the comparator ESA slightly decreased platelet counts.

Together, the clinical data suggest that Mircera may lower platelet counts modestly more than other ESAs and the product label will indicate this lowering although the clinical data do not indicate clinically important risks related to the platelet alteration.

c. Cancer study:

Roche performed Study NH19960 study in Europe to provide exploratory clinical data —— In this study, 153 anemic patients with non-small cell lung cancer were randomized 1:1:1:1 to 1 of 3 Mircera dose cohorts or Darbepoietin alfa. The study was suspended by the Data Safety Monitoring Board on March 26, 2007 due to excessive deaths in the Mircera group. Roche submitted an interim study report (data collection and data clean-up is continuing) to the license application along with interim electronic datasets.

Overall, deaths occurred among 29/114 (25%) Mircera-exposed subjects and 4/39 (10%) Darbepoetin alfa-exposed subjects. These findings included 2 "sudden deaths" in the Mircera group but no "sudden deaths" in the Darbepoietin group. A dose-response effect was not evident for mortality in the Mircera dose cohorts, as follows:

Mircera cohort	deaths
6.3 mcg/kg	7/38
9.0 mcg/kg	13/38
12 mcg/kg	9/38

Roche performed logistical regression modeling to attempt to identify any baseline factors that could contribute to the excessive mortality in the Mircera group; no covariates could be identified as accounting for the mortality imbalance. The study groups did not differ in rates of thromboembolic events or in the rate of "progressive disease" determination by the site investigators.

Together, the cancer study provides important evidence that, at least in non-small cell lung cancer patients, Mircera treatment may increase mortality. Hence, the product label will describe this finding. Additionally, the sponsor will be requested to address the potential for misinformation related to extensive "class labeling" of cancer risks in the Mircera label. One concern for labeling is that, given Mircera's dosing convenience, and the clinical perception that all ESAs perform the same as a class, Mircera may mistakingly be assumed as a reasonable alternative for some cancer patients.

d. Risk Management Plan:

Roche supplied a document referred to as a "Risk Management Plan" with the original submission of the license application. However, this document supplies only a summary description of the product labeling (warnings, precautions, adverse reactions) and notes that routine pharmacovigilance procedures will be performed along with focused investigation of potential cases of pure red cell aplasia (including performance of anti-erythropoietin antibody assays by Roche). This "Risk Management Plan" is essentially identical to that performed by sponsors of other ESAs and is reasonable.

Statistical Review:

The statistical review was performed by Dr. Richard Chen, lead statistician for the BLA. The findings from her review were secondarily reviewed by Dr. Jyoti Zalkikar, Biometric Team Leader.

I have read Dr. Chen's statistical review report and I concur with his statistical analyses, findings and comments that the sponsor has provided persuasive evidence of Mircera efficacy and his notation that safety considerations are especially important for the labeling of ESAs, including Mircera.

Clinical Pharmacology and Biopharmaceuticals (OCPB) Review

The clinical pharmacology and biopharmaceutical review was performed by Dr. Jang-Ik Lee. The findings from the review were secondarily reviewed by Dr. Hong Zhao, Team Leader. Dr. Pravin Jadhav provided a phaarmacometrics review.

I have read the clinical pharmacology and biopharmaceuticals review report and I concur with the observations and comments. Dr. Lee actively participated in labeling discussions regarding Mircera and I concur with his final pharmacology findings (as incorporated into the Mircera label). These findings note that the half life of Mircera, following IV administration, was approximately 134 hours (average; approximately twice that of Darbepoietin alfa). The terminal half life was an average of 139 hours. Hemodialysis had no effect upon Mircera clearance (based upon comparisons between non-dialysis patients and hemodialysis patients)

Chemistry and Microbiology

The Chemistry review was performed mainly by Drs. Dov Pluznik, Ingrid Markovic, Serge Beaucage and Lai Xu. Together, the chemistry reviewers cite the need for additional information prior to licensure of Mircera. These requests are described within the complete review letter.

An assay for immunogenicity detection was reviewed by Dr. Susan Kirshner who has requested additional information from Roche and has supplied draft text for the product label.

Facility review and site inspectional findings support Mircera licensure.

Pharamcology/Toxicology

The pharmacology/toxicology review was performed by Dr. Yanli Ouyang and was secondarily reviewed by Dr. Adebayo Laniyonu.

I have read the pharmacology/toxicology recommendations and I concur with the observations that the important animal toxicity findings relate to exaggerated hematopoiesis (an expected outcome). The reviewers noted that the submitted pharmacology/toxicology data support the licensure for Mircera with no need for additional nonclinical studies.

Pediatric Safety and Efficacy

As previously noted, the sponsor is to collect pediatric usage information in the post-marketing period from a previously proposed pediatric study of patients over 5 years of age.

Proposed Labeling

During the review cycle, FDA and the sponsor worked to develop the product label. However, additional information is necessary from the sponsor (as noted in the complete review letter) in order to finalize labeling. Given the date of the original submission, the sponsor's proposed label is not in PLR format and the sponsor will be requested to supply PLR formatted labeling. The proposed labeling also includes Patient labeling which will be reviewed in consort with the final proposed labeling. Ms. Sharon Mills, BS from the Division of Surveillance, Research and Communications Support Division provided a consult upon the Patient labeling.

Office of Drug Safety/Division of Medication Errors and Technical Support (ODS/DMETS/)

Nora Roselle, PharmD, provided a DMETS review of the proposed product label, container label and proprietary name. The team provided recommendations for altered colors on package labeling which will be addressed in the final review of the carton and container labels. The sponsor has been informed of the necessary changes and has supplied a response.

Division of Scientific Investigation (DSI)

Ms. Dianne Tesch provided a report of the FDA inspectional findings at selected clinical sites. The secondary reviewer on his report was Dr. Leslie Ball. The inspectors found the clinical data reliable. Only minor protocol violations were detected. I have read the report and concur with the findings.

Financial Disclosure

As noted in Dr. John Lee's review, the sponsor has submitted required financial disclosure information and the information is acceptable.

Interdisciplinary Review Team for QT Studies
Response to a Request for Consultation: QT Study Review

BLA	#125164/0
Brand Name	MIRCERA
Generic Name	Pegserepoetin alfa
Sponsor	Hofmann La Roche
Indication	Anemia associated with chronic kidney disease
Dosage Form	Injection (IV or SC)
Therapeutic Dose	Starting dose 0.6 µg/kg body weight once Q2 weeks
Duration of Therapeutic Use	Chronic
Maximum Tolerated Dose	Not reported
Application Submission Date	April 18, 2006
Review Classification	BLA review
Date Consult Received	August 3, 2006
Date Consult Due	November 3, 2006
Clinical Division	Division of Medical Imaging and Hematology Products (HFD-160)
PDUFA Date	February 17, 2007

Reviewers: Shari Targum, M.D. 11/20/06

Joanne Zhang, Ph.D. 11/20/2006

Christine Garnett, Pharm.D. 20 NOV 2006

Through: Norman Stockbridge, M.D., Ph.D.

1.0 RECOMMENDATION

1. We are unable to comment on the question of minimum titration.
2. From our perspective, the Sponsor's QT study is inadequate for making a determination of the QT effect (see Section 2.0 for further explanation). Depending on your division's risk-benefit analysis, you might consider requesting a well-designed QT study which would include a positive control.

