1. TITLE PAGE

Study Title:	A Multicenter, Randomized, Double-blind Study Comparing De Novo Once Monthly and Once Every 2 Week Darbepoetin alfa Dosing for the Correction of Anemia in Subjects With Chronic Kidney Disease Not Receiving Dialysis
Investigational Product:	Darbepoetin alfa (Aranesp®)
Indication:	Treatment of anemia in subjects with chronic kidney disease (CKD) not receiving dialysis
Brief Description:	This was a multicenter, double-blind, active-controlled, phase 3 study to determine whether the efficacy of once monthly (QM) darbepoetin alfa was noninferior to that of once every 2 week (Q2W) darbepoetin alfa for correction of anemia in subjects with CKD not on dialysis who were anemic and not receiving an erythropoiesis-stimulating agent. Subjects were randomized 1:1 to receive darbepoetin alfa either Q2W or QM. Randomized subjects received an initial subcutaneous darbepoetin alfa dose of 0.75 µg/kg (Q2W group) or 1.5 µg/kg (QM group), rounded to the nearest unit dose, using a pre-filled syringe. Thereafter, doses were titrated to achieve and then maintain hemoglobin levels within a target range of 10.0 to 12.0 g/dL and at least 1.0 g/dL above baseline over a 32-week treatment period.
Study Sponsor:	Amgen Ltd, 240 Cambridge Science Park, Milton Road, Cambridge CB4 0WD, United Kingdom Tel: +44(0)1223 420305
Study No.:	20060163
EudraCT Number	2006-003173-27
Study Phase:	3
Study Initiation Date:	15 June 2009 (date that the first subject was enrolled)
Study Completion Date:	10 April 2012 (date of the last subject's final study visit)
Principal Investigator(s):	This study was conducted at 95 centers in Europe, Australia, and Mexico. Centers and principal investigators are listed in Appendix 4.
Contact Person:	[redacted]
Good Clinical Practice:	This study was conducted in accordance with International Conference on Harmonisation (ICH) Good Clinical Practice (GCP), the European Clinical Trials Directive regulations/ guideline, and applicable country regulations. Essential documents will be retained in accordance with ICH GCP.
Report Date:	09 August 2012

2. SYNOPSIS

Name of Sponsor: Amgen Ltd., Cambridge, United Kingdom

Name of Finished Product: Aranesp®

Name of Active Ingredient: Darbepoetin alfa

Title of Study: A Multicenter, Randomized, Double-blind Study Comparing De Novo Once Monthly and Once Every 2 Week Darbepoetin alfa Dosing for the Correction of Anemia in Subjects With Chronic Kidney Disease Not Receiving Dialysis

Investigator(s) and Study Center(s): This study was conducted at 95 centers in Europe, Australia, and Mexico. Centers and principal investigators are listed in Appendix 4.

Publication(s): None

Study Period: This clinical study report includes results from 15 June 2009 (date that the first subject was enrolled) to 10 April 2012 (date last subject's final study visit)

Development Phase: 3

Objectives

Primary Objective: To determine whether the efficacy of once monthly (QM) darbepoetin alfa was noninferior to that of once every 2 week (Q2W) darbepoetin alfa for the correction of anemia in subjects with chronic kidney disease (CKD) not receiving dialysis.

Secondary Objective: To evaluate whether the safety and tolerability of QM darbepoetin alfa was similar to that of Q2W darbepoetin alfa for patients with CKD not receiving dialysis.

Methodology

This was a multicenter, double-blind, active-controlled phase 3 study comparing QM and Q2W dosing of darbepoetin alfa. Subjects with CKD not on dialysis who were anemic and not receiving an erythropoiesis stimulating agent (ESA) were randomized 1:1 to receive de novo administration of either Q2W or QM darbepoetin alfa for 32 weeks. Randomized subjects received an initial subcutaneous (SC) dose of darbepoetin alfa determined using the weight-based calculation of 0.75 µg/kg Q2W or 1.5 µg/kg QM, rounded to the nearest unit dose, using a pre-filled syringe. Doses were titrated to achieve and then maintain hemoglobin (Hb) levels within a target range of 10.0 to 12.0 g/dL and at least 1.0 g/dL above baseline. Dose and dosing interval were blinded to subjects, center personnel, and all Amgen study personnel and designees involved with study conduct. Subjects were assessed at an end-of-study visit 2 weeks after the final dose of investigational product (week 33) or at the time of early study withdrawal.

