SYNOPSIS PR04-27-021

NAME OF SPONSOR/COMPANY: Ortho Biotech Clinical Affairs, LLC NAME OF FINISHED PRODUCT: PROCRIT® 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.: PR04-27-021

Title of Study: A Pilot Study to Evaluate the Response Rate of PROCRIT® (epoetin alfa) at 80,000 Units Every Three Weeks in Anemic Patients With Cancer Not Receiving Chemotherapy or Radiation Therapy

Publication (References): Shasha D, Dawkins F, Wilhelm FE. Epoetin alfa 80,000 U every three weeks (Q3W) in anemic cancer patients (pts) not receiving chemotherapy (CT) or radiation therapy (RT). Blood 2006;108(11):3755.

Principal Investigator: Daniel Shasha, MD, Beth Israel Medical Center; New York, NY

Study Initiation/Completion Dates: 21 FEB 2005 to 07 DEC 2005 | **Phase of development:** 3b

Objectives:

Primary: To investigate the effect of epoetin alfa on hematopoietic response when administered at 80,000 units subcutaneously every 3 weeks (q3w) to anemic patients with cancer not receiving chemotherapy or radiation therapy.

Secondary: To assess the time to a hematopoietic response for this dosing regimen and to assess the effect of the dosing regimen on measures of quality of life (QOL), transfusion requirements, and safety and tolerance.

Methodology: This was an open-label, nonrandomized, multicenter, pilot study conducted at 9 sites in the United States. Fifty patients with non-myeloid malignancy who met all inclusion/exclusion criteria were to receive epoetin alfa 80,000 units subcutaneously q3w. The last study visit was to take place 3 weeks after the last dose of epoetin alfa, ie, at Week 13. Hemoglobin (Hb), hematocrit, and blood pressure were monitored at weekly clinic visits. QOL (measured using the Linear Analog Scale Assessment [LASA] and Functional Assessment of Cancer-Anemia [FACT-An] instruments) was assessed at Week 1 (baseline), Week 7, and Week 13/Early Withdrawal (WD).

Number of Patients: Planned: 50; Enrolled:51; Completed: 42

Diagnosis and Main Patient Selection Criteria: Patients were to be men or women ≥18 years of age with a histologically confirmed non-myeloid malignancy, a baseline Hb ≤ 11 g/dL, and who were not receiving chemotherapy or radiation therapy nor anticipated to receive chemotherapy or radiotherapy during the course of the study. Patients were to have an ECOG performance status score of 0 to 2, a life expectancy ≥4 months, and adequate renal and hematologic function.

Test Product, Dose and Mode of Administration: The starting dose of epoetin alfa was 80,000 units subcutaneously q3w; a maximum of 4 dose administrations was allowed. If at any time the Hb level rose to > 12 g/dL or increased by more than 1.5 g/dL in any 3-week period, the dose of epoetin alfa therapy was reduced as follows: from 80,000 units q3w to 60,000 units q3w, from 60,000 units q3w to 40,000 units q3w, or from 40,000 units q3w to 30,000 units q3w. If at any time the Hb level rose to > 13 g/dL, epoetin alfa therapy was withheld until the Hb level fell to ≤12 g/dL and then resumed at a dose reduction as defined above.

Duration of Treatment: 13 weeks (4 doses administered at 3-week intervals followed by a 3-week follow-up period).

Criteria for Evaluation:

Efficacy: The primary efficacy endpoint was hematopoietic response, defined as ≥2 g/dL rise in Hb and/or a Hb level of ≥12 g/dL at any time during the course of the study (with the goal not to exceed 13 g/dL). Secondary efficacy endpoints were measurement of the effects of epoetin alfa on transfusion requirements, change in QOL scores as measured by the LASA tool and the FACT-An, and time to hematopoietic response, and time to ≥1 g/dL change in Hb from baseline.

Safety: Incidence and severity of adverse events (AEs) and thrombotic vascular events (TVEs), physical examinations, vital signs (blood pressure), clinical laboratory results (including Hb and Hct), and ECOG performance status.

SYNOPSIS (CONTINUED)

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Statistical Methods: All enrolled patients who received at least 1 dose of study medication and had at least 1 post-baseline efficacy observation (Hb or transfusion) were included in the modified intent-to-treat (MITT) population and efficacy analyses. All enrolled patients who received at least 1 dose of study medication were included in the safety population and safety analyses.

Efficacy Analysis:

The primary efficacy variable was the percent of patients achieving a hematopoietic response. This response was calculated as the percent of patients with ≥2 g/dL increase in Hb from baseline and/or a Hb ≥12 g/dL. Hb values obtained within 28 days after a transfusion were considered invalid and were excluded from analysis. A 95 % confidence interval was also calculated for the estimates.

The secondary efficacy variables were :

Hemoglobin: Mean Hb at each scheduled visit and mean change in Hb from study baseline to each scheduled visit, as well as to the last scheduled Hb value available, were summarized. A 95% confidence interval around the mean was also calculated. Time to a hematopoietic response (Hb increase ≥2 g/dL from baseline (Day 1) and/or Hb ≥12 g/dL) was estimated using the Kaplan-Meier method. Time to achieve a ≥1 g/dL change in Hb from baseline (Day 1) was estimated using the Kaplan-Meier method.

Transfusion: Packed red blood cell (pRBC) units transfused per person were quantified using descriptive statistics (ie, total, mean, median, standard deviation, interquartile ranges). A 95% confidence interval around the mean was also calculated. The proportion of patients pRBC transfused was summarized from Day 1 to Day 28 and from Day 29 to the end of study. A 95% confidence interval for the proportion was also calculated.