2.0 SUMMARY OF FINDINGS

1. Limitations to the Sponsor's QT study include the following:
    a. The study lacks a positive control arm; therefore, assay sensitivity cannot be determined.
    b. 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.

c. From the mean QTc results, we note a large standard deviation, implying a sizable degree of variability in ΔQTc. A large variability in the QT/QTc data is also suggested in Figures 10 and 11 (see review).

d. 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.

e. Since ECGs were not available to us in the ECG warehouse, we are unable to verify that the QT measurements were made appropriately.

3.0 GOAL OF THE REVIEW

We have been asked by the review division if the proposal for minimum titration is acceptable. We are asked to evaluate the acceptability (negative/positive) of the Sponsor's QT Study.

4.0 BACKGROUND

4.1. Indication: Treatment of anemia associated with chronic kidney disease.

4.2. Drug Class: Continuous erythropoietin receptor activator

4.3. Regulatory Classification: A BLA for this drug has been submitted and is currently under review in the Division of Medical Imaging and Hematology.

4.4. Market approval status

This drug is not approved for use for any indication in the United States, nor is approved for use for any indication in any other country.

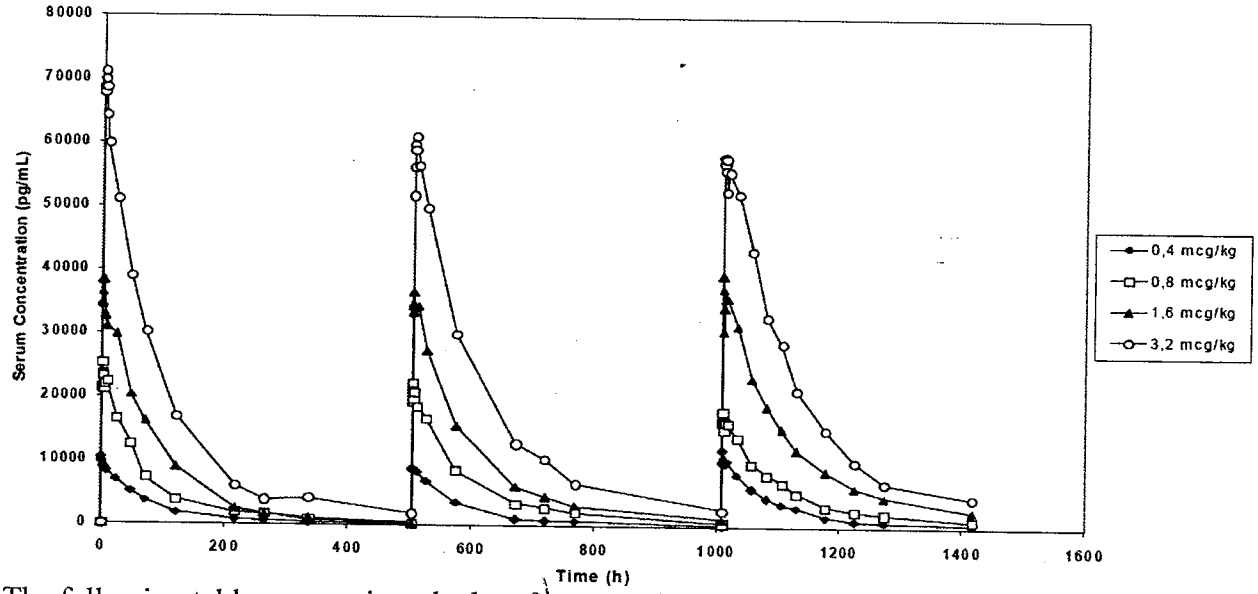
5.0 DRUG INFORMATION

5.1. Preclinical Information: Not reviewed

5.2. Clinical Pharmacology

The following figure illustrates the pharmacokinetics of pegserepoetin alfa following multiple IV doses to healthy subjects on Days 1, 22, and 43

Figure 1. Concentration-time profile for pegserepoetin alfa



The following table summarizes the key features of pegserepoetin alfa clinical pharmacology.

Table 1. Highlights of Clinical Pharmacology

Therapeutic dose	0.6 µg/kg IV or SC every 2 weeks initially. adjusted based on hemoglobin response to 180 mg per subject or greater	
Maximum dose tested in Clinical Pharmacology studies	Single Dose	3.2 µg/kg
	Multiple Dose	3.2 µg/kg every 2 weeks for 6 weeks
Exposures Achieved	3.2 µg/kg IV every 3 weeks	Cmax: 69.7 ± 16.7 ng/mL on Day 43
	3.2 µg/kg SC every 2 weeks	Cmax: 15.4 ± 6.6 ng/mL on Day 43
Maximum tolerated dose	Not reported	
Principal adverse events	Hypertension	
Absorption	Absolute Bioavailability	F = 50 - 60%
	Tmax	For SC: median 72 hours (range, 12-216 hours) For IV, values range from 0.25 to 5 hours
Distribution	V_{ss}	67 ± 28 mL/kg
	V_z/F	not determined, estimated to be 120 mL/kg
	% bound	Not applicable
Elimination	Route	•proteolytic degradation
	Terminal t½	•Parent: 139 ± 67 hours

	CL/F	0.90 ± 0.42 mL/hr
	Accumulation: $\frac{AUC_{2wk\ (Day\ 43)}}{AUC_{2wk\ (Day\ 1)}}$	•Parent: 1.7
Range of linear PK	Dose proportional increases in AUC: 0.4 - 1.6 µg/kg	
Intrinsic Factors	Age	No studies conducted
	Sex	No studies conducted
	Race	No difference between Caucasians and Japanese
Extrinsic Factors	Drug interactions	•No *in vivo* drug interaction studies •not a CYP substrate, inhibitor, inducer
	Food Effects	•not studied, not expected to be
High Clinical Exposure scenario	Not known	

6.0. SPONSOR'S SUBMISSION

6.1. Overview:

The Sponsor submitted a clinical study report of a double-blind, placebo-controlled (no positive control) crossover study in healthy volunteers (see Section 6.2.1) and a summary report of ECG results from five protocols (BP16198B, BP16239B, BP16346D, WP16383E, and WP16422D).

No ECGs related to this BLA were available in the ECG warehouse.

6.2. Study Design(s)

6.2.1. Phase 1 Safety Study

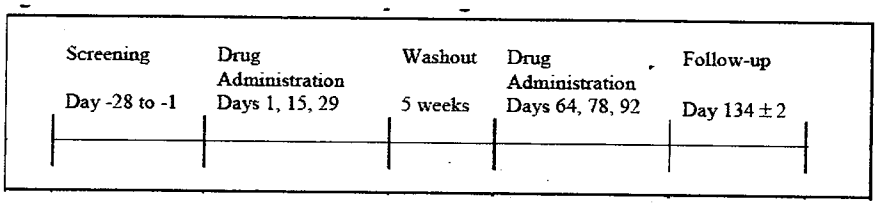
6.2.1.1. Title: A double-blind, placebo-controlled, randomized, crossover study to assess the effect of RO 050-3821 on QT interval after multiple doses in healthy volunteers (Study dates: July 7-November 27, 2003).

6.2.1.2. Protocol Number: BP17278

6.2.1.3. Primary Objective: To investigate the effect of RO 050-3821 on QT prolongation in healthy volunteers; the secondary objective was to investigate the relationship between QT prolongation and the concentration of RO 050-3821 in serum of healthy volunteers.

