Name of Sponsor: Amgen Ltd

Name of Finished Product: Aranesp®

Name of Active Ingredient: Darbepoetin alfa

Title of Study: Randomized, Double-Blind, Equivalence Study of the Efficacy of Darbepoetin Alfa Manufactured by Serum-Free Bioreactor Technology and Darbepoetin Alfa Manufactured by Roller-Bottle Technology for the Treatment of Anemia in Patients with Chronic Kidney Disease Receiving Hemodialysis (Study 20040104)

Investigator(s) and Study Center(s): This study was conducted at 65 sites in Europe, Canada, and the United States.

Publication(s): None

Study Period: 05 March 2005 (first subject randomized) to 24 May 2006 (last subject completed)

Development Phase: 3

Primary Objective:

The primary objective was to evaluate whether the efficacy of darbepoetin alfa SF is equivalent to that of darbepoetin alfa RB for the treatment of anemia in subjects with CKD who were receiving hemodialysis as measured by the mean change in hemoglobin between baseline and the evaluation period and the ratio of dosing requirements between baseline and the evaluation period.

Secondary Objective

The secondary objective was to demonstrate that the safety and tolerability of darbepoetin alfa SF is similar to that of darbepoetin alfa RB for the treatment of anemia in subjects with CKD who were receiving hemodialysis.

Methodology: This multicenter, randomized, double-blind, equivalence study enrolled subjects with CKD receiving hemodialysis. After an initial screening/baseline period, eligible subjects were randomized 1:1 to receive either darbepoetin SF or darbepoetin RB. Randomization was stratified by the route of darbepoetin alfa administration at baseline. Subjects received darbepoetin alfa SF or RB for up to 28 weeks (20-week dose-titration period followed by an 8-week evaluation period). The initial dose of darbepoetin alfa was the same as that received before randomization rounded to the nearest unit dose. The route and frequency of administration were the same as before randomization. Darbepoetin alfa dose was adjusted throughout the study to maintain subjects' hemoglobin concentrations between 10.0 to 13.0 g/dL and within -1.0 to +1.5 g/dL of the subject's baseline hemoglobin value. The study concluded with a post-treatment assessment 1 week after the last dose of darbepoetin alfa.

Number of Subjects Planned: The planned sample size was 420 subjects (210 in each treatment group).

Number of Subjects Randomized: 446 subjects (222 darbepoetin alfa SF, 224 darbepoetin alfa RB) were randomized into the study; 442 subjects (219 darbepoetin alfa SF, 223 darbepoetin alfa RB) were administered at least 1 dose of darbepoetin alfa.

Sex: 273 (62%) men; 169 (38%) women

Mean Age: 65 years (standard deviation [SD], 14.9 years; range: 19 to 95 years)

Ethnicity (Race): 402 (91%) White; 16 (3.6%) Black, 9 (2%) Hispanic; 8 (1.8%) Asian; 7 (1.6%) Other races

Diagnosis and Main Criteria for Eligibility: Eligible subjects were ≥ 18 years of age, receiving hemodialysis for ≥ 3 months before randomization, receiving stable doses of darbepoetin alfa administered intravenously or subcutaneously once weekly or every other week for ≥ 6 weeks before screening, and had hemoglobin values between 10.0 to 13.0 g/dL, no previous exposure to EPREX® or NeoRecormon®, and adequate iron stores (serum ferritin ≥ 100 μg/L).

Investigational Product, Dose and Mode of Administration: Darbepoetin alfa was the only investigational product administered to subjects in this study. Darbepoetin alfa manufactured by the serum-free process (darbepoetin alfa SF) was the investigational therapy. Darbepoetin alfa SF was provided as a clear, colorless, sterile protein solution in pre-filled syringes at the following unit doses: 10, 15, 20, 30, 40, 50, 60, 80, 100, or 150 μg. The initial dose of darbepoetin alfa was the same as that received before randomization rounded to the nearest unit dose. The initial frequency and route of administration of darbepoetin alfa were the same as the subject was receiving before randomization.

Duration of Treatment: Duration of treatment was up to 28 weeks.

Reference Therapy, Dose and Mode of Administration: Darbepoetin alfa manufactured by the current roller bottle process (darbepoetin alfa RB) was the reference therapy. Darbepoetin alfa RB was provided as a clear, colorless, sterile protein solution in pre-filled syringes at the following unit doses: 10, 15, 20, 30, 40, 50, 60, 80, 100, or 150 μg. The initial dose of darbepoetin alfa was the same as that received before randomization rounded to the nearest unit dose. The initial frequency and route of administration of darbepoetin alfa were the same as the subject was receiving before randomization.