Quality of Life: Overall and mean QOL scores at each scheduled visit and change in mean overall and domain QOL scores from baseline to each scheduled visit, as well as to the last scheduled QOL score available, were summarized. The 95% confidence interval around the means was also calculated. In addition, correlation analyses were performed to assess the relationships between changes in Hb and changes in QOL scores.

Safety Analysis:

AEs were coded using the latest version of the Medical Dictionary for Regulatory Activities (MedDRA) Coding Dictionary, version 7.0. On-study AEs were collected between the first study-related procedure and the last study-related procedure. Follow-up AEs were collected within 30 days after the last study-related procedure. AEs reported on-study and during the follow-up period were summarized separately.

Patients reporting 1 or more AEs were summarized by NCI Grade (National Cancer Institute Common Toxicity Criteria, Version 2.0), body system, possible relationship to epoetin alfa, and action taken regarding any change in dosing of epoetin alfa due to the AE. Serious AEs (SAEs) and AEs leading to discontinuation and death were summarized separately. AEs occurring in 2% and 5% of the population were also summarized.

TVEs and clinically relevant (CR) TVEs were coded using the provided MedDRA TVE coding by body system created by Johnson & Johnson Pharmaceutical Research and Development, L.L.C. (J&JPRD), version dated 31 May 2005. The number and percent of patients experiencing at least 1 TVE were summarized by body system and preferred term.

Screening physical examination data and changes from screening to Week 13/WD were summarized as counts and percents by body system. Systolic and diastolic blood pressures were summarized using univariate statistics for each visit and change from baseline to each visit. All laboratory test results were listed by patient.

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SUMMARY – CONCLUSIONS

Demographics and Extent of Exposure:

All 51 patients who were enrolled in the study received at least one dose of study medication. Of these, 42 (82%) completed the study and 9 (18%) discontinued prematurely. The mean age of patients in the safety population was 71 years. The majority of patients were Caucasian (71%), and similar numbers of males and females were enrolled (24 males and 27 females). The patients' mean body weight was 77 kg. Most (29 patients, 59%) had an ECOG score at baseline of 1. Of the remaining 22 patients, 19 (37%) had a baseline ECOG score of 0, and 3 (6%) had a baseline ECOG score of 2. The mean Hb level at baseline was 10.3 g/dL (range: 8.87–11.50 g/dL).

The mean duration of exposure was 9.53 weeks (range: 3.00 to 12.29; Supporting Data Table 3.1) and the mean total cumulative exposure was 235,686 units (SD 87,023). Both the total number of doses (mean 3.14 and median 4.0) and the average number of days between doses (mean 21.44 and median 21.00) were consistent with the protocol-specified dosing regimen. The mean time to first dose reduction was 37.5 days (median 42.5).

Efficacy Results:

Primary efficacy variable: The percentages of patients achieving a hematologic response (defined as a $\geq$ 2 g/dL increase in Hb and/or Hb $\geq$ 12 g/dL) were approximately 47% at Week 5 (n = 23), 63% at Week 9 (n = 31)and 76% at Week 13 (n = 37). The mean time to achieve a hematopoietic response among the 49 patients in the MITT population was 5.76 weeks.

Secondary efficacy variables: The percentages of patients achieving a mean $\geq$1 g/dL increase in Hb were approximately 71% at Week 5 (n = 35), 80% at Week 9 (n = 39) and 80% at Week 13 (n = 39). The mean time to achieve an increase of $\geq$1 g/dL in Hb was 3.77 weeks. The mean weekly Hb level in the MITT population increased steadily over time to Week 8 and thereafter remained in the range of approximately 11.6-11.8 g/dL (LOCF method of calculation). Furthermore, only 2 patients required transfusions during the course of the study.

Results of QOL measures (LASA and FACT-An) were variable; however, mean values increased consistently over time. Correlation analyses between Hb level and QOL measures indicated the possibility of a positive relationship between Hb levels and QOL among these cancer patients.

Safety Results:

Overall, treatment with 80,000 U q3w epoetin alfa was well tolerated in this population of cancer patients not undergoing chemotherapy or radiation therapy. Only 3 AEs were reported by $\geq$5% of the safety population during the study: arthralgia, back pain, and vomiting. No single AE was reported by $\geq$5% of the safety population during the follow-up period.

Two deaths were reported; 1 during the study and 1 during the follow-up period (within 30 days after the last study-related procedure). In both cases the investigators determined that there was no relationship between the study drug and the patient's death.

A total of 7 SAEs were reported among 7 different body systems for 5 patients during the study. Four of the patients recovered without sequelae and one patient died. A total of 5 SAEs were reported for 4 patients during the follow-up period. One patient recovered without sequelae, one patient had not yet recovered at the end of the follow-up period, one patient died during the follow-up period, and one patient died after the end of the follow-up period. For all SAEs the investigators determined that there was no relationship between the study drug and the SAE. Only 1 TVE was reported during the study. There were no CR TVEs reported. No patients were withdrawn from the study for an AE other than the one reported on-study death.

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There was no consistent increase or decrease over time in mean weekly blood pressure during the study. There was no significant change noted in mean pulse rate, respiratory rate or body weight during the study. Few changes were noted in physical examination findings between baseline and Week 13/WD. Those changes that were noted were distributed among a range of body organ systems. For most patients, ECOG performance status did not change between screening and the final visit. At baseline and at Week 13/WD all patients maintained an ECOG performance status score of 0 to 2.

Conclusion:

Treatment of anemia with 80,000 U q3w epoetin alfa in cancer patients not receiving chemotherapy or radiation therapy demonstrated efficacy with respect to Hb response and transfusion requirements compared to the more frequent treatment regimens currently prescribed. Overall, treatment with 80,000 U q3w epoetin alfa was well tolerated in this population of cancer patients not undergoing chemotherapy or radiation therapy.

Date of the report: 15 May 2007

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