6.2.1.4. Description: This was a single-center, randomized, double-blind, placebo-controlled, two period crossover, with an interval of 5 weeks between the two treatment periods and a follow-up of 6 weeks after the last dose.

Figure 2. Study Design



6.2.1.4.1. Justification for design provided: The sponsor did not justify choice of design.

6.2.1.5 Population: A total of 40 healthy volunteers, 18-65 years old, were randomized to receive three doses of each treatment.

6.2.1.6. Treatment groups: RO 050-3821 3.2 µg/kg IV x 3 doses with a two week interval between doses; and placebo IV x 3 doses with a two week interval between doses. There was no positive control (moxifloxacin) arm.

6.2.1.6.1. Justification for dose provided

The sponsor selected a dose of 3.2 µg/kg for this study because it is the highest possible dose to be given to healthy volunteers.

6.2.1.6.2. Instructions with regard to meals

Subjects received a standard breakfast 30 minutes prior to dosing on day -1 and an identical breakfast on all dosing days. The standard breakfast was to provide 607 Kcal and 24% fat.

6.2.1.7. Study Schedule and Timing of Samples

Table 3 Detailed Schedule of Assessments (per Hour)

Day	-1	-1	-1	-1	-1	-1	1	1	1	1	1	8	11	15	15	15	15	15	22
Hour	0	5min	0.25	0.5	1	12	0	5min	0.25	0.5	1			0	5min	0.25	0.5	1	
Drug[b]							✓							✓					
ECG	✓[a]	✓[a]	✓[a]	✓[a]	✓[a]	✓[a]	✓[a]	✓	✓	✓	✓			✓[a]	✓	✓	✓	✓	
PK							✓[a]	✓	✓	✓	✓			✓[a]	✓	✓	✓	✓	
PD[c]	✓						✓[a]					✓	✓	✓[a]					✓
Elec[d]	✓				✓		✓				✓			✓				✓	

Day	25	29	29	29	29	29	29	29	29	30	31	32	33	34	36	38	40	43	50	57
Hour		0	5min	0.25	0.5	1	3	6	12	24	48	72	96	120	168	216	264	336	504	672
Drug[b]		✓																		
ECG		✓[a]	✓	✓	✓	✓			✓	✓	✓				✓					
PK		✓[a]	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓		
PD[c]	✓	✓[a]									✓		✓		✓	✓	✓	✓	✓	✓
Elec[d]		✓				✓														

Day	63	63	63	63	63	63	64	64	64	64	64	71	74	78	78	78	78	78	85
Hour	0	5min	0.25	0.5	1	12	0	5min	0.25	0.5	1			0	5min	0.25	0.5	1	
Drug[b]							✓							✓					
ECG	✓[a]	✓[a]	✓[a]	✓[a]	✓[a]	✓[a]	✓[a]	✓	✓	✓	✓			✓[a]	✓	✓	✓	✓	
PK							✓[a]	✓	✓	✓	✓			✓[a]	✓	✓	✓	✓	
PD[c]							✓[a]					✓	✓	✓[a]					✓
Elec[d]	✓				✓		✓				✓			✓				✓	

Day	88	92	92	92	92	92	92	92	92	93	94	95	96	97	99	101	103	106	113	120
Hour		0	5min	0.25	0.5	1	3	6	12	24	48	72	96	120	168	216	264	336	504	672
Drug[b]		✓																		
ECG		✓[a]	✓	✓	✓	✓			✓	✓	✓				✓					
PK		✓[a]	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓		
PD[c]	✓	✓[a]									✓		✓		✓	✓	✓	✓	✓	✓
Elec[d]		✓				✓														

a pre-dose

b drug administration 3.2 µg/kg RO0503821 or matching placebo administered intravenously

c includes absolute reticulocyte count, hemoglobin, hematocrit, red blood cells, serum ferritin

d includes calcium, magnesium, potassium

e 3 ECG's per time point were recorded, 1 two minutes before the scheduled time, 1 at the scheduled time and 1 two minutes after the scheduled time

All ECGs were collected in triplicate.

6.2.1.8. QT Measurement

A 12-lead ECG was recorded for all subjects at screening, Day -1, during the study period (see Section 6.2.1.7, above) and at follow-up: For the baseline assessments (Day -1 and Day 63), three ECGs (measured two minutes apart) were recorded for each time point. During the study, a total of 76 ECGs were recorded for each subject. ECGs were read centrally by eRT; manual measurements were performed using a set of graphic tools. The QT interval was measured from the onset of the QRS complex to the end of the T-wave. Interval duration measurements were transferred to the data management system following a quality control process (5% of all measurements and 100% of all outliers). It is not stated which lead(s) were used for QT measurements, or how many cardiologists participated in ECG readings.

6.2.1.9. Controls: The Sponsor used only a placebo control. There was no positive control.

6.2.1.10. Blinding: All treatments were double-blinded.

6.2.1.11. Baseline: The Sponsor collected 6 baseline QTc measurements on the day prior to initiating dosing (Day -1) of the study for each treatment. The timing of baseline QTc was predose, 5, 15, 30, 60, and 144 minutes.

6.2.1.12. Endpoints:

- The study specific QTc interval (QTcS) was considered as the primary study variable. The interval was derived from all drug-free ECG data using a linear mixed effects model.
- The primary analysis is the time-matched difference between on-treatment and baseline QTcS values at Tmax after the third dose.

6.2.1.13. Pharmacokinetic assessments: PK parameters calculated were AUC0-14d, Cmax, T1/2, Tmax, AUC0-∞, CL and Vd.

Reviewer Comments:

1. The analysis of the primary endpoint is not the recommended method as described in ICH E14.

6.2.1.14. Statistics: The purpose of the study BP17278 was to assess the effect of RO0503821 on QT/QTc prolongation. The statistical analysis was divided into a central tendency analysis and a categorical analysis. For the central tendency analysis, the time-matched difference between on-treatment and baseline QTcS values (TMΔQTcS) at population tmax was the primary study variable and was analyzed with the following ANOVA model (with untransformed ΔQTcS):

$y_{ijklm} = \mu + \alpha_i + s_{j(i)} + \tau_k + \pi_l + \varepsilon_{ijkl}$ (i = f,m; j=1,...,N; k=active , Placebo; l=1,2),

where μ denotes the general mean of the untransformed variable (ΔQTcS), α_i the gender effect, s_j the effect of subject j (nested in gender), τ_k the direct effect of treatment k, π_l the effect of period l ,ε_{ijkl} the random deviation and N the number of subjects included into the analysis. The random deviations were assumed to be independently normally distributed with a zero mean and a common variance σ^2.

For the categorical analysis, contingency tables with time-matched maximum change from baseline and absolute values for QT/QTc intervals were created.

6.2.2. Research Report 1018021: Summary Report of ECG results

The Sponsor submitted a report of ECG analyses from five phase I clinical studies which were not thorough QT/QTc studies. Four of them were ascending dose studies (two single-blind, two open labels) and one was an open crossover with 4 treatment period study.

The doses used in these five studies were not higher than the dose used in the double-blind study reviewed in Section 6.2.1.

