Product: Darbepoetin alfa
Clinical Study Report: 20050210
Date: 10 July 2008

SYNOPSIS

Name of Sponsor: Amgen Ltd.

Name of Finished Product: Aranesp®

Name of Active Ingredient: Darbepoetin alfa

Title of Study: A multicenter, single-arm study evaluating the extension from weekly to once every other week darbepoetin alfa administration in subjects with chronic kidney disease receiving dialysis

Investigators and Study Centres: This study was conducted at 17 study centres in Europe (Austria, France, Italy, and Germany).

Publication(s): None

Study Period: 06 April 2006 (first subject signed informed consent) to 07 June 2007 (the date of the last subject assessment for which data are included in this report)

Development Phase: 3

Objectives:

Primary

To assess the proportion of subjects successfully achieving a mean haemoglobin ≥ 11.0 g/dL during the evaluation period following extension from once weekly (QW) to once every other week (Q2W) darbepoetin alfa administration.

Secondary

The secondary objectives were

- to determine haemoglobin values over the duration of the study,
- to determine darbepoetin alfa doses over the duration of the study, and
- to assess the safety of darbepoetin alfa administered Q2W.

Methodology: This multicenter, open-label, single-arm, study enrolled subjects with chronic kidney disease (CKD) who were receiving dialysis (either haemodialysis [HD] or peritoneal dialysis [PD]) and stable QW darbepoetin alfa therapy. Enrolled subjects were switched to Q2W darbepoetin alfa dosing for 32 weeks (study weeks 1 to 33); the route of administration was not changed (ie, intravenous [IV] or subcutaneous [SC]). Following screening, eligible subjects received (at Week 1, the first visit of the treatment period) an initial dose of darbepoetin alfa equal to the subject's total dose over the two darbepoetin alfa administrations prior to enrolment rounded to the nearest prefilled syringe (PFS) dose. Subsequent darbepoetin alfa doses occurred at a Q2W frequency. During the treatment period, doses were titrated to maintain the haemoglobin target of ≥ 11.0 g/dL and ≤ 13.0 g/dL. Efficacy was assessed during the evaluation period in the final 8 weeks of the study (study weeks 25 to 33).

Number of Subjects Planned: One hundred subjects were planned.

Number of Subjects Enrolled: In total, 114 subjects were enrolled in the study; of these, 113 received at least 1 dose of darbepoetin alfa. Demographic data for these 113 subjects are presented below.

Sex: 49 (43%) women, 64 (57%) men
Mean (standard deviation [SD]; range) Age: 66.8 (13.0; 23 to 86) years
Race: 112 (99%) white/Caucasian, 1 (1%) Asian

Diagnosis and Main Criteria for Eligibility: Subjects eligible for participation were ≥ 18 years of age, diagnosed with CKD and receiving dialysis (HD or PD) for at least 3 months prior to enrolment, receiving stable QW darbepoetin alfa doses for ≥ 6 weeks prior to enrolment (defined as ≤ 25% change in dose over the 6-week period immediately prior to enrolment and no change in frequency), had two screening haemoglobin concentrations (taken at least 7 days apart) between ≥ 11.0 and ≤ 13.0 g/dL, and adequate iron stores (serum ferritin ≥ 100 μg/L).

Investigational Product, Dose, and Mode of Administration, Manufacturing Batch Number: Darbepoetin alfa was provided for IV or SC administration as a clear, colourless, sterile protein solution in PFSs containing unit doses of 10, 15, 20, 30, 40, 50, 60, 80, 100, 130, 150, 200 or 300 μg. Using the same route as that prior to enrolment, the initial Q2W dose was equal to the subject's total dose over the two darbepoetin alfa administrations prior to enrolment, rounded to the nearest PFS dose. Thereafter, doses were administered every 14 days (ie, Q2W).

Duration of Treatment: The duration of treatment was 32 weeks.

Reference Therapy, Dose and Mode of Administration, Manufacturing Batch Number: No reference therapy was administered in this study.