During the treatment phase and at the end-of-study visit, adverse events, vital signs, Hb and other clinical laboratory parameters, concomitant medications, anti-erythropoietic protein antibodies, and patient-reported outcomes (PRO) (Medical Outcomes Study Short Form-36 [SF-36] questionnaire) were evaluated at regular, prespecified intervals.

Number of Subjects Planned: Approximately 334 subjects

Number of Subjects Enrolled: 358 subjects

Diagnosis and Main Criteria for Eligibility: Eligible subjects met the following key criteria: ≥18 years of age; estimated glomerular filtration rate (eGFR) of 15 - 59 mL/min/1.73 m^2 (modified Modification of Diet and Renal Disease equation); 2 consecutive screening Hb values taken at least 7 days apart and prior to randomization <10.0 g/dL; transferrin saturation (TSAT) ≥ 15%; no upper or lower gastrointestinal bleeding within 6 months prior to enrollment; no ESA use within 12 weeks before enrollment; no uncontrolled hypertension or systemic hematologic disease; and no recent history (within 12 weeks before enrollment) of acute myocardial ischemia, unstable angina, myocardial infarction, hospitalization for congestive heart failure, stroke or transient ischemic attack, limb ischemia, deep vein thrombosis; or thromboembolism.

Investigational Product, Dose and Mode of Administration, Manufacturing Batch Number: Investigational product (darbepoetin alfa) was provided for SC administration as a clear, colorless, sterile protein solution in a pre-filled syringe at the following unit doses: 10, 20, 30, 40, 50, 60, 80, 100, 130, 150, 200, and 300 µg. Allowable doses were 10, 20, 30, 40, 50, 60, 80,

100, 130, 150, 200, 300, 400, and 600 µg. The initial Q2W or QM dose was determined using the weight-based calculation of 0.75 µg/kg or 1.5 µg/kg, respectively, rounded to the nearest unit dose. Thereafter, active doses were administered Q2W or QM. To maintain the study blind, subjects randomized to darbepoetin alfa QM received placebo QM at visits where active medication was not received. An interactive voice response system was used to determine the initial dose and to manage subsequent dosing adjustments. The pre-filled syringes contained darbepoetin alfa or placebo. Lot numbers for darbepoetin alfa and placebo used in this study are provided in Appendix 18.

Reference Therapy, Dose and Mode of Administration, Manufacturing Batch Number: Darbepoetin alfa administered Q2W was the reference group for this study.

Duration of Treatment: Subjects received darbepoetin alfa either Q2W or QM for 32 weeks.

Study Endpoints

The primary efficacy endpoint was the Hb change between baseline and the evaluation period (weeks 29 - 33).

Secondary efficacy endpoints were the following:

- achievement of both a Hb level ≥ 10.0 g/dL and a ≥ 1.0-g/dL increase from baseline at any timepoint following de novo darbepoetin alfa administration
- achievement of both a mean Hb level ≥ 10.0-g/dL and a ≥ 1.0-g/dL increase from baseline during the evaluation period
- time to first Hb level ≥ 10.0 g/dL and a ≥ 1.0-g/dL increase from baseline
- Hb level at each scheduled time point
- darbepoetin alfa doses over the duration of the study and during the evaluation period
- ratio of darbepoetin alfa doses over the duration of the study and during the evaluation period to the darbepoetin alfa dose at baseline
- dose at first Hb level ≥ 10.0 g/dL and a ≥ 1.0-g/dL increase from baseline

Safety endpoints were the following:

- Hb rate of rise (ROR) and maximum Hb increase over a 2-week period following de novo darbepoetin alfa administration
- adverse events following de novo darbepoetin alfa administration
- laboratory parameters and blood pressure at each scheduled timepoint
- Hb excursions above 12.0, 13.0, and 14.0 g/dL following de novo darbepoetin alfa administration
- anti-erythropoietic protein antibodies

The PRO endpoint was the change in PRO scores (SF-36) from baseline to week 17 and week 33.

