Name of Sponsor: Amgen Ltd, United Kingdom

Name of Finished Product: Aranesp®

Name of Active Ingredient: Darbepoetin alfa

Title of Study: A Randomized Open-Label Study of Darbepoetin alfa Administered Every Three Weeks With or Without Parenteral Iron in Anemic Subjects with Nonmyeloid Malignancies Receiving Chemotherapy (Study 20040156)

Investigator(s) and Study Center(s): This study was conducted at 95 sites in Europe.

Publication(s):

Bastit L, Gaede B, Yao B, et al. Darbepoetin alfa (DA) every 3 weeks (Q3W) +/- parenteral iron in patients (pts) with chemotherapy-induced anaemia (CIA). *Ann Oncol.* 2006;17(Supp 9):ix293(Abstract 1015P).

Lerchenmueller C, Husseini F, Gaede B, et al. Intravenous (IV) iron supplementation in patients with chemotherapy-induced anemia (CIA) receiving darbepoetin alfa every 3 weeks (Q3W): iron parameters in a randomized controlled trial. *Blood.* (ASH Annual Meeting Abstracts). 2006;108:Abstract 1552.

Vandebroek, A, Altintas S, Gaede B, et al. Darbepoetin alfa administered every 3 weeks with or without parenteral iron in anaemic patients with nonmyeloid malignancies receiving chemotherapy: interim results from a randomised open-label study. 11th Congress of the European Hematology Association; 2006; Amsterdam.

Vandebroek, A, Gaede B, Altintas S, et al. A randomized open-label study of darbepoetin alfa administered every 3 weeks with or without parenteral iron in anemic subjects with nonmyeloid malignancies receiving chemotherapy. *J Clin Oncol.* (ASCO Annual Meeting Proceedings Part I). 2006;24(18S):8612.

Study Period: 27 September 2004 (first site initiated) to 01 August 2006 (last subject completed)

Development Phase: 3b

Introduction and Objectives:

The primary objective of this study was to compare hematopoietic response after 16 weeks of treatment with 500 mcg once every 3 weeks (Q3W) darbepoetin alfa and either intravenous (IV) iron or following standard practice (oral iron or no iron supplementation).

The secondary objectives of this study included the following:

- To compare the impact on the time to hematopoietic response of 16 weeks of treatment with 500 mcg Q3W darbepoetin alfa with either IV iron or following standard practice
- To compare the impact on red blood cell (RBC) transfusions of 16 weeks of treatment with 500 mcg Q3W darbepoetin alfa with either IV iron or following standard practice
- To compare the impact on change in hemoglobin of 16 weeks of treatment with 500 mcg Q3W darbepoetin alfa with either IV iron or following standard practice

- To compare the ability to achieve therapeutic objectives of anemia treatment (achieving and maintaining hemoglobin levels consistent with the National Comprehensive Cancer Network guidelines) of 16 weeks of treatment with 500 mcg Q3W darbepoetin alfa with either IV iron or following standard practice

- To compare the impact on patient-reported outcomes (PROs) of treatment with 16 weeks of 500 mcg Q3W darbepoetin alfa with either IV iron or following standard practice

- To assess the overall safety of 500 mcg darbepoetin alfa administered Q3W via the auto-injector with IV iron or following standard practice

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Methodology: This was a multicenter, open-label, randomized study of darbepoetin alfa administered at a fixed dose of 500 mcg Q3W in subjects with nonmyeloid malignancies receiving chemotherapy and IV iron or following standard practice (oral iron or no iron supplementation). The study consisted of a 14-day screening period during which eligibility was determined, followed by randomization in a 1:1 allocation to either darbepoetin alfa 500 mcg Q3W and IV iron (DA + IV) or darbepoetin alfa 500 mcg Q3W and following standard practice (oral iron or no iron supplementation) (DA). Randomization was stratified by tumor type (lung/gynecological or other tumors) and baseline hemoglobin category ($\geq$ or < 10.0 g/dL). The darbepoetin alfa dose was adjusted in order to carefully manage the hemoglobin level to achieve a target value of 12.0 g/dL and avoid exceeding 13.0 g/dL or an increase in hemoglobin concentration > 2.0 g/dL/28 days. For subjects randomized to the DA + IV group, IV iron was preferably administered Q3W (ie, on the same day as darbepoetin alfa). Sites were allowed to divide the total dose of 200 mg elemental iron and administer the first part of the dose at the applicable Q3W visit with the remaining part of the dose at the subsequent interim visit, if required by their clinical practice, applicable regulations, or logistical arrangements. This practice was permitted as long as the total dose over 3 weeks was 200 mg. Intravenous iron was withheld if serum ferritin exceeded 1000 ng/mL and restarted at the next darbepoetin alfa dosing visit if serum ferritin was $\leq$ 1000 ng/mL. Subjects in the standard practice arm (DA) were not allowed to receive IV iron on study. Subjects were administered darbepoetin alfa for a total of 16 weeks (5 doses).

