SYNOPSIS OF RESEARCH REPORT [redacted] (PROTOCOL NH20052)

COMPANY: F. Hoffmann-La Roche Ltd NAME OF FINISHED PRODUCT: MIRCERA® NAME OF ACTIVE SUBSTANCE(S): Methoxy polyethylene glycol-epoetin beta (RO0503821)	(FOR NATIONAL AUTHORITY USE ONLY)

TITLE OF THE STUDY / REPORT No. / DATE OF REPORT	An open-label, randomized, multicenter, parallel-group study to demonstrate correction of anemia using once every four weeks subcutaneous injections of RO0503821 in patients with chronic kidney disease who are not on dialysis / [redacted] January 2010		
INVESTIGATORS / CENTERS AND COUNTRIES	Principal investigator: [redacted] 64 centers in 16 countries		
PUBLICATION (REFERENCE)	None		
PERIOD OF TRIAL	31 December 2007 to 07 October 2009	CLINICAL PHASE	III
OBJECTIVES	**Primary objective**: The primary objective of the study was to demonstrate the efficacy of RO0503821 treatment administered sc once every 4 weeks for correction of anemia in CKD patients who were not on dialysis and who were not treated with erythropoiesis-stimulating agents (ESAs). **Secondary objectives:** • To assess hemoglobin (Hb) concentration over time • To assess time to response • To assess the incidence of RBC transfusion • To assess the safety and tolerability of multiple sc doses of RO0503821 during the correction/evaluation periods in this patient population • To compare, in each treatment group, the percentage of patients with at least 1 Hb exceeding 12.0 g/dL during the first 8 weeks of the study • To assess the proportion of patients who achieved a stable Hb response • To assess the total number of dose adjustments needed to achieve stabilized response **Diagnostic objectives:** • To assess the risk stratification value of N-terminal pro-brain natriuretic peptide (NT-proBNP) for		

SYNOPSIS OF RESEARCH REPORT [redacted] (PROTOCOL NH20052)

COMPANY: F. Hoffmann-La Roche Ltd NAME OF FINISHED PRODUCT: MIRCERA® NAME OF ACTIVE SUBSTANCE(S): Methoxy polyethylene glycol-epoetin beta (RO0503821)	(FOR NATIONAL AUTHORITY USE ONLY)

	cardiovascular events in CKD patients who were not on dialysis undergoing ESA treatment • To assess the risk predictive value of NT-proBNP and/or troponin T for therapeutic monitoring in CKD patients who were not on dialysis undergoing ESA treatment • To assess the prediction potential of NT-proBNP for dialysis initiation.
STUDY DESIGN	This was a randomized, open-label, multicenter, controlled, parallel-group (2-arm), non-inferiority study comparing sc RO0503821 administered once every 4 weeks to darbepoetin alfa treatment once every week and once every 2 weeks during the correction and evaluation periods.
NUMBER OF SUBJECTS	Planned: 300 patients (150 per treatment group) Actual: 307 patients randomized (153 patients to RO0503821 and 154 patients to darbepoetin alfa)
DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION	Adult patients (18 years old or older) with chronic renal anemia who were not on renal replacement therapy and were not treated with an ESA and who required correction of anemia were enrolled into this trial.
TRIAL DRUG / STROKE (BATCH) No.	Injectable solution of RO0503821, supplied in vials or PFS Multiple batch numbers (vials and PFS) were used in the study. A complete list is available in the Study Documentation section of the clinical study report.
DOSE / ROUTE / REGIMEN / DURATION	RO0503821 starting dose was 1.2 µg/kg sc injected once every 4 weeks. Duration was 20 weeks for the correction period (dose titration) and 8 weeks for the evaluation period.
REFERENCE DRUG / STROKE (BATCH) No.	Injectable solution of darbepoetin alfa, supplied in PFS or vials Multiple batch numbers (vials and PFS) were used in the study. A complete list is available in the Study Documentation section of the clinical study report.
DOSE / ROUTE / REGIMEN / DURATION	Darbepoetin alfa starting dose was according to local labeling specification, e.g., 0.45 µg/kg sc injected once every week or

