SYNOPSIS OF RESEARCH REPORT [redacted] (PROTOCOL BA17284)

COMPANY: F. Hoffmann-La Roche Ltd. NAME OF FINISHED PRODUCT: RO0503821 NAME OF ACTIVE SUBSTANCE(S): RO0503821	(FOR NATIONAL AUTHORITY USE ONLY)

TITLE OF THE STUDY / REPORT No. / DATE OF REPORT	Clinical Study Report – BA17284 - A randomized, controlled, open-label, multi-center, parallel-group study to demonstrate the efficacy and safety of RO0503821 when administered with pre-filled syringes for the maintenance treatment of anemia in patients with chronic kidney disease who are on dialysis / Report No. [redacted] / March 2006.		
INVESTIGATORS / CENTERS AND COUNTRIES	This study was conducted by 62 investigators/sites in 11 countries: Canada, USA, Taiwan, Thailand, France, Germany, Great Britain, Italy, Poland, Portugal and Spain.		
PUBLICATION (REFERENCE)	None		
PERIOD OF TRIAL	First Patient Screened: August 4, 2004 Last Patient Last Observation: September 22, 2005	CLINICAL PHASE	III
OBJECTIVES	Primary: • To demonstrate that RO0503821 administered with pre-filled syringes maintains hemoglobin (Hb) concentrations in dialysis patients on prior intravenous (IV) or subcutaneous (SC) epoetin maintenance treatment of chronic renal anemia. Secondary: • To assess the safety and tolerability of RO0503821 administered with pre-filled syringes in this patient population.		
STUDY DESIGN	This study was a randomized, controlled, open-label, multi-center, parallel-group (2-arm), non-inferiority study comparing RO0503821 once every two weeks (1x/2 weeks, pre-filled syringes) to continued epoetin treatment (vials).		
NUMBER OF SUBJECTS	Planned 264 patients 132 RO0503821 132 Epoetin	Actual 336 patients 168 RO0503821 168 Epoetin	
DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION	Adult patients (≥ 18 years) with chronic renal anemia on hemodialysis (HD) or peritoneal dialysis (PD) who received IV or SC epoetin maintenance treatment.		
TRIAL DRUG / STROKE (BATCH) No.	RO0503821 / (50 µg/0.3 mL) [redacted] (100 µg/0.3 mL) [redacted] (150 µg/0.3 mL) [redacted] (200 µg/0.3 mL) [redacted] and (400 µg/0.6 mL) [redacted] / single-use pre-filled syringes containing either 0.3 mL or 0.6 mL solution.		
DOSE / ROUTE / REGIMEN / DURATION	RO0503821 was administered either IV or SC 1x/2 weeks during weeks 1 through 36. The starting RO0503821 dose was based upon the previous epoetin dose as follows:		

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	<table><tr><th>Previous weekly epoetin dose (IU/week)</th><th>Weekly RO0503821 dose (µg/2 weeks)</th></tr><tr><td><8000</td><td>60</td></tr><tr><td>8000-16000</td><td>100</td></tr><tr><td>>16000</td><td>180</td></tr></table> The dose of RO0503821 was adjusted to maintain the individual patient's Hb within a target range of ± 1.0 g/dL of their baseline Hb and between 10 and 13.5 g/dL throughout the dose titration/evaluation period (weeks 1 to 36). Throughout the study, the dose adjustments of RO0503821 were performed as described in Section 2.4.6.1 of this report.
REFERENCE DRUG / STROKE (BATCH) No.	NeoRecormon® (epoetin beta) manufactured by Hoffmann-La Roche was provided for participating study centers located outside of the USA and Canada. NeoRecormon® was provided in multidose vials. Epogen® (epoetin alfa) manufactured by Amgen was not supplied by Roche, but was obtained by the participating sites located in the USA. Eprex® (serum albumin epoetin alfa) manufactured by [redacted] was not supplied by Roche, but was obtained by the participating sites located in Canada. Roche-supplied NeoRecormon® used in the study (50'000 IU, 100'000 IU) was provided with commercial packaging in English with country specific labels. Epogen® and Eprex® were not packaged and labeled by Roche but were obtained by the sites.
DOSE / ROUTE / REGIMEN / DURATION	Epoetin (the comparator drug) was administered to the patients as labeled for each comparator (either IV or SC). Patients randomized to the epoetin reference group continued receiving epoetin alfa or beta at their current weekly dose and dosing interval (1-3x/week) during weeks 1 through 36. The dose of epoetin was adjusted to maintain the individual patient's Hb within a target range of ± 1.0 g/dL of their baseline Hb and between 10 and 13.5 g/dL throughout the dose titration/evaluation period (weeks 1 to 36). Throughout the study, the dose adjustments of epoetin alfa and beta were performed as described in the products' labeling.