Number of Subjects Planned: 400 (200 in each treatment group)

Number of Subjects Enrolled: Three hundred ninety-eight subjects were randomized into this study (201 DA + IV, 197 DA). Three hundred ninety-six subjects (200 DA + IV, 196 DA) received $\geq$ 1 dose of darbepoetin alfa.

Sex: 240 (61%) women; 156 (39%) men

Mean Age: 61 years (standard deviation [SD] 11.5 years; range: 20 to 85 years)

Ethnicity (Race): 390 (98%) White, 2 (1%) Asian, 2 (1%) Black, 2 (1%) Other

Diagnosis and Main Criteria for Eligibility: Eligible subjects had a nonmyeloid malignancy, hemoglobin concentration < 11.0 g/dL, and an Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2. In addition, eligible subjects must have been of legal age to consent and planned to receive $\geq$ 8 weeks of cyclic cytotoxic chemotherapy.

Investigational Product, Dose and Mode of Administration, Manufacturing Batch Number: Darbepoetin alfa 500 mcg with IV iron administered Q3W was considered the investigational treatment group during this study. Darbepoetin alfa was supplied in 150, 300, and 500 mcg autoinjectors (prefilled glass syringes containing 500 mcg/mL darbepoetin alfa in solution). The syringes also contained sodium phosphate, sodium chloride, polysorbate 80, with a pH 6.2. Intravenous iron was administered as sodium ferric gluconate complex in sucrose for IV administration (eg, Ferrlecit®) or iron sucrose injection (eg, Venofer®) at an equivalent dose of 200 mg elemental iron Q3W. Intravenous iron dextran was not allowed during this study.

Duration of Treatment: 16 weeks (5 doses)

Reference Therapy, Dose and Mode of Administration, Manufacturing Batch Number:
Darbepoetin alfa 500 mcg Q3W administered to subjects following standard practice (oral iron or no iron supplementation) was considered the reference treatment group during this study. Darbepoetin alfa was supplied in 150, 300, and 500 mcg autoinjectors (prefilled glass syringes containing 500 mcg/mL darbepoetin alfa in solution). The syringes also contained sodium phosphate, sodium chloride, polysorbate 80, with a pH 6.2.

Study Endpoints

Primary Efficacy Endpoint:

The primary efficacy endpoint was the proportion of subjects achieving a hematopoietic response (hemoglobin concentration ≥ 12.0 g/dL or rise in hemoglobin concentration of ≥ 2.0 g/dL) during the treatment period.

Secondary Efficacy Endpoints:

- Time to hematopoietic response in days
- The proportion of subjects with at least one RBC transfusion from week 5 (day 29) to the end of the treatment period (EOTP)
- Time to RBC transfusion from week 5 (day 29) to EOTP
- Change in hemoglobin from baseline over time
- Change in hemoglobin from baseline to EOTP
- The proportion of subjects achieving a hemoglobin concentration ≥ 11.0 g/dL, in the absence of RBC transfusions in the preceding 28 days, from week 5 to EOTP
- Time to achieving a hemoglobin concentration ≥ 11.0 g/dL, in the absence of RBC transfusions in the preceding 28 days, from week 5 to EOTP
- The average hemoglobin after achieving a hemoglobin concentration ≥ 11.0 g/dL
- Patient-reported outcomes (PROs):
    - Change in Functional Assessment of Cancer Therapy-Fatigue (FACT-F) subscale score from baseline to EOTP
    - Change in FACT-General (FACT-G) Physical Well-being subscale from baseline to EOTP
    - Change in FACT-G total score from baseline to EOTP
    - Change in EQ-5D thermometer and EQ-5D Health State Index from baseline to EOTP

Safety Endpoints:

- Incidence and severity of adverse events
- Incidence of hemoglobin concentration > 13.0 and > 14.0 g/dL at any time on study

- Incidence of an increase in hemoglobin concentration > 2 g/dL in a 28 day window and any negative clinical consequences
- Changes in laboratory and vital sign parameters over time
- Incidence of dose reductions during the treatment phase
- Incidence of targeted concomitant medication use during the treatment phase
- Incidence of confirmed antibody formation to darbepoetin alfa