Study Endpoints

Primary Efficacy Endpoints

The primary efficacy endpoints compared darbepoetin alfa SF and RB for the following:

- Change in hemoglobin concentration between baseline and the evaluation period
- Ratio of weekly dose at the evaluation period to the weekly dose at baseline

Secondary Efficacy Endpoints

- Change from baseline hemoglobin at each measurement time point
- Maintaining a mean hemoglobin within target range during the evaluation period
- Average darbepoetin alfa dose over evaluation period
- Change from baseline dose at each measurement time point

Safety Endpoints

- Darbepoetin alfa seroreactivity
- Subject incidence, nature, and severity of adverse events
- Hemoglobin variability

- Changes from baseline laboratory and vital sign parameters
- Subject incidence of red blood cell (RBC) transfusions

Statistical Methods:

Efficacy

The primary and secondary efficacy endpoints were analyzed using a primary analysis set (per-protocol) and full analysis set. Subjects were included in the primary analysis set if they received ≥ 1 dose in the treatment group to which they were randomized, had ≥ 1 hemoglobin measurement during the evaluation period (weeks 21 to 28), and did not receive a RBC transfusion between the first dose of investigational product (week 1) and the day of the last hemoglobin measurement during the evaluation period. Subjects were included in the full analysis set if they received ≥ 1 dose in the treatment group to which they were randomized.

Two-sided 95% confidence intervals (CIs) for the change in hemoglobin concentration from baseline to the evaluation period for each treatment group and the difference in the mean change between darbepoetin alfa SF and RB (SF - RB) were computed. The mean dose ratio and log-transformed dose ratio for each treatment group and a 90% confidence interval (CI) for the difference in mean log-transformed dose ratios between darbepoetin alfa SF and RB were calculated. All transformations used the natural log (base e) scale.

To demonstrate equivalence, the 2-sided 95% confidence interval for the difference in mean change in hemoglobin between darbepoetin alfa SF and RB must have been within ±0.5 g/dL and the 2-sided 90% CI for the difference in dose ratio between darbepoetin alfa SF and RB must have been within log(0.8) and log(1.25).

Secondary efficacy endpoints were summarized using descriptive statistics, including the number of non-missing values, mean, median, standard deviation, lower and upper 25th percentiles, and minimum and maximum for continuous variables and the number and percent of values in each category for categorical variables.

Safety

Safety was analyzed using the safety analysis population, which included all subjects who received ≥ 1 dose of darbepoetin alfa. The subject incidence of each adverse event was tabulated by preferred term, severity and relationship to treatment. Hemoglobin-related safety parameters, including rate of rise (ROR), increases over 2- and 4-week windows, changes between time points, variability and excursions (hemoglobin concentration > 14.0 g/dL), as well as changes from baseline in other laboratory variables and vital signs, were summarized using descriptive statistics. The proportion of subjects developing anti-erythropoietic protein antibodies was calculated.

Summary of Results:

Subject Disposition:

Four hundred forty-six subjects were randomized into the study and 442 subjects (219 darbepoetin alfa SF, 223 darbepoetin alfa RB) received ≥ 1 dose of darbepoetin alfa. A similar proportion of subjects in each treatment group completed the study (83% SF, 82% RB).

Three hundred sixty-two subjects (81%; 183 SF, 179 RB) were included in the primary analysis set. The most common reason subjects were excluded from the primary analysis set was no hemoglobin measurement during the evaluation period (25 SF, 34 RB). Four hundred thirty-eight subjects (98%; 217 SF, 221 RB) were included in full analysis set. Four of these subjects (3 SF,

1 RB) did not receive investigational product and 4 (2 from each group) were excluded because of GCP violations. Four hundred forty-two subjects (220 SF, 222 RB) were included in the analysis set for the evaluation of all safety endpoints.

Efficacy Results:

The difference in mean change in hemoglobin concentration from baseline to the evaluation period between the darbepoetin alfa SF and RB groups for the primary analysis set was -0.19 g/dL (95% CI: -0.42, 0.03 g/dL). The 2-sided 95% CI was entirely within the protocol-specified equivalence margin (±0.5 g/dL), demonstrating that darbepoetin alfa SF is equivalent to darbepoetin alfa RB for hemoglobin maintenance.

