

Name of the Sponsor: Amgen Australia Pty Ltd	Name of Finished Product: Aranesp®	Name of Active Ingredient: Darbepoetin alfa
Title of Study: An Open-Label Study of Aranesp® (darbepoetin alfa) Administration Once Every Four Weeks In Anemic Chronic Kidney Disease (CKD) Subjects (Study 20030112)		
Investigators and Study Centers: This multicenter study was conducted at 9 centers in Australia.		
Publications: Disney A, de Jersey P, Kirkland G, et al. Aranesp® (darbepoetin alfa) administered once monthly (QM) maintains hemoglobin (Hb) levels in chronic kidney disease (CKD) patients [abstract]. <i>EDTA</i> . 2005. Disney A, de Jersey P, Kirkland G, Mantha M. A study of Aranesp® (darbepoetin alfa) administered once monthly in anemic chronic kidney disease (CKD) patients [abstract]. <i>ASN</i> . 2004;SU-PO245. Disney A, Gentgall M, MacMillan J, Bannon EM, Viswalingam A. A study of Aranesp® (darbepoetin alfa) administered once monthly in anaemic chronic kidney disease patients [abstract]. <i>EDTA-ERA XLI Congress</i> . 2004;Abstract Book:323a. Abstract MP273.		
Study Period: 16 July 2003 to 15 October 2004		Development Phase: Phase 3
Introduction and Objectives: <i>Primary:</i> To assess the proportion of CKD subjects maintaining mean hemoglobin ≥ 10.0 g/dL when administered subcutaneous (SC) darbepoetin alfa once monthly (QM) <i>Secondary:</i> <ul style="list-style-type: none"> • To determine hemoglobin values over the duration of the study • To determine darbepoetin alfa doses required to maintain hemoglobin concentrations ≥ 10.0 g/dL when administered QM • To assess the safety and tolerability of darbepoetin alfa when administered QM 		
Methodology: This multicenter, open-label, single-arm study enrolled subjects with CKD not receiving dialysis, who were receiving stable SC doses of darbepoetin alfa administered once every 2 weeks (Q2W). After the screening/baseline period, eligible subjects received darbepoetin alfa QM from study weeks 1 to 29. Efficacy was assessed during the evaluation period, which was the final 12 weeks of the study (study weeks 21 to 33). The starting dose for a subject was equivalent to that subject's total dose in the month preceding enrollment. The dose of investigational product was adjusted throughout the study to maintain the subjects' hemoglobin concentrations between 10.0 to 13.0 g/dL.		
Number of Subjects Planned: The planned sample size was approximately 100 subjects.		

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<p>Number of Subjects Enrolled: 66 Sex: 34 (52%) women; 32 (48%) men Mean Age: 66 years (SD: 13.8; range: 30 to 87) Ethnicity (Race): 62 (94%) white; 3 (5%) Asian; 1 (2%) other</p>
<p>Diagnosis and Main Criteria for Eligibility: Eligible subjects were ≥ 18 years of age with CKD not receiving dialysis; receiving stable doses of SC darbepoetin alfa Q2W for at least 6 weeks before the screening/baseline visit; not expected to initiate dialysis or undergo renal replacement therapy for the duration of the study; had at least 2 hemoglobin values of 10.0 to 13.0 g/dL obtained at least 1 week apart and within 5 weeks before the screening/baseline visit; had an additional hemoglobin value of 10.0 to 13.0 g/dL at baseline; had creatinine clearance 15 to 40 mL/min as estimated by the Cockcroft-Gault equation; had serum B₁₂ and folate values above the lower limit of the normal range; had serum ferritin > 100 μg/L or transferrin saturation $\geq 19.5\%$; and gave written informed consent.</p>
<p>Investigational Product, Dose and Mode of Administration: Commercial darbepoetin alfa (Aranesp[®]) was ordered directly by the site pharmacies. The following dose strengths were used in this study: 10, 20, 30, 40, 50, 60 and 100 μg. Darbepoetin alfa was administered by SC injection.</p> <p>The initial dose was equivalent to the subject's total dose in the month preceding enrollment. Subsequent doses were titrated to maintain the hemoglobin concentration in the target range (10.0 to 13.0 g/dL).</p>
<p>Duration of Treatment: Subjects received darbepoetin alfa QM for 28 weeks.</p>
<p>Reference Therapy, Dose and Mode of Administration: None</p>
<p>Primary Endpoint The proportion of subjects maintaining a mean hemoglobin concentration of ≥ 10.0 g/dL during the evaluation period (study weeks 21 to 33) when administered darbepoetin alfa QM</p> <p>Secondary Endpoints</p> <ul style="list-style-type: none"> • Hemoglobin values over the duration of the study • Darbepoetin alfa doses over the duration of the study • Safety of darbepoetin alfa as determined by adverse events, laboratory parameters, and blood pressure

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Statistical Methods:

All efficacy and safety endpoints were analyzed using the data set that included all subjects who received at least 1 dose of darbepoetin alfa.