Statistical Methods

Efficacy analyses were based on the treatment group to which a subject was randomized and were conducted for the primary analysis set (PAS) and full analysis set (FAS). The PAS included all subjects receiving ≥ 1 dose of darbepoetin alfa in the treatment group to which they were randomized and with ≥ 1 evaluable Hb measurement during the evaluation period (weeks 29-33). The FAS included all subjects who received ≥ 1 dose of darbepoetin alfa.

For the primary endpoint, the Hb change from baseline to the evaluation period was modeled with baseline Hb as a covariate, and the least square mean was presented by treatment along with the least square mean (95% confidence interval [CI]) difference between treatments. If the 2-sided 95% CI lay entirely above -0.50 g/dL, darbepoetin alfa QM was considered noninferior to darbepoetin alfa Q2W with regard to correction of Hb.

Descriptive statistics were presented for secondary efficacy endpoints. Dosing data were reported using geometric means. Weekly dose equivalents were derived from the received dose and the frequency of administration (ie, weekly dose equivalent = 0.5 * Q2W dose and 0.25 * QM dose). Darbepoetin alfa dose ratios were calculated by dividing the weekly dose equivalent during the study (or evaluation period) by the initial weekly equivalent dose. The time to first Hb level ≥ 10 g/dL and ≥ 1.0-g/dL increase from baseline was estimated using the Kaplan-Meier method. The proportions and 2-sided 95% CIs of subjects who achieved a Hb level ≥ 10.0 g/dL and ≥ 1.0-g/dL increase from baseline at any time point during the study and during the evaluation period were presented.

Safety analyses were conducted using the FAS. The subject incidences of adverse events were tabulated by system organ class and preferred term. The following Hb-related parameters were summarized descriptively: percentage of subjects with a Hb excursion > 12.0, > 13.0, and > 14.0 g/dL; Hb ROR at each time point and ≥ 2.0 and ≥ 3.0 g/dL/4 weeks at any point, maximum Hb increase over any 2-week window. The time required to return to the target range after a Hb > 12.0, > 13.0, or >14.0 g/dL excursion was estimated using the Kaplan-Meier method. Laboratory parameters, vital signs, physical examination results, concomitant medications, and the incidence of anti-erythropoietic protein antibodies were also summarized descriptively.

PRO analyses were conducted using the PRO analysis set, which included all subjects in the FAS who had data recorded at baseline and week 17 and/or week 33. Descriptive statistics were presented for PRO norm-based scores and transformed 0-100 scores. PRO scores were also analyzed using a repeated measures model adjusting for the baseline PRO score as covariate (primary) and for subjects who had had PRO data for the endpoint (sensitivity analysis of observed data) and using last value carried forward (LVCF) for missing data (sensitivity analyses).

Summary of Results

Subject Disposition: A total of 358 subjects were enrolled in the study, with 178 and 180 randomized to receive darbepoetin alfa Q2W and QM, respectively. Three hundred and fifty-five subjects (175 Q2W, 180 QM) received investigational product and were included in the FAS. Two hundred and ninety-six subjects (142 Q2W, 154 QM) received investigational product and had ≥ 1 Hb measurement during the evaluation period (weeks 29 to 33) and were included in the PAS. Of the 355 subjects in the FAS, 323 (156 Q2W, 167 QM) had a baseline and ≥ 1 post-baseline PRO assessment and were included in the PRO analysis set. In the Q2W group, 141 subjects completed treatment with investigational product, and 142 subjects completed the study. In the QM group, 156 subjects completed treatment with investigational product and 155 subjects completed the study.

Baseline Demographics

Baseline demographics were balanced between treatment groups.

