SYNOPSIS

NAME OF SPONSOR/COMPANY: Ortho Biotech Clinical Affairs, L.L.C. NAME OF FINISHED PRODUCT: Epoetin Alfa NAME OF ACTIVE INGREDIENT(S): Epoetin Alfa	INDIVIDUAL STUDY TABLE REFERRING TO PART OF THE DOSSIER Volume: Page:	(FOR NATIONAL AUTHORITY USE ONLY)

Protocol No.: PR02-27-047

Title of Study: A Randomized, Open-Label Study of Epoetin Alfa (PROCRIT®) Versus Darbepoetin Alfa (ARANESP™) to Evaluate Hematologic Response Rate in Anemic Cancer Patients Receiving Chemotherapy

Principal Investigator: Roger Waltzman, M.D., St. Vincent's Comprehensive Cancer Center, New York, NY.

Publication (Reference): Walzman RJ et al. *The Oncologist* 2005;10:642-50; Waltzman RJ et al. *Proc Amer Soc Clin Oncol* 2005;23:736S. Abstract 8030; Waltzman RJ et al. *Blood* 2004;104:144b. Abstract 4233. Waltzman RJ et al. *Proc Amer Soc Clin Oncol* 2004;23:763. Abstract 8153. Jakubowski AA et al. *Blood* 2003;102:170b. Abstract 4391.

Study Initiation/Completion Dates: 07 April 2003 to 30 October 2004	**Phase of development:** 4

Objectives: The primary objective of the study was to compare hematologic response to epoetin alfa (40,000 units subcutaneous [SC] once weekly) and darbepoetin alfa (200 µg SC every 2 weeks) in anemic cancer subjects receiving chemotherapy. Secondary objectives included the following: 1) to evaluate the safety of epoetin alfa and darbepoetin alfa; 2) to evaluate the effect of epoetin alfa and darbepoetin alfa on hemoglobin (Hb) values over time; 3) to evaluate the effect of anemia in cancer subjects receiving chemotherapy on quality of life (QOL) as measured by subject self-reported Linear Analog Scale Assessment (LASA) and Functional Assessment of Cancer Therapy-Anemia (FACT-An); and 4) to measure resource utilization of administering epoetin alfa and darbepoetin alfa.

Methodology: This was a prospective, randomized, open-label, multicenter study to compare epoetin alfa and darbepoetin alfa in anemic subjects with cancer receiving chemotherapy. Eligible subjects were randomly assigned to receive either epoetin alfa or darbepoetin alfa in a 1:1 ratio. Randomization was stratified by study center and type of chemotherapy (platinum- versus non-platinum-based). The starting dose of epoetin alfa was 40,000 units (IU) administered once a week (QW) by subcutaneous (SC) injection, while the starting dose of darbepoetin alfa was 200 µg administered once every 2 weeks (Q2W) by SC injection. The initial administration of study drug was required to coincide with Day 1 of a subject's chemotherapy cycle. Study treatment was administered for up to 16 weeks. Dose adjustment, based on Hb response, was made according to guidelines from the National Comprehensive Cancer Network (NCCN). Dose escalation was permitted for nonresponders (Hb increase of ≤1 g/dL) after 4 weeks (to 60,000 IU QW epoetin alfa) or 6 weeks (to 300 µg Q2W darbepoetin alfa). The dose of study drug was withheld if Hb was > 13 g/dL, and re-initiated with a 25% dose reduction if Hb became ≤12 g/dL. A similar dose reduction was required for a too rapid rise in Hb (≥1.3 g/dL in a 2-week period for epoetin alfa and ≥1.0 g/dL in a 2-week period for darbepoetin alfa). Red blood cell (RBC) or packed red blood cell (PRBC) transfusions could be given at the discretion of the investigator.

During the study, subjects were evaluated monthly for 16 weeks. Monthly evaluations included Hb and hematocrit (Hct) levels, vital signs (blood pressure, pulse rate, temperature, respiration rate), and changes in chemotherapy. Between monthly visits, Hb, Hct and blood pressure were measured weekly. Quality of life assessments (FACT-An and LASA) were completed at baseline, Week 5, Week 9 and the end of study. Clinical laboratory evaluations (including serum anti-EPO antibodies), Eastern Cooperative Oncology Group (ECOG) performance status, and a physical examination (including body weight and height) were performed at baseline and study end. Transfusion use, adverse events, and concomitant medication usage were monitored throughout the study.

Number of Subjects (planned and analyzed): The minimum and maximum sample sizes planned for this study were 300 and 400 subjects, respectively, with provisions for an interim analysis of the primary efficacy endpoint. The interim analysis involving the first 305 subjects revealed statistical superiority in favor of epoetin alfa and study enrollment was terminated as planned. A total of 358 subjects were randomized, received study treatment, and were analyzed for safety. A total of 305 subjects were included in the planned interim analysis of the primary efficacy endpoint, and 352 subjects were included in the analysis of secondary efficacy endpoints (modified intent-to-treat, [mITT] population).