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Statistical Methods:

Efficacy
The full analysis set for the primary efficacy analysis included all randomized subjects who received ≥ 1 dose of darbepoetin alfa. The primary endpoint analysis was repeated using the per-protocol analysis set, which included all subjects in the full analysis set who had a baseline hemoglobin concentration < 11.0 g/dL and received between 75% and 125% (inclusive) of the protocol-specified cumulative dose of darbepoetin alfa through the EOTP or early withdrawal and either no IV iron (DA group) or ≥ 50% of the protocol-specified IV iron dose (DA + IV group). The transfusion analysis set consisted of all subjects in the full analysis set who remained on study until at least day 29. This analysis set was used for the analysis of efficacy endpoints measured between week 5 (study day 29) to the EOTP. The PRO analysis set included all subjects in the full analysis set who had a baseline and ≥ 1 postbaseline PRO score.

The proportion of subjects achieving a hematopoietic response, the proportion of subjects with ≥ 1 RBC transfusion from week 5 (day 29) to EOTP, and the proportion of subjects of achieving a hemoglobin concentration ≥ 11.0 g/dL, in the absence of RBC transfusions in the preceding 28 days, from week 5 to EOTP were estimated using the Kaplan-Meier approach. Estimates of the difference between the treatment groups, adjusted for baseline factors, and their associated 95% confidence intervals (CIs), were calculated by the weighted average of the stratum differences in the proportions with weights proportional to the inverse of the variance of the stratum difference. A 95% CI for the overall difference was constructed using a normal approximation and a large-sample χ^2 test was performed to test for overall treatment differences. These comparisons were each carried out as 2-sided tests at the 0.05 significance level.

For time to hematopoietic response, time to RBC transfusion, and time to achieving hemoglobin concentration ≥ 11.0 g/dL, Kaplan-Meier curves were presented for each treatment group. The Kaplan-Meier medians (if estimable) were also derived, along with their 2-sided 95% CIs. Time to hematopoietic response was compared between groups using Cox Proportional Hazards models adjusting for baseline factors.

Analyses for the primary and secondary efficacy endpoints were stratified by baseline hemoglobin concentration (<10 g/dL vs ≥ 10 g/dL) and tumor type (lung/gynecological vs others).

Safety
The safety analysis set included all subjects who received ≥ 1 dose of darbepoetin alfa. Subjects who received IV iron at any time during the study were included in the investigational treatment group (DA + IV), regardless of randomization. All safety endpoints were descriptively summarized by treatment group.

A Data Review Team (DRT) regularly reviewed unblinded safety data during the study and made recommendations to Amgen regarding the conduct of the study in order to safeguard subject interests while preserving the integrity and credibility of the study. The DRT was an Amgen multifunctional group consisting of a physician, a biostatistician, and a safety specialist who were not directly involved in the conduct of the study.

Two interim analyses focusing on the safety of the darbepoetin alfa 500 mcg Q3W regimen and on the safety of darbepoetin alfa 500 mcg dosing plus IV iron supplementation were conducted. The primary efficacy endpoint was specifically excluded from these analyses.

Summary of Results:

Subject Disposition:

Three hundred ninety-eight subjects (201 DA + IV, 197 DA) were randomized into this study and 396 subjects (200 DA + IV, 196 DA) received ≥ 1 dose of darbepoetin alfa. Sixty-seven percent and 76% of subjects in the DA + IV and DA groups, respectively, completed the study.

Efficacy Results:

Three hundred ninety-six subjects (200 DA + IV, 196 DA) were included in the full analysis set for efficacy endpoints. Seventy-four percent of subjects (68% DA + IV, 79% DA) were included in the per-protocol analysis set. The primary reason for exclusion from this analysis set was receipt of < 75% of the planned dose of darbepoetin alfa (23% DA + IV, 12% DA). Ninety-four percent of subjects (92% DA + IV, 96% DA) were included in the transfusion set and 86% (84% DA + IV, 88% DA) were included in the PRO analysis set.

The adjusted difference between DA + IV and DA in the Kaplan-Meier percentage of subjects achieving hematopoietic response was 13% (95% CI: 3%, 23%; p = 0.011). In addition, Cox proportional hazard model analysis demonstrated that subjects in the DA + IV group had a 30% greater chance of achieving a hematopoietic response compared with the DA group (hazard ratio: 1.30 [95% CI: 1.01, 1.67; p = 0.038]).