Sex: 144 (40.6%) male; 211 (59.4%) female

Mean (standard deviation [SD]) Age: 67 (14.7) years

Ethnicity/Race: 329 (92.7%) white or Caucasian; 1 (0.3%) black or African American; 25 (7.0%) other

Efficacy Results

The results of the primary efficacy analysis demonstrated that darbepoetin alfa QM was noninferior to darbepoetin alfa Q2W for the correction of anemia. Treatment with darbepoetin alfa Q2W and QM resulted in an adjusted mean (95% CI) increase in hemoglobin from the baseline to the evaluation period of 2.16 (1.98, 2.33) and 1.97 (1.80, 2.14) g/dL, respectively. The adjusted mean (95%CI) difference between treatment groups was -0.19 (-0.43, 0.05) g/dL. The lower limit of the 95% CI for the treatment difference was greater than -0.5 g/dL and, thus, met the prespecified criterion for noninferiority of darbepoetin alfa QM. Sensitivity analyses of the primary endpoint (unadjusted analysis using the PAS, repeated measures analysis using the FAS, and analyses of baseline Hb concentrations, age, and gender subgroups) were consistent with the primary efficacy analysis.

The results of the secondary endpoint analyses also supported the similarity between darbepoetin alfa QM and darbepoetin alfa Q2W. Greater than 90% of subjects in both treatment

groups of the PAS achieved Hb ≥ 10.0 g/dL and a ≥ 1.0 g/dL increase in Hb from baseline at some time during the study (98% Q2W, 98% QM) and during the evaluation period (92% Q2W, 92% QM). The median time to achieve Hb ≥ 10.0 g/dL and a ≥ 1.0 g/dL increase from baseline was 5 weeks for both treatment groups in the PAS.

Trends in mean Hb concentration over time were similar between treatment groups in the PAS, increasing from baseline to week 13 (9.2 to 11.6 g/dL) for the Q2W group and to week 11 (9.1 to 11.2 g/dL) for the QM group and then remaining stable through the end of the study (week 33) for both groups. The mean (SD) Hb concentration during the evaluation period was 11.3 (1.07) and 11.1 (1.08) g/dL for the Q2W and QM groups, respectively, in the PAS.

On average, weekly equivalent doses and weight-adjusted weekly equivalent doses of darbepoetin alfa decreased from baseline over the study for both treatment groups in the PAS, although less of a decrease was observed for the QM group. The mean (SD) weekly equivalent dose over the evaluation period was 15 (20.4) µg/week for the Q2W group and 20 (25.0) µg/week for the QM group. The mean (SD) weight-adjusted weekly equivalent dose over the evaluation period was 0.20 (0.232) µg/kg/week for the Q2W group and 0.27 (0.306) µg/kg/week for the QM group. The ratios of darbepoetin alfa dose at each scheduled time point relative to the baseline dose reflected the weekly dose results. The mean (SD) dose ratio during the evaluation period was 0.55 (0.619) for the Q2W group and 0.73 (0.830) for the QM group. At the time that a Hb ≥ 10.0 g/dL and ≥ 1.0 g/dL increase from baseline was first achieved, mean (standard error [SE]) weekly equivalent dose was 26 (0.93) µg/week for the Q2W group and 30 (1.48) µg/week for the QM group. The mean (SE) weight-adjusted weekly equivalent dose was 0.35 (0.010) µg/kg/week for the Q2W group and 0.41 (0.017) µg/kg/week for the QM group.

The results of sensitivity analyses for the secondary endpoints using the FAS were consistent with those for the PAS.

PRO Results

The results of PRO assessments during this study indicate that darbepoetin alfa's effect on health-related quality of life was similar between Q2W and QM dosing. The repeated measures analysis adjusting for baseline score indicated that the change from baseline at week 33 in each subscale and summary scale was similar between treatment groups for norm-based scores, with mean (95% CI) treatment differences between -1.34 (-3.38, 0.70) and 0.69 (-1.59, 2.96). Results from sensitivity analyses using the observed data and LVCF for missing values were consistent with those for the repeated measures analyses. The mean change from baseline at week 17 in norm-based scores was also similar between treatment groups, as were mean changes from baseline at weeks 17 and 33 for transformed 0-100 scores.