Table 2. Listing of five studies with ECG data

Protocol No.	Study Design	Route	Regimen	Dose (μg/kg)
BP16198B	Single-blind, placebo-controlled, ascending dose	SC	Single dose	0, 0.1, 0.2, 0.4, 0.8, 1.6, 2.4, 3.2
		SC	Two equal doses 2 weeks apart	0, 2.0
BP16239B	Single-blind, placebo-controlled, ascending dose	IV	Single dose	0, 0.4, 0.8, 1.6, 3.2
BP16346D	Open, placebo-controlled, parallel-group, ascending dose	IV	Three equal doses 3 weeks apart	0, 0.4, 0.8, 1.6, 3.2
WP16383E	Open crossover with 4 treatment periods	IV	One dose per period	0.8
		SC	One dose per period	0.8, 1.6, 3.2
WP16422D	Open, placebo-controlled, parallel-group, ascending dose	SC	Four equal doses 2 weeks apart	0, 0.4, 0.8, 1.6, 3.2

In addition, the ECG timing differed between the above five studies. There are no PK data or QT-concentration analyses included in this study report.

6.3. Results

The following figures highlight available data.

Figure 3. Mean ± SD of QTcS measured after administration of the third dose of RO 050-3821 and placebo.

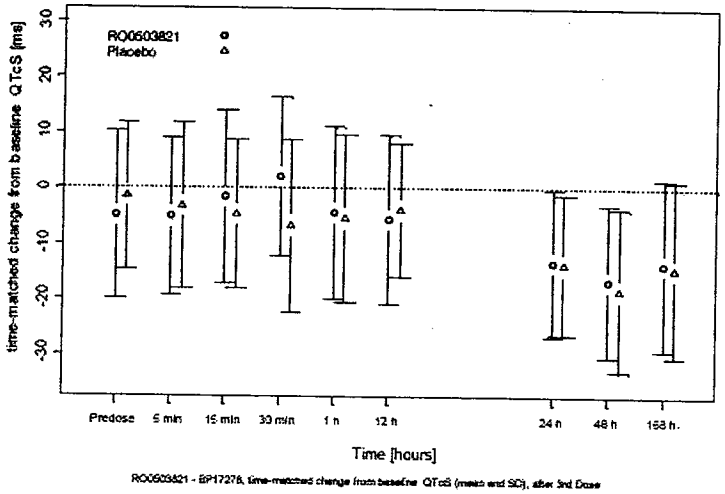
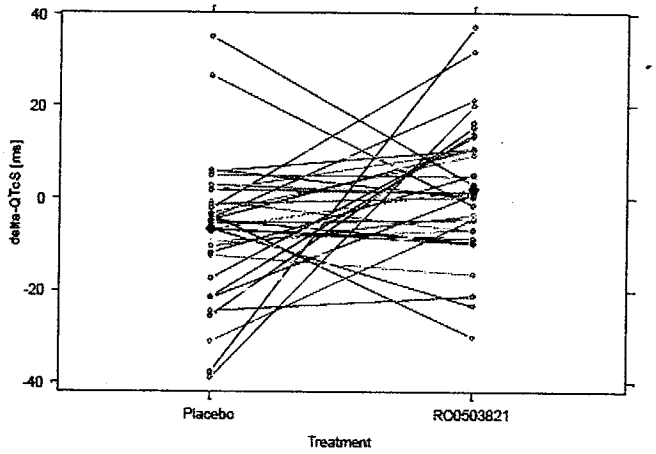


Figure 4. Stick Plot for baseline-adjusted QTcS measured after administration of the third dose of RO 050-3821 and placebo.



Open circles are the individual values and the lines connect the data from the same subject. Closed diamonds give the mean values of the treatment.

6.3.1. Primary Analysis

The results for the ANOVA of baseline-adjusted QTcS at the population Tmax (1 h) after the third dose is shown in the following table. The difference between means was 0.860 ms with a 95% confidence interval of -4.80 to 6.60 ms.

Table 3. ANOVA results for time-matched difference between on-treatment and baseline QTcS values at Tmax (1 h) following the third dose of RO 050-3821.

Factor	numDF	denDF	F-value	p-value
Sex	1	36	3.94	0.055
Treatment	1	35	0.06	0.80
Period	1	35	3.88	0.057

Based on the sponsor's study report, for study BP17278, it appears that, at some time points, the 90% upper bound of the mean difference of the drug and placebo after baseline adjustment are greater than 10 msec.

We performed our own time-matched analysis. First, each person's QTc values were subtracted from his/her baseline values in a time-matched fashion for both placebo and the drug arms. Then the difference of the drug and placebo after baseline adjustment was computed. Finally, the 90% upper bound was calculated based on the mean (average all subjects) difference obtained in step 2. Our analysis results are provided in the following tables.

Table 4. Reviewer Analysis: QTcFridericia

QTc Fridericia

Day within treatment period	Sample Schedule in Minutes	N	Mean	Std Dev	Lower 90% CL for Mean	Upper 90% CL for Mean
1	5	36	-2.49	22.33	-8.78	3.80
1	15	37	0.73	20.64	-5.00	6.46
1	30	38	1.69	17.94	-3.22	6.60
1	60	39	4.52	18.78	-0.55	9.59
15	5	38	-0.65	21.99	-6.67	5.37
15	15	37	2.46	24.74	-4.41	9.33
15	30	38	2.8	24.57	-3.93	9.52
15	60	38	1.95	25.63	-5.06	8.97
29	5	37	-4.68	23.39	-11.17	1.81
29	15	36	0.79	19.94	-4.83	6.40
29	30	38	7.57	24.53	0.86	14.29
29	60	38	1.58	23.24	-4.78	7.94
29	720	38	-3.06	21.75	-9.01	2.89

Table 5. Reviewer Analysis: QTc via the sponsor's linear model

QTc by the sponsor's linear model

Day within treatment period	Sample Schedule in Minutes	N	Mean	Std Dev	Lower 90% CL for Mean	Upper 90% CL for Mean
1	5	36	-0.19	20.94	-6.09	5.71
1	15	37	-1.77	24.09	-8.45	4.92
1	30	38	0.38	21.65	-5.55	6.30
1	60	39	-1.03	16.09	-5.38	3.31
15	5	38	1.9	30.51	-6.45	10.25
15	15	37	5.72	31.78	-3.10	14.54
15	30	38	0.72	29.67	-7.40	8.84
15	60	38	-0.19	32.98	-9.22	8.83
29	5	37	-1.06	27.86	-8.80	6.67
29	15	36	4.55	26.28	-2.85	11.95
29	30	38	9.71	25.83	2.65	16.78
29	60	38	-3.98	25.3	-10.91	2.94
29	720	38	-1.11	26.88	-8.46	6.25

Table 6. Reviewer Analysis: Raw QT

		Raw QT				
Day within treatment period	Sample Schedule in Minutes	N	Mean	Std Dev	Lower 90% CL for Mean	Upper 90% CL for Mean
1	5	36	-1.78	19.65	-7.31	3.76
1	15	37	0.21	20.29	-5.42	5.84
1	30	38	1.12	17.09	-3.56	5.80
1	60	39	3	16.01	-1.32	7.32
15	5	38	0.43	23.15	-5.91	6.76
15	15	37	3.4	25.24	-3.60	10.41
15	30	38	2.31	24.09	-4.29	8.90
15	60	38	1.41	26.04	-5.72	8.54
29	5	37	-3.74	22.53	-10.00	2.51
29	15	36	1.45	19.8	-4.12	7.03
29	30	38	7.76	22.62	1.57	13.95
29	60	38	0.23	22.04	-5.80	6.26
29	720	38	-1.81	20.75	-7.48	3.87

6.3.2. Categorical Analysis:

No subject experienced a ΔQTc (any correction method) ≥ 60 msec from baseline. There appeared to be no increase in ΔQTc 30-60 msec with active drug vs. placebo (source: Table 8, study report, not shown).

