SYNOPSIS OF RESEARCH REPORT (PROTOCOL MA17502)

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

TITLE OF THE STUDY / REPORT No. / DATE OF REPORT	Effectiveness of a once weekly subcutaneous (sc) epoetin beta treatment in haemodialysis patients		
INVESTIGATORS / CENTRES AND COUNTRIES	41 centres in 7 European Countries (Sweden, France, Germany, Belgium, Portugal, Greece and Italy)		
PUBLICATION (REFERENCE)	None		
PERIOD OF TRIAL	08 Apr 2005 to 27 Nov 2006	CLINICAL PHASE	IV
OBJECTIVES	The primary objective of this study was to assess the efficacy of sc epoetin beta once weekly (QW) treatment to maintain stability of haemoglobin (Hb) in haemodialysis patients previously receiving intravenous (iv) darbepoetin alfa QW. The secondary objectives were: • To assess and compare Hb level and variability in different study periods and groups • To explore the conversion factor from darbepoetin alfa to epoetin beta • To assess and compare dosing of QW sc epoetin beta and iv darbepoetin alfa QW • To assess and document the safety and tolerability of epoetin beta in haemodialysis patients.		
STUDY DESIGN	Randomised 3-arm, open-label, multi-centre, international phase IV study		
NUMBER OF SUBJECTS	Total randomised = 236, ITT = 236		
DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION/EXCLUSION	• Adult patients (≥ 18 years old) • Stable haemodialysis patients with renal anaemia treated with iv darbepoetin alfa QW for at least 12 weeks prior to study enrolment • Stable Hb-values in the 12 weeks prior to enrolment • Absolute reticulocyte number >10,000 cells/µL in the 12 weeks before enrolment • No evidence of loss of efficacy under darbepoetin alfa treatment in patient history • Dialysis requirements: Kt/V ≥ 1.2 • Life expectancy >2 years • Negative anti-erythropoietin antibody test (AEAB) • No active malignant disease.		
TRIAL DRUG	NeoRecormon® Multidose vials, containing 100,000 IU epoetin beta. Lyophilisate with sterile, preserved (4 mg/mL benzyl alcohol and 0.02 mg/mL benzalkonium chloride) water for reconstitution.		
DOSE/ROUTE/REGIMEN/DURATION	Patients were switched from QW iv darbepoetin alfa treatment to QW sc epoetin beta treatment with one of the following conversion factors at baseline (Day 1): Epoetin beta dose (IU/week) = darbepoetin alfa dose (µg/week) × 160 Epoetin beta dose (IU/week) = darbepoetin alfa dose (µg/week) × 200 Epoetin beta dose (IU/week) = darbepoetin alfa dose (µg/week) × 250		

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CRITERIA FOR EVALUATION	
EFFICACY:	**Primary parameter:** the proportion of patients with stable Hb values in Evaluation Phase (4 weeks) **Secondary parameters:** mean weekly dose of sc epoetin beta QW to maintain stable Hb, previous dose of iv darbepoetin alfa QW, Hb variability throughout the Retrospective, Adaptation and Evaluation Phases.
SAFETY:	Specific non-serious and serious adverse events, clinical laboratory tests, vital signs and dialysis adequacy.
STATISTICAL METHODS	**Efficacy:** All efficacy analyses were performed following the Intent-to-Treat (ITT) principle. Hb and dosing data were analysed in descriptive summary tables over time. Data from the prospective sc epoetin beta phase of the study were compared with the data of the retrospective iv darbepoetin alfa phase. Estimates of conversion factor were made using regressional techniques based on individual slopes. **Safety:** Adverse events were coded with MedDRA and tabulated with frequency tables for system organ class and preferred terms. The analyses of safety laboratory parameters and vital signs were performed with descriptive statistics and, in addition, listings of markedly abnormal values and/or changes. No interim analyses were performed. After 14 months of enrolment, only 236 patients had been randomised and it was considered that the planned 700 patients would not be recruited to this study due to inadequate recruitment secondary to low investigator interest, despite multiple efforts by the Sponsor. It was therefore decided to terminate the study at this time. In the pooled sample of all 3 treatment arms, 558 evaluable patients were considered enough to estimate the proportions of patients with stable Hb values with a precision of ± 2.5% (expecting 90% stable patients, using normal approximation). Likewise, 144 evaluable patients would be enough to estimate the proportions of patients with stable Hb values with a precision of ± 5%. Under the same conditions, with 48 evaluable patients in each treatment arm, the proportions could be estimated with a precision below 9%. Assuming a 20% drop out rate, it was considered that 180 patients should be enrolled into the study for this level of precision of estimates for the primary endpoint. Given the reduced sample size and precision, comparisons concerning endpoints in this study should only be considered with caution.