Efficacy

The proportion of subjects maintaining a mean hemoglobin concentration ≥ 10.0 g/dL during the evaluation period (weeks 21 to 33) was calculated with the associated 95% confidence interval (CI). Secondary endpoints were summarized using descriptive statistics. For continuous variables, the mean, standard deviation (SD), median, quartiles (25th and 75th percentiles), minimum, and maximum were calculated. For categorical variables, the number and proportion were calculated. Ninety-five percent CIs were provided for means, medians, and percentages of specific endpoints.

Safety

Subject incidence of adverse events was tabulated by system organ class, high level terms, and preferred terms. Changes from baseline in laboratory variables and vital signs were summarized using descriptive statistics. The number of subjects receiving red blood cell transfusions, the number of red blood cell transfusions administered, and the relationship of transfusions to adverse events were summarized. The number and proportion of subjects developing anti-erythropoietic protein antibodies, if any, were calculated.

Summary - Results:**Subject Disposition:**

Sixty-six subjects were enrolled in this study, received at least 1 dose of darbepoetin alfa, and were included in the analysis set for safety and efficacy endpoints. Fifty-six subjects completed the study.

Efficacy Results:

Fifty-five of the 66 subjects (83% [95% CI: 74%, 92%]) in the efficacy analysis set maintained mean hemoglobin concentration ≥ 10.0 g/dL during the evaluation period (primary endpoint). Of the 56 subjects who completed the study, 53 subjects (95% [95% CI: 89%, 100%]) maintained mean hemoglobin concentration ≥ 10.0 g/dL during the evaluation period.

The mean hemoglobin concentration remained between 11.3 and 11.9 g/dL throughout the study. The mean (SD) change in hemoglobin concentration between baseline and the evaluation period was -0.55 (0.98) g/dL.

The median QM darbepoetin alfa dose at baseline was 80 μg (range: 10 to 200); the median QM darbepoetin alfa dose remained stable (between 75 and 80 μg) throughout the study. The median of the subject-mean QM doses over the evaluation period was 80 μg (range: 15.0 to 306.7); and the median change in QM dose between baseline and the evaluation period was 0.00 μg (mean = 7.47 μg [95% CI: 0.34, 14.60]). Thus the median QM dose remained stable over the duration of the study.

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Safety Results:

One or more adverse events were reported for 82% of subjects. Adverse events were mostly mild to moderate in severity and were consistent with adverse events expected for the subject population studied. The most common adverse events were hypertension (18%), nausea (15%), and chronic renal failure (14%). Adverse events were reported as related to treatment for 1 (2%) subject. Serious adverse events were reported for 35% of subjects, but no serious adverse event was considered related to treatment by the investigator. No subjects discontinued study because of adverse events. One (2%) subject died during the study; the cause of death was myocardial ischemia and was not considered by the investigator to be related to treatment.

Laboratory parameters and blood pressure did not change notably over the course of the study and did not suggest any adverse effects associated with darbepoetin alfa dosed QM. No subject developed antibodies to darbepoetin alfa or recombinant human erythropoietin (rHuEPO) during the study. One subject tested positive for binding, non-neutralizing antibodies to darbepoetin alfa and rHuEPO at baseline; a post-treatment sample was not available for testing because the subject discontinued the study. This subject had hemoglobin concentrations, darbepoetin alfa dosages, and an adverse event profile consistent with subjects without anti-erythropoietic protein neutralizing antibodies.

In summary, the safety profile reported in this open-label study was consistent with that expected for subjects with CKD not receiving dialysis. The study results do not suggest any safety concerns associated with the administration of darbepoetin alfa QM in this patient population.

Conclusions:

This study demonstrated that administration of darbepoetin alfa QM maintained hemoglobin concentrations without additional safety concerns in CKD subjects not receiving dialysis who were already stable on darbepoetin alfa administered Q2W.