With respect to absolute QTc values, there were no subjects with QTc/QT values above 500 msec.

For QTcS and QTcF, there was no subject considered in the "prolonged" category.

6.3.3. Other ECG analyses

There were no subjects reported to have an abnormal U-wave in this study. There were no patterns of T-wave abnormalities on drug (and not on placebo).

6.3.4. Exposure-Response Analysis

6.3.4.1. PK Analysis

The mean concentration of RO 050-3821 at pre-dose (3.29 ng/mL) was similar to that at 14 days (3.88 ng/mL). This result confirms that the pharmacokinetic steady-state was reached on day 29 before the third administration, which is consistent with a mean half-life of 74 h.

Figure 5. Mean time course of RO 050-3821 after the 1st, 2nd, and 3rd doses. Following the first and second administrations of RO 050-3821, samples for pharmacokinetic analysis were taken up to 1 h post-dose.

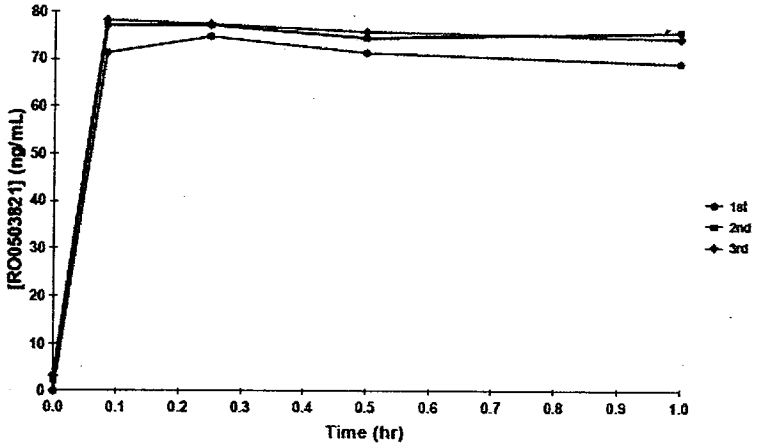
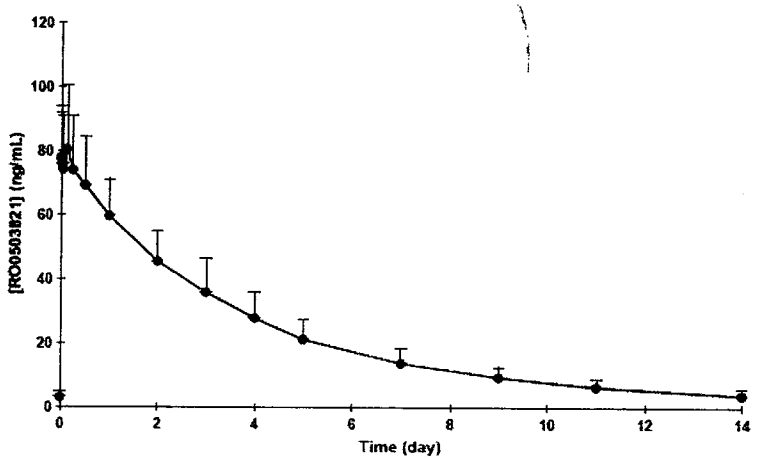


Figure 6. Mean time course of RO 050-3821 after the 3rd dose. Samples were taken up to 14 days post-dose.



The sponsor stated that peak concentrations of RO 050-3821 were higher then the expected values at therapeutic doses in patients. In anemic patients with multiple myeloma, the mean C_{max} value was approximately 26 ng/mL after doses of 4.2 µg/kg every three weeks.

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Table 7. Mean PK Parameters Following the Third Dose

	$t_{1/2}$ (h)	t_{max} (h)	C_{max} (ng/mL)	AUC_{inf} (h*ng/mL)	$AUC_{0\text{-}14days}$ (h*ng/mL)	CL (mL/h/kg)
N	39	39	39	39	39	39
Mean	74.1	2.12	88.6	7788	7348	0.478
SD	16.5	2.58	17.9	1723	1553	0.249
SE	2.64	0.413	2.87	276	249	0.0399
Min	18.4	0.08	51.3	1644	1689	0.301
Median	74.6	1.00	88.7	8124	7759	0.412
Max	97.5	12.00	119	11357	10619	1.89
CV%	22.3	121.4	20.3	22.1	21.13	52.1

6.3.4.2. Concentration-QTc Analysis

The sponsor did not conduct a concentration-QTc analysis.

7.0. REVIEWERS' ASSESSMENT

7.1. Analysis of Five Phase I Studies

There are limitations to the interpretation of the results of the five phase I studies. Those studies were not performed with the rigorous ECG acquisition and analysis that is characteristic of a thorough QT study.

7.2. Concentration-QTc Analysis

Exposure-response analysis was conducted for RO 050-3821 to assess its effect on QTc interval. The pharmacokinetic model (individual post-hoc model estimates) was used to drive concentration-QTc modeling to ensure use of all QT measurements (sequential modeling).

Appendix 8.1 includes codes used for pharmacokinetic and pharmacodynamic modeling.

7.2.1. Pharmacokinetic Modeling

A one compartment pharmacokinetic model (model 1) described the concentration-time data. Figure 8 shows the goodness of fit plots and Table 8 lists the pharmacokinetic model parameters.

Figure 9 illustrates the relationship between model parameters and available patient specific covariates. The one-compartment model fits data well; however, there is an effect of body weight on clearance (CL) and volume of distribution (V). Including these covariates did not improve the model fit and were, therefore, not included in the model. In addition, the sponsor's pharmacokinetic model from a phase II study (report 101359) was also attempted, however, none of the models improved the fit to the data. The base was used to obtain individual predicted concentrations for the pharmacodynamic model.

Table 8. Pharmacokinetic model parameters (estimate ± SE%)

	Base model
Objective function value	4880.1
CL (L/hr)	0.034 ± 4.9
IIV CL (%)	29 ±40.7
V (L)	3.41 ±3.1
IIV V (%)	18 ±20.5
Residual variability	
Additive (ng/mL)	0.55 ±25.6
Proportional (%)	15.7 ±12.8

7.2.2. Pharmacodynamic Modeling

The sponsor provided data using three methods of QT-RR correction. The study specific correction (QTcS) was selected based on prior experience of experts in this area. Figure 10 represents relationship between QT interval and RR interval (mean of triplicate measurements) during placebo treated period. Figure 11 represents relationship between QTcS interval and RR interval (mean of triplicate measurements) during placebo treated period. The use of study-specific correction adequately accounts for the relationship between QT and RR interval.

Figure 12 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 13 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 apparent differences in time course of dQTcS on placebo and on RO 050-3821.

Figure 14 represents relationship between time-matched placebo corrected dQTcS (ddQTcS) and concentration of RO 050-3821. A linear pharmacodynamic model with the following parameterization was attempted.

$$ddQTcS_{ij} = Intercept_i + Slope_i \bullet Concentration_{ij}$$

Where the slope and intercept for subject i were estimated was concentrations available at j sampling points.

Figure 14 represents relationship between ddQTcS and observed RO 050-3821 concentration. The slope and intercept estimates are included in Table 9 below.