SYNOPSIS OF RESEARCH REPORT [redacted] (PROTOCOL NH20052)

COMPANY: F. Hoffmann-La Roche Ltd NAME OF FINISHED PRODUCT: MIRCERA® NAME OF ACTIVE SUBSTANCE(S): Methoxy polyethylene glycol-epoetin beta (RO0503821)	(FOR NATIONAL AUTHORITY USE ONLY)

	0.75 µg/kg sc injected once every 2 weeks. Duration was 20 weeks for the correction period (dose titration) and 8 weeks for the evaluation period
CRITERIA FOR EVALUATION	
EFFICACY:	**The joint primary efficacy endpoints were** 1) the Hb response rate until the end of the evaluation period and 2) the change in Hb concentration (g/dL) between the baseline and evaluation periods. **The secondary efficacy endpoints were**: • the Hb values and their changes from baseline over time • the time to Hb response assessed via Kaplan-Meier methods • the incidence of RBC transfusions during the entire study duration • the percentage of patients who had at least 1 Hb exceeding 12.0 g/dL during the first 8 weeks of the study • the proportion of patients who achieved a stable Hb response • total number of dose adjustments needed to achieve stabilized response
PHARMACODYNAMICS:	None
PHARMACOKINETICS:	None
SAFETY:	Safety parameters included AEs, safety hematology and blood chemistry laboratory tests (including iron parameters), intact PTH, serum creatinine, creatinine clearance, proteinuria, anti-erythropoietin antibody testing, and vital signs.
STATISTICAL METHODS	All primary and secondary efficacy analyses were performed in the ITT population, i.e., all patients randomized. **Primary efficacy analyses:** • The first primary efficacy endpoint was the response rate. Response was defined as an increase in Hb of at least 1.0 g/dL compared to baseline and an Hb concentration

SYNOPSIS OF RESEARCH REPORT [redacted] (PROTOCOL NH20052)

COMPANY: F. Hoffmann-La Roche Ltd NAME OF FINISHED PRODUCT: MIRCERA® NAME OF ACTIVE SUBSTANCE(S): Methoxy polyethylene glycol-epoetin beta (RO0503821)	(FOR NATIONAL AUTHORITY USE ONLY)

≥ 10.0 g/dL without RBC transfusion (before response) until the end of the evaluation period. The intention of the first primary analysis was to demonstrate that the lower limit of the 95% CI for the response rate in the RO0503821 arm was greater than 60%.

- The second primary efficacy endpoint was the group difference in the mean change in Hb between the baseline and evaluation periods (weeks 21 to 29), based on an ANCOVA analysis by treatment, baseline Hb and baseline CRP split in 2 categories (≤30 mg/L, >30 mg/L).

A 2-sided 95% CI was calculated for the mean difference between RO0503821 once every 4 weeks versus darbepoetin alfa. RO0503821 treatment was regarded as non-inferior to the darbepoetin alfa reference group if the lower limit of the CI was greater than -0.75 g/dL. The p-value for the non-inferiority test was derived via the t-test.

Secondary efficacy analyses:

The Hb values and their changes from baseline over time were presented in summary tables and graphically. The time to Hb response and stable Hb response were analyzed using Kaplan-Meier methods. The incidence of RBC transfusions, the percentage of patients having at least one Hb > 12.0 g/dL during the first 8 weeks, the proportion of patients who achieved a stable Hb response and the total number of dose adjustments needed to achieve stable response were summarized and the treatment groups compared using descriptive methods.

Safety analyses:

The safety population included all patients randomized who received at least 1 dose of the trial medication and a safety follow-up, whether they withdrew prematurely or not. Tables with group summary statistics were provided for all safety parameters. Frequencies and incidence rates of AEs were tabulated by

SYNOPSIS OF RESEARCH REPORT [redacted] (PROTOCOL NH20052)