Study Endpoints

Primary Efficacy:

- Maintenance of a mean haemoglobin during the evaluation period ≥ 11.0 g/dL

Secondary Efficacy:

- Haemoglobin at each scheduled time point (Baseline, weeks 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25,27, 29, 31, 33)
- Darbepoetin alfa doses over the duration of the study

Safety:

- Adverse events during the study
- Laboratory parameters and blood pressure at each scheduled time point
- haemoglobin rate of rise (ROR) during the study and excursions > 14.0 g/dL
- Antierythropoietic protein antibodies

Statistical Methods:

The primary analyses of study endpoints were completed on the data set including all subjects who received at least 1 dose of investigational product (Full Analysis Set). A sensitivity analysis of the primary efficacy endpoint was performed using the subset of subjects who completed the study. The key efficacy and safety analyses were also completed by modality of dialysis (hemodialysis and peritoneal dialysis) and by route of darbepoetin alfa administration (IV, SC).

Descriptive statistics (mean, median, standard deviation), minimum and maximum for continuous variables, 25th and 75th percentiles, and number and percentage of subjects for categorical variables) was presented for all efficacy and safety endpoints. For the primary endpoint, haemoglobin over the evaluation period, and dose over the evaluation period, as well as other specified parameters, the 2-sided 95% confidence intervals (CIs) were presented. The appropriate descriptive statistic for each continuous variable was selected based on the normality of the distributional characteristics.

All efficacy and other endpoints were summarized using descriptive statistics. Two-sided 95% CI were provided for selected variables. Confidence intervals for continuous data were derived from the Student's *t*-distribution (ie, accounting for the degrees of freedom) for means; 95% CIs for the medians used the Hodges-Lehmann estimate adjusted for ties (Hollander and Wolfe, 1973); CIs for categorical variables are exact.

All analyses are based on CIs, and no formal testing of statistical significance (p-values) was undertaken.

Summary – Results

Subject Disposition:

In total, 114 subjects were enrolled in this study; of these, 113 received at least 1 dose of darbepoetin alfa and were included in the Full Analysis Set. Ninety-eight (86%) subjects completed the study.

Efficacy Results:

Overall, 113 of the 114 subjects enrolled in this study received at least 1 dose of darbepoetin alfa and were included in the efficacy analysis; of these, 57% (95% CI: 47%, 66%) achieved a mean haemoglobin concentration of ≥ 11.0 g/dL during the evaluation period. Of the 98 subjects who completed the study, 65% (95% CI: 55%, 75%) achieved a mean haemoglobin concentration of ≥ 11.0 g/dL during the evaluation period. When analyzed by the type of dialysis, 57% (95% CI: 47%, 68%) of subjects receiving haemodialysis and 53% (95% CI: 29%, 76%) receiving peritoneal dialysis maintained a mean haemoglobin concentration ≥ 11.0 g/dL during the evaluation period. Approximately half (53%) of the 85 subjects who had received IV darbepoetin alfa administration at enrolment, and 68% of the 28 who had received SC darbepoetin alfa administration, maintained the mean haemoglobin target.

Mean (SD) haemoglobin concentration decreased from 12.0 (0.49) g/dL at baseline to 11.4 (1.01) g/dL at week 33; the mean (95% CI) haemoglobin concentration over the evaluation period was 11.4 (11.2, 11.5) g/dL, corresponding with a mean change from baseline of -0.65 (-0.84, -0.46) g/dL. With the starting baseline Q2W darbepoetin alfa dose being equal to the total of the last two QW administrations prior to enrolment, the median (range) darbepoetin alfa Q2W doses increased from 60 (20 to 200) μg at baseline to 80 (10 to 800) μg at the end of the study (final dose). The median (range) darbepoetin alfa Q2W dose during the evaluation period was 100 (0 to 300) μg, and the median (range) Q2W dose ratio (evaluation/baseline) was 1.3 (0 to 4.9). Consistent with actual dose, the median (range) weight-adjusted Q2W dose showed a modest increase over the duration of the study from 0.8 (0.2 to 2.9) μg/kg at baseline to 1.0 (0.1 to 2.6) μg/kg at week 33.