Table 9. Pharmacodynamic model parameters

	Estimate	Upper limit 90% CL
Slope	0.02	0.057
Intercept	-1.92	1.01

Based on these results, at mean Cmax of 90 ng/mL after 3.2 µg/kg dose, the expected prolongation in QT interval would be 1.8 msec with an upper one-sided 95% confidence interval of 5.1 msec.

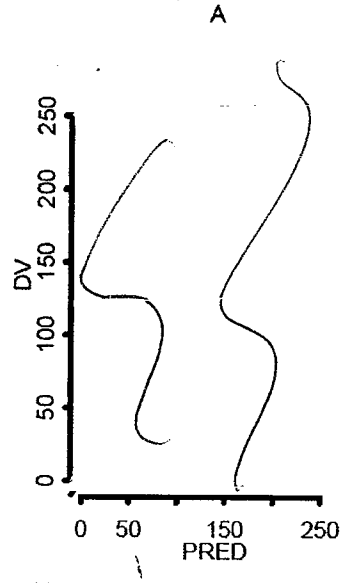
7.2.3. PK-PD Modeling Notes

1. Subject 12 data were not included in the analysis due to unavailability of the placebo data.
2. To calculate dQTcS measure, the baseline was time matched to the nearest minute. However, if the matching baseline measurement was not available the mean baseline for day -1 was used.
3. The clinical visit at day 63 was supposed to be a baseline measurement visit for period 2 but due to apparent carry over effect, the baseline at day -1 was used for period 2 as well. The data for day 63 were thus not included.
4. To calculate ddQTcS measure. If the matching placebo data are not available, the drug data were not used in the analyses and vice versa. A total of 14 out of 848 records were thus deleted.
5. The clinical visits labeled as (1) BACK OF BOOK (2) SCREENING and (3) FOLLOW-UP were not included in the analyses.

7.2.4. Adequacy of Dose

In the current study, plasma concentrations as high as 140 ng/mL were observed. However, in phase III studies (pooled concentration data from BA16736, BA16739 and BA16740), there were concentrations higher than 140 ng/mL, as shown in the following figure. However, the number of patients above 140 ng/mL is a very low fraction and there are no drug interactions of concern that could lead to consistently higher (>140) therapeutic levels.

Figure 7. Concentrations greater than 140 ng/mL were observed in the phase 3 studies (DV- Observed RO 050-3821 concentration in ng/mL and PRED- is model predicted RO 050-3821 concentration in ng/mL).



7.2.5. Adequacy of Sampling Times

In this study, Tmax values following IV administration of RO050-3821 range from 0.08 to 12 hours following the third dose of drug (Non-compartmental analysis). Figure 15 illustrates observed and model (population and individual) predicted concentration time profiles. Clearly, concentrations do not seem to rise after IV administration. However, due to long plasma terminal half life there is little or no difference on concentration achieved until 12 hrs. Therefore, a less precise bioanalytical method (inter-batch imprecision ~10-30%) could cause the Tmax to appear much after the IV administration.

Therefore, sampling times (more frequent immediately after dosing and less frequent at later intervals) were adequate to capture initial high concentrations as well as the spectrum of concentrations that could be achieved by the administration of RO 050-3821.

7.2.6. Adequacy of QT Correction Factor

As described earlier, Figure 10 represents relationship between QT interval and RR interval (mean of triplicate measurements) during placebo treated period. Figure 10 represents relationship between QTcS interval and RR interval (mean of triplicate measurements) during placebo treated period. The use of study-specific correction adequately accounts for the relationship between QT and RR interval. It is appropriate to use a study specific correction factor in a crossover study.

7.2.7. Drug Effect on QTcS Interval

Modeling of the PK and PD data collected in this QT study show there is no apparent relationship between the change in QTc and RO050-3821 concentrations (Upper confidence limit=5.1 msec). In addition, the primary analysis yields variable within and among day results. Briefly, Figure 5 illustrates that there is little or no difference for concentrations achieved after each dose (on Days 1, 15 and 29). However, the results

(upper 90% CL for mean) for time matched placebo corrected QTcS changes at time 30 and 60 mins are highly variable among days (Table 10).

Table 10: Comparison of within and among day results for time-matched placebo corrected QTcS change

Day	Time= 30 min	Time= 60 min
1	6.3	3.31
15	8.84	8.83
29	16.78	2.94

These analyses support the conclusion that RO050-3821 has no effect on the QTc interval. However, there are two major issues with the current study, (1) the variability in the measurement is considerably high and (2) the positive control was not included in the study. Thus, it is difficult to rule out the possibility of positive effect. A thorough analysis for phase III ECG data might be helpful, provided sampling schedules are acceptable. If the analyses of those studies presented by the sponsor &/or interpretability of the further analyses is questionable, a thorough QT study might be necessary. On that end, the sponsor should be asked to communicate with the agency to obtain an agreement on design and analyses of the study.