COMPANY: F. Hoffmann-La Roche Ltd NAME OF FINISHED PRODUCT: MIRCERA® NAME OF ACTIVE SUBSTANCE(S): Methoxy polyethylene glycol-epoetin beta (RO0503821)	(FOR NATIONAL AUTHORITY USE ONLY)

	treatment group and calculated on a per-patient basis rather than on an event basis. Vital sign measurements and laboratory data were assessed for clinically relevant abnormalities as well as changes from baseline.
OTHER ANALYSES	**Pharmacoeconomics**: Hemoglobin concentration was measured once every 2 weeks during the study. Analyses were performed to explore the relationship between frequency of Hb determinations and requirement for dose changes in an attempt to determine whether bi-weekly Hb determinations are necessary for decision making on dose adjustments, or whether 4-weekly Hb determinations would be adequate. **NT-proBNP and troponin T**: Blood samples for analysis of NT-proBNP and troponin T were collected every 8 weeks to identify associations between these parameters and cardiac events and progression to dialysis. **Hepcidin and pro-hepcidin analyses:** Blood and urine samples for biomarker discovery and validation were collected from consenting patients.

METHODOLOGY:

After written informed consent was obtained, patients were screened for eligibility over a period of up to 2 weeks. The Hb level qualifying the patients for randomization was assessed by calculating the mean Hb of 2 measurements during the screening period with at least 1 day between measurements. The iron status was assessed by calculating the mean serum ferritin and the mean transferrin saturation (TSAT) or percentage of hypochromic RBCs of 2 measurements during the screening period with at least 1 day between measurements.

Providing all eligibility criteria were met, patients were randomized into 2 groups (1:1 ratio): RO0503821 (group A) administered sc at a starting dose of 1.2 μg/kg once every 4 weeks, or a reference group receiving darbepoetin alfa (group B) administered sc once weekly or once every 2 weeks according to labeling specifications.

SYNOPSIS OF RESEARCH REPORT [redacted] (PROTOCOL NH20052)

COMPANY: F. Hoffmann-La Roche Ltd NAME OF FINISHED PRODUCT: MIRCERA® NAME OF ACTIVE SUBSTANCE(S): Methoxy polyethylene glycol-epoetin beta (RO0503821)	(FOR NATIONAL AUTHORITY USE ONLY)

EFFICACY RESULTS:

Primary endpoints:

Both primary endpoints were met:

- The first component of the primary endpoint was the Hb response rate. In the RO0503821 group, 144/153 patients (94%) were responders. The lower limit of CI was higher than 60% (95% CI 89.13-97.28, $p<0.0001$). In the darbepoetin alfa group, 144/154 patients (94%) were responders, with a 95% CI of 88.38-96.84, $p<0.0001$.
- The second component of the primary efficacy endpoint was the difference in the mean change in Hb between the two treatment groups. In an ANCOVA analysis, the change in baseline-adjusted mean Hb was 1.62 g/dL for the RO0503821 group and 1.66 g/dL for the darbepoetin alfa reference group, resulting in a treatment difference of -0.036 g/dL for the ITT population. The lower limit of the 95% CI was -0.252, greater than the protocol-specified non-inferiority limit of -0.75, which demonstrated that the RO0503821 group was statistically non-inferior to the darbepoetin alfa reference group ($p<0.0001$) in the ITT population.

Secondary endpoints:

- Hemoglobin increased after initiation of treatment in both arms of the study. However, larger and more rapid increases were seen in the darbepoetin alfa group, reaching a maximum at week 12. Hemoglobin concentrations increased more gradually in the RO0503821 group, with a maximum at week 16.
- As a result, the median time to response in the RO0503821 group was 43 days, compared with 29 days in darbepoetin alfa group, indicating that the correction of anemia was slower in the RO0503821 group.
- As a direct consequence of the more rapid increase in Hb, more darbepoetin-treated patients had Hb values over 12.0 g/dL in the first 8 weeks of the study. A total of 39 patients (26%) in the RO0503821 group had at least one Hb value above 12.0 g/dL, compared to 72 patients (48%) in the darbepoetin alfa group ($p<0.0001$ in an uncorrected Fisher's exact test). This required more dose adjustments in the darbepoetin-treated patients. While 95% of patients in the RO0503821 group and 89% of patients in the darbepoetin alfa required at least one dose adjustment, more patients in the darbepoetin treatment arm required multiple adjustments.
- The incidence of RBC transfusions during the study was higher in the darbepoetin alfa group, where 10 patients (7%) received a total of 15 transfusions, compared with 5 patients (3%) in the RO0503821 group, who were given 7 transfusions.