These results indicate that darbepoetin alfa administered Q2W maintained haemoglobin concentrations in more than half (approximately 57%) of patients with CKD receiving dialysis who were previously receiving darbepoetin alfa once weekly; however, achievement of the primary endpoint in 57% of subjects was associated with an increase in the median darbepoetin alfa dose in the population.

Safety Results:

In total, 80% of the subjects experienced at least 1 adverse event, with the most common adverse events (9 – 12% incidence) being muscle spasms, nausea, abdominal pain, diarrhoea, and dyspnoea. Of the 113 subjects who received at least 1 dose of darbepoetin alfa, 1 (1%) had an adverse event considered by the investigator to be treatment related (hemiparesis [serious adverse event]), and 1 (1%) had a serious transient ischemic attack considered by Amgen to have a causal relationship with investigational product. Five (4%) subjects died (events of sudden death [×2], pancreatic carcinoma metastatic, pulmonary embolism, and staphylococcal sepsis), 34 (30%) subjects experienced serious adverse events, and 3 (3%) subjects withdrew from the study prematurely due to general physical health deterioration, pancreatic carcinoma metastatic, and staphylococcal sepsis (all meeting the definition of a serious adverse event).

The majority of serious adverse events were classified within the body systems of injury, poisoning and procedural complications (12%), infections and infestations (7%), and vascular disorders (6%). The only serious adverse events reported for more than 2 subjects were angina pectoris (3 [3%] subjects), arteriovenous fistula thrombosis (3 [3%] subjects), and dyspnoea (3 [3%] subjects).

Prospectively identified adverse events of special interest (fatal events, cardiovascular events, thromboembolic events, hypertension, seizure) were experienced by 27% of the patients in this study, with embolism/thrombosis being the most commonly reported (12 [11%] subjects). Ten subjects (9%) had hypertensive events during the study; for 2 of these subjects, hypertensive events (preferred term: hypertension) were serious. None of the subjects reporting hypertensive events had haemoglobin concentrations > 14 g/dL during the study. None of the adverse events of special interest was considered by the investigator to have a causal relationship to investigational product.

Five (5%) subjects had a haemoglobin excursion > 14.0 g/dL during the study; of these, 4 subjects had a single excursion and 1 subject had 2 excursions. All haemoglobin excursions were noted at week 3 (n = 1), week 5 (n = 2), and week 7 (n = 2); none occurred during the evaluation period. The median time to return to a haemoglobin level of $\leq$ 13.0 g/dL (after the first value > 14.0 g/dL) was 3 weeks (range: 0 to 8 weeks). Of the 5 subjects with any haemoglobin excursion > 14.0 g/dL, 2 did not complete the study: 1 was lost to follow-up, and 1 died of unrelated pulmonary embolism 3 days after the first haemoglobin excursion (15.2 g/dL).

The mean (range) maximum haemoglobin increase over any 4-week period during the study was 1.26 (-0.7, 4.2) g/dL. Mean (SD) ROR values ranged from -0.36 (1.47) g/dL/4 weeks at week 13 to 0.23 (1.28) g/dL/4 weeks at week 23.

Changes in haematology or chemistry laboratory results from baseline to the end of the study were otherwise not clinically meaningful. Non-neutralizing antibodies were detected in few subjects in this study. Of the 91 (83%) subjects who had antibody results available both at week 1 and at the end of the study, 6 subjects who had pre-existing binding, non-neutralizing anti-erythropoietic antibodies at week 1 maintained their antibody-positive status at the end of study after extension from QW to Q2W darbepoetin alfa administration (3 positive results for binding, non-neutralizing antibodies to darbepoetin alfa; 5 positive results for epoetin alfa). Three subjects developed binding, non-neutralizing antibodies after Q2W dosing (ie, had negative binding assay results before dosing, but positive binding assay results at the end of the study); all 3 subjects had low antibody concentrations below the quantification limit of the assay (< 0.25 μg/mL). All subjects tested in the bioassay were negative for neutralizing antibodies at week 1 (pretreatment) and at the end of the evaluation period.