Safety Results

The safety profile for darbepoetin alfa QM was similar to that of darbepoetin alfa Q2W and consistent with that expected in the CKD patient population. A total of 129 subjects (74%) in the darbepoetin alfa Q2W group and 126 subjects (70%) in the darbepoetin alfa QM group reported at least 1 adverse event during this study. The most common adverse events by preferred term in either treatment group were hypertension (22% Q2W, 18% QM), peripheral edema (10%, 8%), urinary tract infection (5%, 7%), hyperkalemia (4%, 8%), diarrhea (6%, 5%), chronic renal failure (6%, 4%), asthenia (6%, 3%), headache (5%, 4%), and cardiac failure (5%, 3%). Overall, similar trends between treatment groups were observed when adverse events were analyzed by age and gender subgroups.

Serious adverse events were reported for 52 subjects (30%) in the Q2W group and 54 subjects (30%) in the QM group. Three subjects (2%) in the Q2W group and 1 subject (1%) in the QM group had serious adverse events considered related to darbepoetin alfa (congestive cardiac failure [1], visual impairment [1], hypoesthesia and hypertension [1] for Q2W; hypertensive crisis [1] for QM). In each case, the event resolved and the subject continued with investigational product. Seven subjects (4%) in the darbepoetin alfa Q2W group and 5 subjects (3%) in the darbepoetin alfa QM group died during the study. Most of the fatal adverse events were cardiac or renal in nature (3 subjects [1%] total for each type), and none were considered related to darbepoetin alfa by the investigator. Ten subjects (6%) in the darbepoetin alfa Q2W group and 7 subjects (4%) in the darbepoetin alfa QM group were withdrawn from darbepoetin alfa due to an adverse event. Seven subjects (4%) in the darbepoetin alfa Q2W group and 2 subjects (1%) in

the darbepoetin alfa QM group were withdrawn from the study due to an adverse event. None of the adverse events leading to withdrawal were considered related to darbepoetin alfa. The combined subject incidence of adverse events of interest was 81 subjects (46%) for the darbepoetin alfa Q2W group and 76 subjects (42%) for the darbepoetin alfa QM group. No greater risk for darbepoetin alfa QM compared with Q2W dosing was observed for each of the adverse events of interest. The most frequently reported event of interest in both treatment groups was hypertension (40 subjects [23%] Q2W, 38 subjects [21%] QM).

Trends in Hb ROR and Hb excursions were similar for darbepoetin alfa QM compared with Q2W dosing. Mean Hb ROR was < 1.0 g/dL/2 weeks at each time point during the study for both treatment groups. Across all subjects in each treatment group, the mean maximum increase in Hb over any 2-week window during the study was 1.6 g/dL/2 weeks. Forty-six percent and 39% of subjects in the Q2W and QM groups, respectively, had Hb increases ≥ 2.0 g/dL/4 weeks and 12% and 9%, respectively, had Hb increases ≥ 3.0 g/dL/4 weeks during the study. Sixty-seven percent and 51% of subjects in the Q2W and QM groups, respectively, had at least 1 Hb value > 12.0 g/dL during the study. Thirty-four percent and 19%, respectively, had at least 1 Hb value > 13.0 g/dL, and 5% in both groups had at least 1 Hb value > 14.0 g/dL. The median time to return to the Hb target range (10.0 to 12.0 g/dL) following an excursion of > 12.0 or > 13.0 g/dL was similar between treatments groups (5 to 6 weeks). The median time to return to the target range following an excursion > 14.0 g/dL was 4 weeks (range: 3 to 23 weeks) for the Q2W group and 7 weeks (range: 1 to 13 weeks) for the QM group, although the range was wide and the number of subjects was small for each group (n = 9).

No trends were observed between treatment groups in any of the laboratory parameters or vital signs evaluated during this study. The use of iron supplementation, antihypertensive medication, and red blood cell transfusions was also similar between treatment groups. No greater risk for anti-erythropoietic protein antibody development was observed with QM compared with Q2W dosing. Ten (6%) and 16 (10%) subjects in the Q2W and QM groups, respectively, developed binding anti-erythropoietic protein antibodies during the study. None of the subjects tested were positive for neutralizing antibodies.

Conclusions: Darbepoetin alfa QM was noninferior to darbepoetin alfa Q2W for the correction of anemia in subjects with CKD not receiving dialysis. The safety profile for darbepoetin alfa QM was similar to that of darbepoetin alfa Q2W and consistent with that expected in the CKD patient population.