SYNOPSIS OF RESEARCH REPORT [redacted] (PROTOCOL NH20052)

COMPANY: F. Hoffmann-La Roche Ltd NAME OF FINISHED PRODUCT: MIRCERA® NAME OF ACTIVE SUBSTANCE(S): Methoxy polyethylene glycol-epoetin beta (RO0503821)	(FOR NATIONAL AUTHORITY USE ONLY)

- The number of stable responders according to the protocol-specified definition of the secondary endpoint was 105 patients in the RO0503821 group (69%) and 112 patients (73%) in the darbepoetin alfa group. The mean number of dose adjustments per patient needed to achieve a stabilized response was 1.12 in the RO0503821 group and 1.10 in the darbepoetin alfa group.

PHARMACODYNAMIC RESULTS:

None

PHARMACOKINETIC RESULTS:

None

SAFETY RESULTS:

- RO0503821 was generally well tolerated and no major safety concerns arose. The incidence of AEs was slightly lower in the RO0503821 group compared to the darbepoetin alfa-treated patients (73% vs 79%), with similar findings for SAEs (19% vs 25%), although these differences were not statistically significant.
- Related AEs were reported in 10 patients (7%) in the RO0503821 group and 17 patients (11%) in the darbepoetin alfa group. The most common related AE was hypertension: 5% in the RO0503821 group compared to 10% darbepoetin alfa-treated patients. No SAEs or severe AEs were assessed as related to either study medication.
- There were 4 deaths (3% of patients) in the RO0503821 group and 7 deaths (5% of patients) in the darbepoetin alfa group. None of the deaths were assessed as related to study medication.
- There were no clinically significant differences in any of the laboratory parameters.
- Similarly, there were no major differences between treatment groups with respect to vital signs.
- No anti-erythropoetin or anti-RO0503821 antibodies developed after initiation of treatment in any patient.

OTHER ANALYSES RESULTS:

- **Pharmacoeconomics:** Analyses to explore the relationship between the frequency of Hb determinations and dose changes demonstrated that 1) the number of dose changes was comparable to those actually performed in the study; 2) the additional information provided by more frequent (bi-weekly) Hb determinations would not have led to a different practice in Hb management.
- **NT-proBNP and troponin T:** Troponin T values were similar at every time point in patients with and without events, while NT-proBNP values were higher at every time point in patients with

SYNOPSIS OF RESEARCH REPORT [redacted] (PROTOCOL NH20052)

COMPANY: F. Hoffmann-La Roche Ltd NAME OF FINISHED PRODUCT: MIRCERA® NAME OF ACTIVE SUBSTANCE(S): Methoxy polyethylene glycol-epoetin beta (RO0503821)	(FOR NATIONAL AUTHORITY USE ONLY)

clinical events than in those without. Receiver operator curves suggested the prognostic value of NT-proBNP for the clinical event categories congestive heart failure, cardiac arrest, all cardiac events, cardiac AEs of interest, and cardiac AEs of interest plus cardiac death, but not for arrhythmia or myocardial infarction. In addition, the results suggested a prognostic value of this parameter for initiation of dialysis.

- **Hepcidin and pro-hepcidin analyses:** The samples are currently in secure storage. The analyses have been put on hold until a high-throughput assay is available.

CONCLUSIONS:

RO0503821 administered as a single sc injection every 4 weeks with a starting dose of 1.2 µg/kg was effective in correcting anemia in CKD patients who were not on dialysis and not treated with ESAs. Treatment with RO0503821 as prescribed in the study protocol was non-inferior to darbepoetin alfa in correcting anemia and required fewer dose adjustments to achieve correction and maintain Hb in the target range. The Hb increase in the RO0503821 group was more gradual than in the darbepoetin alfa group and fewer patients had Hb values above the target range (26 % vs 48%). Safety findings were characteristic of the study population and comparable between treatment groups.