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CRITERIA FOR EVALUATION	
EFFICACY:	The primary efficacy variable was the change in Hb concentration between the baseline and evaluation periods. The secondary variables were: • The number of patients maintaining average Hb concentration during the evaluation period within ± 1 g/dL of their average baseline Hb concentration. • The incidence of red blood cell (RBC) transfusions during the dose titration and evaluation periods.
PHARMACODYNAMICS:	Not applicable
PHARMACOKINETICS:	Not applicable
SAFETY:	Safety parameters included adverse events (AEs), safety hematology and blood chemistry (including iron) laboratory tests, assessment of dialysis adequacy, anti-erythropoietin antibody testing, vital signs and 12-lead electrocardiograms (ECGs).
STATISTICAL METHODS	To correct for the increases in Hb caused by RBC transfusions, the Hb values measured within 3 weeks after a RBC transfusion were replaced by the Hb value measures before the RBC transfusion in all analyses. Primary efficacy analysis: The primary endpoint was the change in Hb concentration between the baseline and evaluation periods. For this comparison, time adjusted average Hb values have been calculated for both periods. The RO0503821 group was compared to the epoetin reference, using analysis of covariance (ANCOVA), with Hb at baseline, geographical region and route of administration as the covariates. Using the correspondence between tests and confidence intervals, the test for non-inferiority was based on the lower limit of the two-sided 95% confidence interval for the difference between the two groups. When the lower limit was greater than or equal to -0.75 g/dL, the RO0503821 group was regarded as non-inferior to the epoetin reference group. In addition to the correction for RBC transfusions, last observation carried forward (LOCF) methodology was used for missing Hb values. Secondary efficacy analysis: The number of patients maintaining average Hb concentration during the evaluation period within ± 1 g/dL of their average baseline Hb concentration and the

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incidence of RBC transfusions during the dose titration and evaluation periods were summarized and the treatment groups compared using descriptive methods.

Safety data: Data were listed, summarized and plotted.

Sample size:
The sample size determination was based on a non-inferiority limit of -0.75 g/dL and a two-sided confidence interval approach with a coverage probability of 95%; the common standard deviation for both groups was assumed to be 1 g/dL. Assuming 20% of the patients would not be eligible for inclusion in the per-protocol (PP) population, approximately 132 patients per treatment group (264 patients in total) were required to conclude non-inferiority with 90% power, assuming that the true difference between the RO0503821 group and the reference was not larger than 0.3 g/dL.

METHODOLOGY:

After written informed consent was obtained, the patients were screened for eligibility during a 4-week period (weeks -4 to -1). During this period, patients continued to receive epoetin alfa or beta at the same weekly dose, route (IV or SC) and dosing interval (1-3x/week) as before screening. Baseline Hb (mean of all Hb values measured in weeks -4 to -1) for each patient was assessed under stable epoetin dosage conditions: patients with a stable baseline Hb concentration between 10.5 and 13 g/dL were eligible.

The 4-week screening period was followed by a dose titration period (28 weeks) and an evaluation period for assessment of efficacy parameters (8 weeks). At the end of the screening/baseline period, eligible patients were randomized in a 1:1 ratio to continue epoetin alfa or beta at their current weekly dose, route and dosing interval (1-3x/week) (group B) or to change to RO0503821 (pre-filled syringes) 1x/2 weeks (group A) with the same route of administration. Patients randomized to group A received a starting dose of RO0503821 that was based on the epoetin dose administered during the week preceding the switch to the study drug.