The mean difference in log-transformed ratio of dose during the evaluation period to the baseline dose between the SF and RB treatment groups was 0.06 (90% CI: -0.03, 0.16). The 2-sided 90% CI was entirely within the protocol-specified equivalence margin of log(0.80) to log(1.25), or -0.223 to 0.223, demonstrating that darbepoetin alfa SF is equivalent to darbepoetin alfa RB with respect to dose.

Equivalence between darbepoetin alfa SF and RB was also demonstrated for hemoglobin maintenance and dose in a sensitivity analysis performed on the full analysis set. These results demonstrate that darbepoetin alfa SF is as effective as darbepoetin alfa RB for both hemoglobin maintenance and dose.

Consistent with the results of the primary endpoint analyses, hemoglobin concentrations were stable throughout the study for both treatment groups. In the primary analysis set, mean (SD) change in hemoglobin concentrations from baseline during the treatment period ranged from -0.17 (1.12) to 0.16 (1.04) g/dL for darbepoetin alfa SF and from -0.00 (1.16) to 0.27 (1.09) g/dL for darbepoetin alfa RB. Seventy percent of subjects in both treatment groups had hemoglobin concentrations within the target range during the evaluation period.

Dosing trends were similar for darbepoetin alfa SF and RB. Median (range) baseline weekly dose was 30 (5 to 150) μg/week for both treatment groups in the primary analysis set. Median (range) weekly doses during the evaluation period were 25.00 (0 to 175.0) and 20.00 (0 to 143.8) μg/week for the darbepoetin alfa SF and RB groups, respectively. Median change in dose from baseline was 0 μg/week at each time point for both treatment groups, except for one time point (-2.50 μg/week for darbepoetin alfa RB at week 28). The mean change in dose from baseline decreased during the first 12 and 11 weeks to approximately -7 μg/week for darbepoetin alfa SF and RB, respectively, and then remained relatively stable for both treatment groups.

Safety Results:

Of the 442 subjects included in the safety analysis set, 174 (79%) in the darbepoetin alfa SF group and 174 (78%) in the darbepoetin alfa RB group reported ≥ 1 adverse event during the study. The most common adverse events in both treatment groups were muscle spasms (13% SF, 9% RB) and hypotension (10% SF, 9% RB). Treatment-related adverse events were reported for 6 subjects (3%) in the darbepoetin alfa SF group and 8 (4%) in the darbepoetin alfa RB group. The proportion of subjects experiencing serious adverse events was similar between the treatment groups (29% SF, 32% RB). Two [1%] subjects in the darbepoetin alfa SF group and 4 [2%] in the darbepoetin alfa RB group experienced serious adverse events considered treatment-related by the investigator. Seven subjects (3%) in the darbepoetin alfa SF group and 4 (2%) in the darbepoetin alfa RB group were withdrawn from the study because of an adverse event, none of which were considered treatment-related by the investigator. Fourteen subjects (6%) in the darbepoetin alfa SF group and 15 (7%) in the darbepoetin alfa RB group died during the study. Three fatal adverse events, 1 (sudden death) in the darbepoetin alfa SF group and 2 (thrombosis and cerebral circulatory failure) in the darbepoetin alfa RB group, were considered treatment-related by the investigator.

Trends in hemoglobin ROR, maximum change over 2- or 4-week windows, and variability were similar between treatment groups. Twenty percent and 22% of subjects in the darbepoetin alfa SF and RB groups, respectively, had ≥ 1 hemoglobin excursion (> 14.0 g/dL) during the study. Hemoglobin concentrations decreased and remained ≤ 13.0 g/dL for most of these subjects (95% SF, 90% RB). The median time required for hemoglobin to return to ≤ 13.0 g/dL was 3 and 4 weeks for the darbepoetin alfa SF and RB groups, respectively. Darbepoetin alfa was withheld for 89% and 73% of subjects after the hemoglobin excursion in the darbepoetin alfa SF and RB groups, respectively, and was subsequently restarted in 80% and 63% of subjects, respectively, once their hemoglobin concentrations were < 13.0 g/dL. Eighty-nine percent and 90% of the subjects with excursions completed the study in the darbepoetin alfa SF and RB groups, respectively.

Mean clinical laboratory values and mean vital signs did not change notably over the course of the study for either treatment group. A low prevalence of binding antibodies was observed for both treatment groups at baseline (5% SF, 7% RB) and after treatment with darbepoetin alfa (5% SF, 7% RB). All subjects tested in the bioassay were negative for neutralizing antibodies.