METHODOLOGY:

Eligible patients on haemodialysis and under iv darbepoetin alfa QW who had signed and dated their informed consents were enrolled in the study. Serum samples for AEAB test, vitamin B_{12} and folic acid were collected before enrolment in the study. Patients with positive AEAB tests were to be withdrawn from the study. Data from the 12 weeks prior to enrolment (Retrospective Phase) were documented including Hb and hematocrit (Hct), weekly dose of iv darbepoetin alfa, serum iron, transferrin, Transferrin Saturation (TSAT) and ferritin, weight and blood pressure. After it had been confirmed that the patients were suitable for the study, the patients were allocated to their conversion factor via randomisation and the treatment with sc epoetin beta was commenced according to the conversion factor. All enrolled patients were prospectively observed for 24 weeks (a 20 week Adaptation Phase, with visits every 4 weeks plus 1 additional visit in Week 2) and a 4 week Evaluation Phase with weekly visits). At these visits, Hb, Hct, serum iron, transferrin, TSAT, ferritin, liver enzymes (gamma-glutamyltransferase [GGT], alanine aminotransferase [ALT], aspartate aminotransferase [AST], and alkaline phosphatase [AP]), therapeutic effectiveness, sc epoetin beta dose, route and frequency of administration, AEs, patient history and concomitant treatments were documented.

EFFICACY RESULTS:

Epoetin beta treatment, QW sc, maintained stable Hb levels in haemodialysis patients who had previously received iv darbepoetin alfa QW, with 53% of patients having stable mean Hb levels during the Evaluation Phase of the study.

There appeared to be a higher proportion of patients with stable mean Hb levels in the Epoetin-200 treatment arm (64%) compared to the Epoetin-250 (45.0%) and Epoetin-160 (50.6%) treatment arms, although the number of differences was small.

Mean Hb for the Retrospective Phase was 12.00, 11.88 and 11.91 g/dL in the conversion groups 160, 200 and 250 respectively and

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11.26, 11.61 and 11.56 g/dL respectively in the Evaluation Phase.

There was a small overall decrease in the mean Hb value in the Evaluation Phase of the study when compared to the Retrospective Phase of the study (-0.54 g/dL). This was slightly greater in the Epoetin-160 treatment arm (-0.83 g/dL) compared to the Epoetin-200 and Epoetin-250 treatment arms (-0.41 g/dL and -0.39 g/dL).

In the Retrospective Phase of the study, the mean weekly dose of iv darbepoetin alfa was 31.52 µg. This was seen to be similar for all three treatment arms. The mean weekly dose of sc epoetin beta in the Evaluation Phase was 6153.8 IU overall and 5840.5, 6232.7 and 6395.2 IU respectively for the 160, 200 and 250 conversion groups.

When assessed using a regression slope analysis, the estimate conversion factor for darbepoetin alfa to epoetin beta in this study was 297.36. The regression analysis of the AUC estimates found no relevant differences between the treatment groups. However, analyses to estimate an overall conversion factor were confounded due to low sample size and seem inconsistent with the analyses of Hb stability and dosing in the three arms.

SAFETY RESULTS:

The overall tolerability of epoetin beta was seen to be similar in all three treatment arms in this study. No relevant differences in AEs and SAEs were seen between the three dose groups. Of the 236 randomised patients there were 124 patients (52.5%) with AEs, and 79 patients (33.5%) with SAEs during this study. Only 1 patient (0.4%) was discontinued due to a drug-related AE. The numbers of AEs were similar across the treatment arms. The most common AE reported in this study was decreased haemoglobin seen in 33 patients (14.0%) overall. These events were all reported to be SAEs and 8 cases (in 7 patients) were reported to be related to the study medication. No other AE occurred in ≥ 5% of patients. There were 11 patients (4.7%) who died during this study due to AEs. One death (cerebral haemorrhage), in the Epoetin-160 treatment group was reported to be related to the study medication. No trends of clinical significance were observed for laboratory parameters. In all three treatment arms the most common marked laboratory abnormalities were seen for erythrocytes and transferrin below normal range, ferritin, and CRP above normal range.

CONCLUSIONS:

Results of this phase IV study show that converting patients from iv QW darbepoetin alfa to sc QW epoetin beta treatment can be achieved with little change in mean Hb, in patients with renal anaemia undergoing dialysis for chronic renal failure. The study suggests that application of conversion factors in the region of 1 mcg iv QW darbepoetin: 200 IU sc QW epoetin beta is a pragmatic approach to patient conversion and should not precipitate rapid, clinically significant changes in Hb variability. Conversion factors of substantially less than 1:200 seem least optimal. Reliable calculation of a more precise conversion factor has not been possible due to the small population size, however, the stability of Hb seen in this study suggests that the conversion factors were appropriate for this population. The conversion factor of 160 appeared to be less suitable for this population than the 200 and 250 conversion factors. In this study, sc QW epoetin beta demonstrates a safety profile consistent with that reported in the Summary of Product Characteristics, with very few AEs and SAEs being considered due to study medication. No relevant differences in AEs and SAEs were seen between the three dose groups.