The adjusted difference between treatment groups in the Kaplan-Meier percentage of subjects receiving ≥ 1 transfusion was -11% (95% CI: -18%, -3%; p = 0.005). In addition, unadjusted Kaplan-Meier curves show that DA + IV had a lower rate of subjects requiring transfusions throughout the treatment period compared with DA.

The adjusted difference between treatment groups in the Kaplan-Meier percentage of subjects achieving a hemoglobin concentration ≥ 11.0 g/dL was 10% (95% CI: 2%, 18%; p = 0.011). Unadjusted Kaplan-Meier curves from Week 1 to EOTP also show that DA + IV had a higher rate of subjects achieving a hemoglobin concentration ≥ 11.0 g/dL throughout the treatment period compared with DA. In addition, 88% of subjects in both treatment groups maintained an average hemoglobin concentration ≥ 11.0 g/dL after first achieving this target level.

The adjusted mean change in hemoglobin concentration between baseline and EOTP was slightly higher for DA + IV (1.67 g/dL) compared with DA (1.43 g/dL), although the difference between treatment groups was not statistically significant (0.25 g/dL [95% CI: -0.13, 0.62]). When assessed over time, mean hemoglobin concentration and mean change in hemoglobin concentration from baseline were higher for DA + IV from the interim week 4 visit through the EOTP. Similar results were observed when the last observation was carried forward method was used for any missing data.

The mean (SE) change in FACT-F scores between baseline and the EOTP was similar between treatment groups when assessed using an analysis of covariance model (2.40 [0.79] and 2.17 [0.77] for DA + IV and DA, respectively). The 95% CI for the difference between treatment groups from the ANCOVA model was -1.84 to 2.29, which was not statistically significant. Fifty percent and 43% of subjects in the DA + IV and DA groups, respectively, reported a ≥ 3-point increase from baseline in FACT-F scores at the EOTP.

Safety Results:

Two hundred three subjects in the DA + IV group and 193 in the DA group received ≥ 1 dose of darbepoetin alfa and were included in the safety analysis set. Of these subjects, 159 (78%) in the DA + IV group and 160 (83%) in the DA group reported ≥ 1 adverse event during the study. Most adverse events reported for each treatment group were mild to moderate in severity and typical of the study population. The most common adverse event for both treatment groups was nausea (19% for both). In addition, 19% of subjects in the DA group also experienced fatigue, although the incidence of this event was lower for subjects in the DA + IV group (11%).

Adverse events related to darbepoetin alfa and iron, respectively, were reported for 10 (5%) and 17 (8%) subjects in the DA + IV group and 5 (3%) and 3 (2%) subjects in the DA group. The proportion of subjects experiencing serious adverse events was similar between the treatment groups (30% DA + IV, 34% DA). Four (2%) subjects in the DA + IV group and 3 (2%) in the DA group experienced serious adverse events considered related to darbepoetin alfa by the investigator. Twenty-six subjects (13%) in the DA + IV group and 17 (9%) in the DA group were withdrawn from treatment and/or the study because of an adverse event. Five subjects (2 [1%] DA + IV, 3 [2%] DA) were withdrawn because of adverse events considered related to darbepoetin alfa. Twenty-one subjects (10%) in the DA + IV group and 15 (8%) in the DA group died during the study. One fatal adverse event (pulmonary embolism) reported for a subject in the DA + IV group was considered related to darbepoetin alfa by the investigator.

The proportions of subjects with a maximum hemoglobin concentration > 13.0 g/dL or > 14.0 g/dL were higher for the DA + IV group (43% and 18%, respectively) compared with the DA group (33% and 12%, respectively). The mean (SD) maximum hemoglobin concentration was 12.6 (1.66) g/dL and 12.3 (1.55) g/dL for DA + IV and DA, respectively. The proportion of subjects with a maximum increase in hemoglobin concentration > 2.0 g/dL/28 days was similar between treatment groups (46% DA + IV, 47% DA).

Mean hematology and serum chemistry values during the study were consistent with the comorbidities for the subject population. Iron parameters were generally higher for the DA + IV iron group compared with the DA group; however, most subjects were iron replete (ie, transferrin saturation ≥ 15% or serum ferritin ≥ 100 mcg/L) during the study for both treatment groups (76% DA + IV, 75% DA).

A low prevalence of binding antibodies (2% DA + IV, 4% DA) was observed in this study and all subjects tested in the bioassay for neutralizing antibodies were negative.