SYNOPSIS (CONTINUED)

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Diagnosis and Main Criteria for Inclusion: Subjects were to be men or women at least 18 years of age, have a histologically-confirmed solid tumor malignancy, scheduled to receive cyclic chemotherapy for at least 12 weeks after enrollment, and have an Hb concentration of ≤11 g/dL. Subjects who had received any erythropoietic agent within the previous 3 months, had received more than 2 prior chemotherapy regimens, and for whom radiation therapy was planned during the study period were excluded. Subjects were to have an ECOG performance status score of 0 to 2, a life expectancy of at least 6 months, and adequate renal, hepatic, and hematologic function.

Test Product, Dose and Mode of Administration, Batch No.: Epoetin alfa (PROCRIT®) was supplied as a single use, 1-mL vial containing 40,000 units of epoetin alfa and 2.5 mg human albumin. The starting dose was 40,000 IU QW by SC injection, and the dose could not exceed 60,000 IU QW. Lot numbers for epoetin alfa were P009114 (20,000 U/mL, NDC #59676-320-01) and P005091, P005264, P007668, P007982, P007983, P008329, P009152, P009153, P009336, P009415, P009417, P00967, P010968, P024755, P024845 (40,000 U/L, NDC #59676-340-01).

Reference Therapy, Dose and Mode of Administration, Batch No.: Darbepoetin alfa (ARANESP™) was supplied as a single use, 1-mL vial containing 200 µg darbepoetin alfa and 2.5 mg human albumin. The starting dose was 200 µg Q2W by SC injection, and the dose could not exceed 300 µg. Lot numbers for darbepoetin alfa were P007155, -007542, P009455, -010960 (100 µg/1 mL, NDC #55513-013-04) and P007543, P007655, P007789, P007997, P007998, P008744, P010951, P010954 (200 µg/1 mL, NDC #55513-014-01.

Duration of Treatment: 16 weeks.

Criteria for Evaluation:

Efficacy: The primary endpoint was the Hb response by Week 5, defined as the proportion of subjects achieving a ≥1 g/dL Hb increase by Week 5 (i.e., after 4 weeks of treatment). Key secondary efficacy endpoints were the time to Hb increase of 1 g/dL, the proportion of subjects achieving a ≥1 g/dL or ≥2 g/dL increase in Hb by Week 9 and end of study (Week 17 or time of early withdrawal for subjects who were discontinued prematurely), the change from baseline in Hb over time, the proportion of subjects receiving a transfusion between Day 29 and end of study, the number of units transfused from Day 29 to end of study, and the frequency distribution of transfusion episodes from Day 29 to end of study. QOL assessments included the change from baseline in FACT-An Fatigue subscale score and LASA Energy and Daily Activities scores at Week 5, Week 9, and end of study.

Safety: Safety parameters included the incidence of adverse events (including thrombotic vascular events [TVEs]), changes from baseline in clinical laboratory tests, the presence of serum anti-EPO antibodies, and changes from baseline in vital signs, ECOG performance status scores, physical examination findings, and tumor response at end of study.

Statistical Methods:

Efficacy: The primary endpoint was analyzed on the preplanned interim population using a logistic regression model with treatment and chemotherapy type as factors. The overall significance level for this analysis was $p \leq 0.0125$, 1-sided.

All secondary efficacy endpoints were analyzed using the modified intent-to-treat (mITT) population, which included all randomized subjects who received at least 1 dose of study drug and who had data for at least 1 post-baseline efficacy variable. Statistical significance for all secondary efficacy endpoints was interpreted using $p \leq 0.05$, 2-sided.

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Efficacy (continued): The time to Hb increase of 1 g/dL was summarized using Kaplan-Meier estimates, and compared between treatment groups using the log-rank test stratified by chemotherapy type and a Cox regression model with chemotherapy type and baseline Hb as covariates. The proportion of subjects achieving a ≥1 g/dL to <2 g/dL or ≥2 g/dL increase in Hb, and the proportion of subjects receiving at least 1 transfusion, were analyzed as described for the primary endpoint. An analysis of covariance (ANCOVA) with baseline Hb as a covariate was used to compare the number of PRBC units transfused and the change in Hb levels at designated timepoints. An ANCOVA model with treatment group and chemotherapy type as fixed effects and baseline Hb as a covariate was used to compare changes in QOL scores.

All Hb values obtained within 28 days following PRBC transfusion were set to missing for the efficacy analyses. A last value carried forward (LVCF) approach was used to analyze Hb data.

Safety: Adverse events were summarized by body system, preferred term, and treatment group. Adverse events were also summarized by severity and relationship to study drug. Summary statistics (mean, standard deviation, median, and range) and changes from baseline were provided by treatment group for clinical laboratory tests and vital sign measurements. Shift tables of changes in physical examination findings between baseline and end of study were provided by treatment group.