Figure 8. Diagnostic plots for pharmacokinetic base model

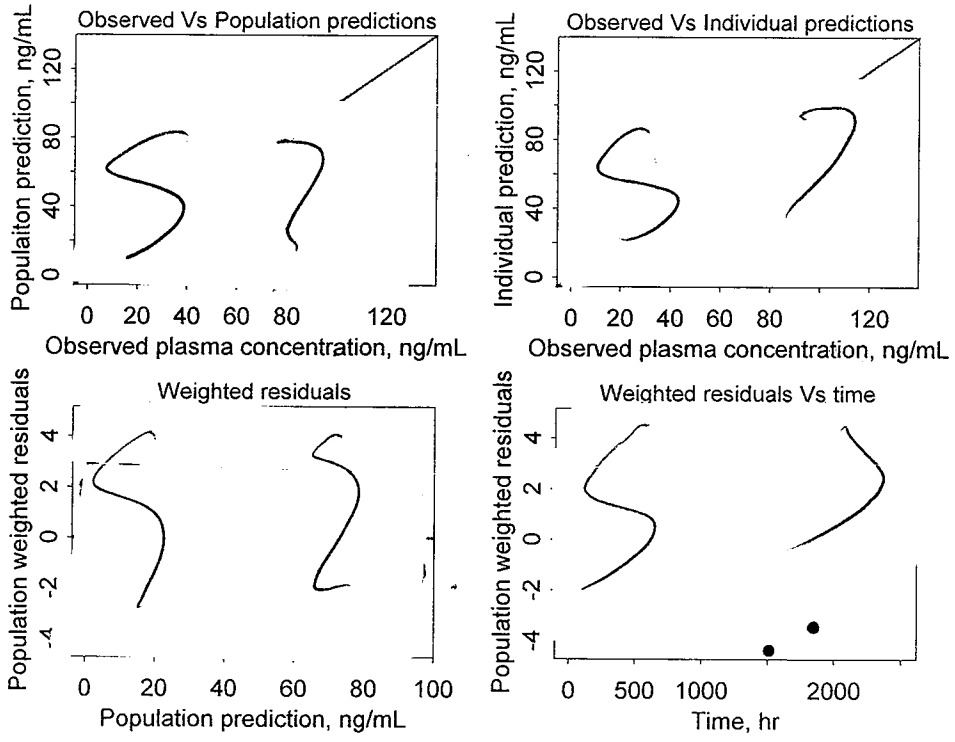


Figure 9. Effect of covariates (weight and age) on CL and V in the base model

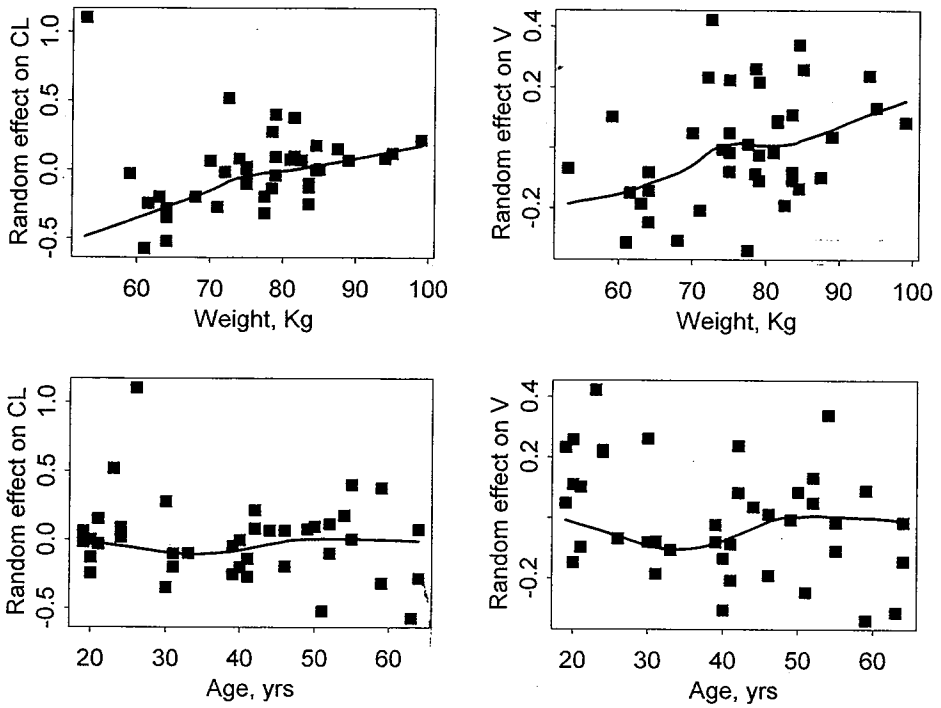


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Figure 10. QT and RR relationship (placebo treated period)

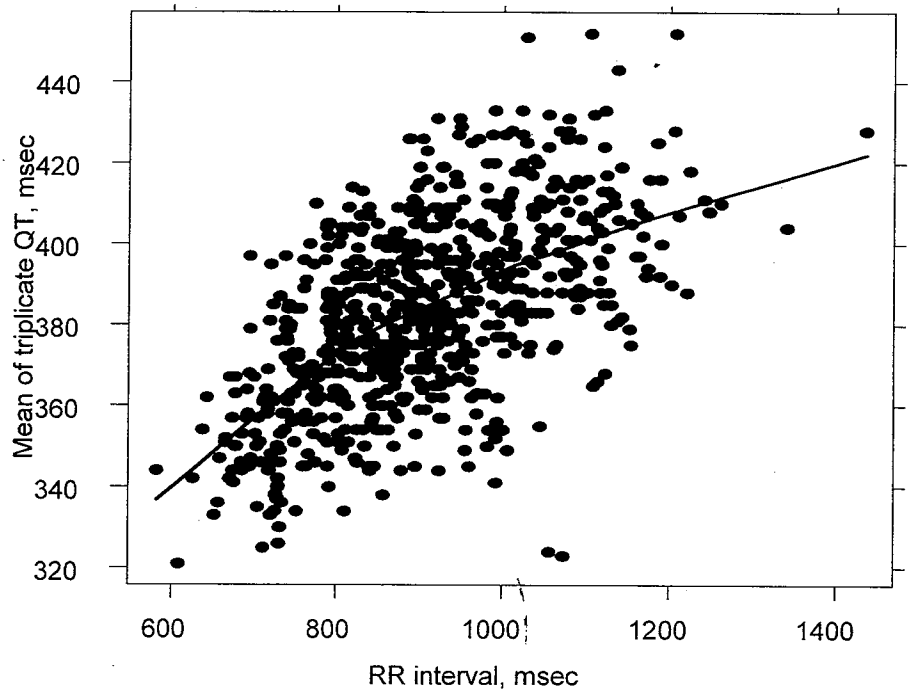


Figure 11. QTcS and RR relationship (placebo treated period)

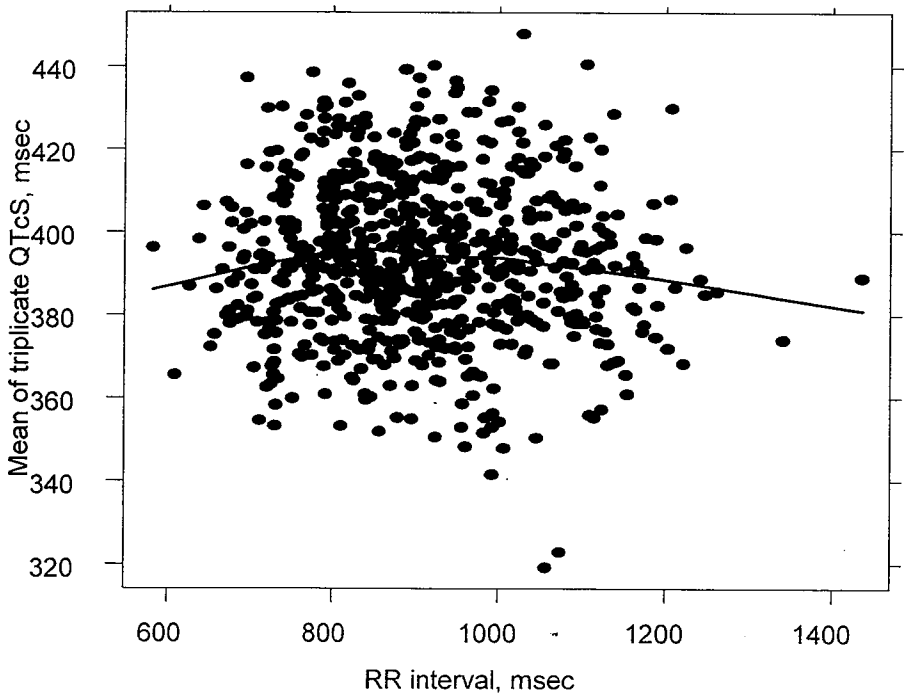


Figure 12. Mean QTcS (± SE) (msec) time (hr) course normalized for visit day for RO-503821