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EFFICACY RESULTS:

Primary Endpoint:

- At the end of the 8-week evaluation period, the primary efficacy result using the ANCOVA model showed that the lower limit of the 95% confidence interval for the mean difference in Hb between baseline and week 36 was -0.116 g/dL for the RO0503821 group. Since the lower limit was greater than -0.75 g/dL, the RO0503821 group is regarded as clinically non-inferior to the epoetin reference group. The results were consistent in the four data sets analyzed (PP, ITT, eligible and observation complete populations) with $p < 0.0001$ in all four populations. The effect of route of administration was not significant ($p = 0.52$), and therefore, had no impact on the primary efficacy analysis.

Secondary Endpoints:

- In the ITT population, during the 8-week evaluation period, the number of patients maintaining a stable Hb (defined as mean Hb within ± 1 g/dL of baseline mean) was 68.5% in the RO0503821 group and 67.7% in the epoetin group.

- The incidence of RBC transfusions up to the end of the evaluation period was 9.7% in the RO0503821 group and 11.3% in the epoetin group.

PHARMACODYNAMIC RESULTS:

Not applicable

PHARMACOKINETIC RESULTS:

Not applicable

SAFETY RESULTS:

The overall incidence of AEs was similar between the two treatment groups: 94.5% of patients in the RO0503821 group and 94.6% in the epoetin group experienced at least one AE. AEs for patients in the RO0503821 and epoetin groups, respectively, occurred most commonly in the following SOCs: infections and infestations (60% and 63%), injury, poisoning and procedural complications (45% and 44%) and gastrointestinal disorders (38% and 40%). The most common AEs in the RO0503821 and epoetin groups, respectively, were hypertension (18% and 14%), diarrhea (both 13%) and upper respiratory tract infection (16% and 6%). The majority of AEs reported were of mild or moderate intensity and assessed by the investigators as unrelated to trial medication.

The incidence of SAEs was lower in the RO0503821 group compared with the epoetin group: 30.9% in the RO0503821 group and 41.1% in the epoetin group. The most common SAEs in the RO0503821 and epoetin groups, respectively, occurred in the following SOCs: infections and infestations (11% and 17%), cardiac disorders (8% and 8%) and gastrointestinal disorders (5% and 7%). The majority of SAEs were considered unrelated to trial medication.

A total of 5 patients (2 patients in the RO0503821 group [headache, hypersensitivity] and 3 patients in the epoetin group [intestinal ischemia, cardiac arrest, gastrointestinal fungal infection and subdural hematoma]) discontinued treatment prematurely due to an AE.

Among the patients who died in the study (4% in the RO0503821 group and 6% in the epoetin group), baseline risk factors for vascular events and hemorrhages were more common than in the overall study

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population. The patients in the RO0503821 and epoetin groups who died had similar baseline risk factor profiles. Increases in Hb and high levels of Hb in the 4 weeks preceding the events were found in a minority of patients who died in both treatment groups. Large decreases in Hb and low levels of Hb were more common in the 4 weeks preceding an event which resulted in death in both treatment groups.

There were no consistent trends in laboratory parameters nor a pattern of AEs related to laboratory abnormalities. Platelet values, while lower in the RO0503821 group than in the epoetin group, were within the standard reference range for both groups throughout the study. No anti-erythropoietin or anti-RO0503821 antibodies were detected.

CONCLUSIONS:

Treatment with RO0503821 as prescribed in the study protocol was non-inferior to treatment with epoetin in maintaining Hb levels ($p < 0.0001$) in patients on stable maintenance treatment. Variability in Hb values over time was comparable in the treatment arms. The dose adjustment guidance in the protocol resulted in Hb values which were virtually identical between the baseline and evaluation periods. Safety findings were characteristic of the population under study and comparable between treatment groups.