RESULTS – CONCLUSIONS

Over the entire study, the mean cumulative dose of study drug was 418,479.9 IU for epoetin alfa and 1178.4 µg for darbepoetin alfa. The percentage of subjects who had their dose increased to 60,000 IU QW epoetin alfa at Week 5 (33%) or to 300 µg Q2W darbepoetin alfa at Week 7 (34%) was similar.

EFFICACY RESULTS:

Primary efficacy endpoint: Analysis of the primary efficacy endpoint was performed using the preplanned interim population of the first 305 subjects to complete the Week 5 visit. Using the preplanned interim analysis population, a total of 71 (47%) subjects receiving epoetin alfa 40,000 IU QW, compared with 50 (33%) subjects receiving darbepoetin alfa 200 µg Q2W achieved at least a 1 g/dL increase in Hb after 4 weeks of study treatment. This difference in the Hb response rate in favor of epoetin alfa was statistically significant (p=0.0078, one-sided).

Secondary efficacy endpoints: Based on Kaplan-Meier estimates, the time to an Hb increase of ≥1 g/dL was significantly sooner in the epoetin alfa group (median, 35 days) than in the darbepoetin alfa group (median, 46 days) (p=0.0057, log-rank test). Beginning at Week 3 and continuing to the end of the study, subjects receiving epoetin alfa had statistically significantly larger mean increases in Hb compared with those treated with darbepoetin alfa (p≤0.023). The mean change in Hb from baseline to Week 17/Study End was 55% higher in the epoetin alfa group (1.24 g/dL) than in the darbepoetin alfa group (0.80 g/dL). By the end of the study, the proportion of patients who had achieved an Hb increase of ≥2 g/dL (58% and 42%, respectively) was significantly higher with epoetin alfa treatment than with darbepoetin alfa (p=0.004).

The proportion of subjects receiving PRBC transfusions from Day 29 to study end did not differ significantly between the 2 treatment groups (p=0.2078). The earlier and larger erythropoietic response seen for weekly epoetin alfa in this randomized trial was associated with statistically significantly fewer mean units of PRBCs transfused (2.5 units) from Day 29 to study end compared with Q2W darbepoetin alfa (3.9 units) (p=0.0334).

Similar mean improvements in QOL as assessed by the LASA Energy Level, LASA Daily Activities, and FACT-An Fatigue subscales from baseline to Week 9 and end of study were observed following treatment with epoetin alfa and darbepoetin alfa, and a positive correlation between the changes in QOL scores and Hb levels was seen.

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SAFETY RESULTS: Overall, epoetin alfa and darbepoetin alfa had similar safety and tolerability profiles. The incidence of adverse events was similar for the epoetin alfa (96%) and darbepoetin alfa (95%) groups. Reported adverse events were generally those expected for a cancer population undergoing chemotherapy. The most frequently reported adverse events were neutropenia (17% and 26% in the epoetin alfa and darbepoetin alfa groups, respectively), nausea (33% and 26%, respectively), diarrhoea (26% and 20%, respectively), vomiting (20% and 18%, respectively), and fatigue (22% and 27%, respectively). Virtually all (≥98%) adverse events were judged by the investigator to be unrelated to study drug therapy. A similar number of subjects (n=15, 8%) in each treatment group were withdrawn from the study due to an adverse event, most of which were related to the subjects' underlying cancer rather than study drug.

Predefined clinically significant TVEs were reported for 20 (11%) subjects in the epoetin alfa group and 17 (9%) subjects in the darbepoetin alfa group, few of which were judged by the investigator to be related to study drug. The most common clinically significant TVEs were deep vein thrombosis (11 and 7 subjects in the epoetin alfa and darbepoetin alfa groups, respectively), pulmonary embolism (6 and 5 subjects, respectively), and atrial fibrillation (2 and 3 subjects, respectively).

Fifty-nine subjects (25 in epoetin alfa group and 34 in the darbepoetin alfa group) had an adverse event for which the outcome was listed as "death"; for 7 (4%) subjects in the epoetin alfa group and 21 (12%) in the darbepoetin alfa group death resulted from an adverse event that had an onset between the start of treatment and the last visit date. The majority of deaths in both groups were related to disease progression. Serious adverse events with an onset date prior to or on the last visit date occurred with a similar incidence in the epoetin alfa (n=45, 25%) and darbepoetin alfa (n=51, 28%) groups. Most SAEs were reflective of subjects' underlying cancer or chemotherapy regimen.

With the exception of larger increases in Hb in the epoetin alfa group compared with the darbepoetin alfa group, there were no apparent differences between the 2 treatment groups in mean values over the course of the study for hematology and serum chemistry parameters. No subject tested positive for serum anti-EPO antibodies at baseline or at the final study visit.

There was little variation in vital sign measurements or physical examination findings during the study in either treatment group.

CONCLUSION: In anemic cancer subjects undergoing chemotherapy, weekly SC administration of epoetin alfa 40,000 IU elicited a significantly larger and earlier hematologic response compared with darbepoetin alfa 200 µg given every 2 weeks. Both erythropoietic agents produced comparable improvements in QOL, and both had similar safety and tolerability profiles.

Date of the report: 14 April 2006

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