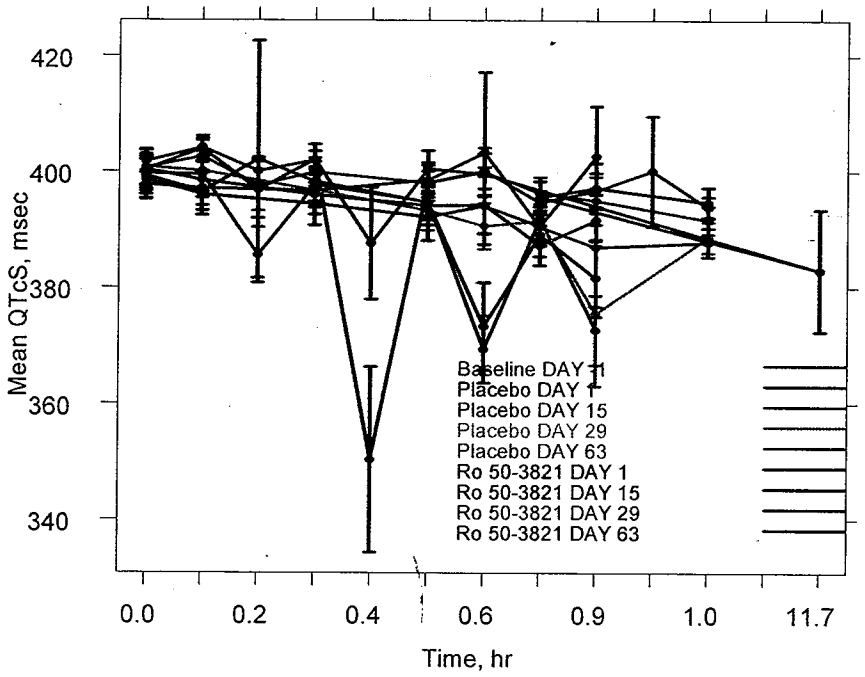


Figure 13. Mean dQTcS (± SE) (msec) time (hr) course by visit day for RO-503821

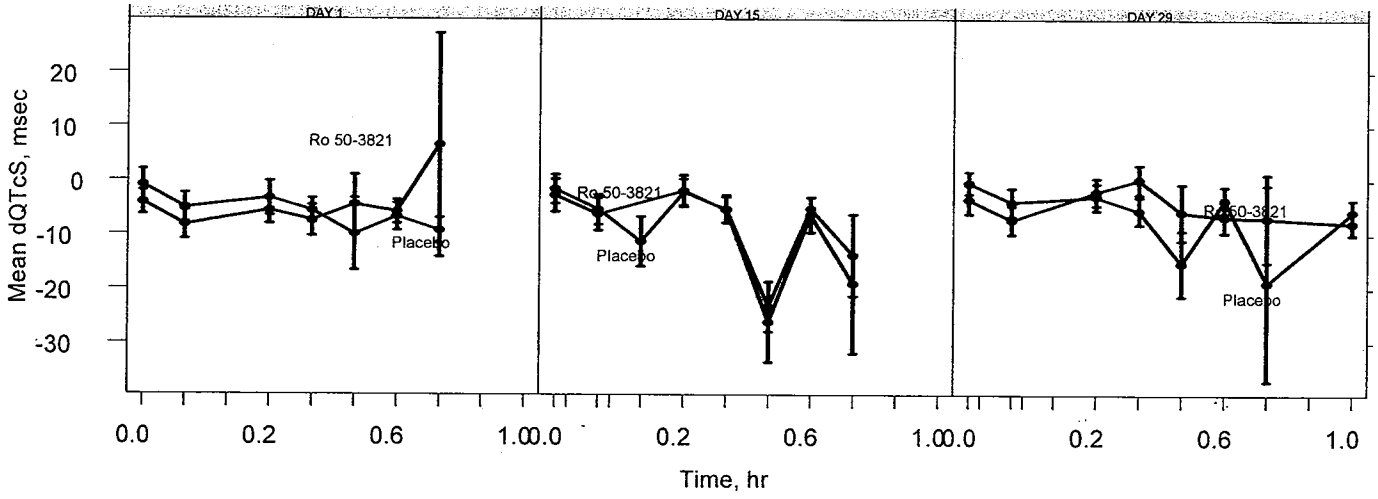


Figure 14. Individual predicted RO-503821concentration (ng/mL) and observed ddQTcS (msec) relationship

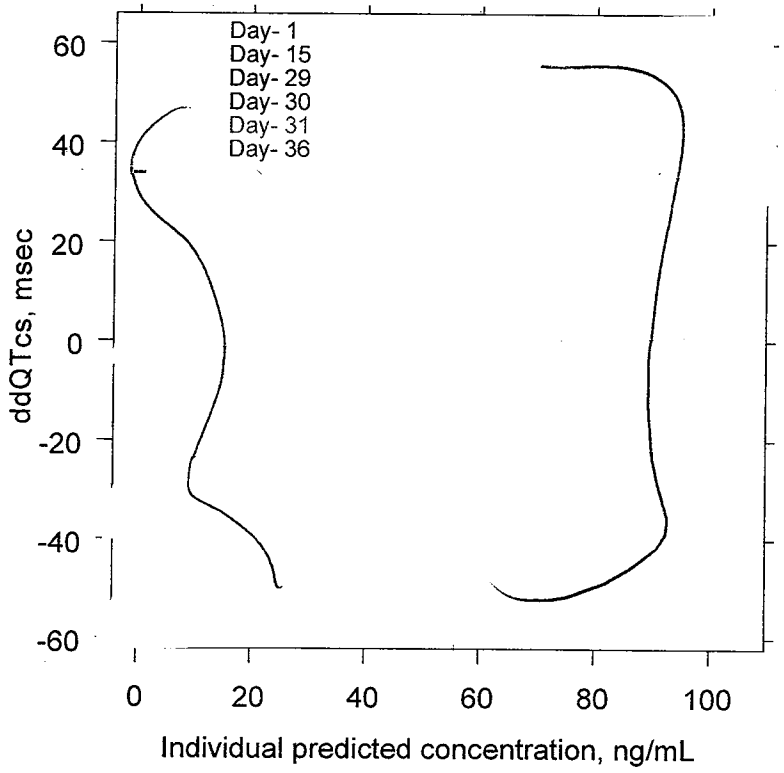
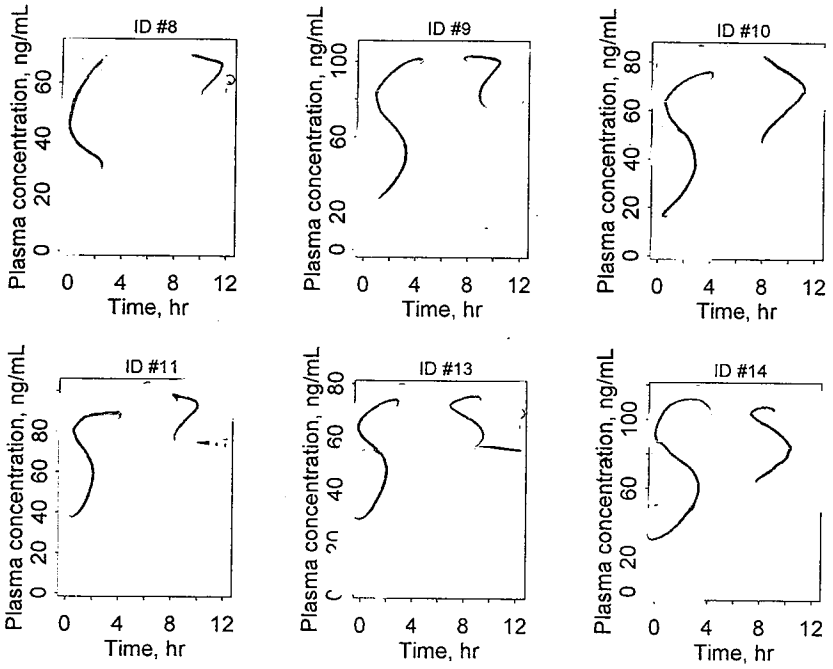


Figure 15. Individual concentration time profile (Day 29 or Day 64) (symbols- observed RO 050-3821, dotted line- individual predicted RO 050-3821, solid line- population predicted RO 050-3821)



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