SYNOPSIS

NAME OF SPONSOR/COMPANY: Ortho Biotech Clinical Affairs, LLC 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.: PR03-27-002

Title of Study: A Pilot Study to Evaluate the Response Rate of PROCRIT® (Epoetin Alfa) at 60,000 Units Every Two Weeks in Anemic Patients with Cancer Not Receiving Chemotherapy or Radiation Therapy

Principal Investigator: Daniel Shasha, M.D. - Beth Israel Medical Center, New York, New York; United States

Publication (Reference): (1) Shasha D, Henry D, Williams D. Epoetin alfa (EPO) 60,000 U every 2 weeks (Q2W) in patients (pts) with cancer not receiving chemotherapy (CT) or radiotherapy (RT). Proc Am Soc Clin Oncol 2005;23(16S Part I of II):555s. Abstract 8229. (2) Shasha D, Henry D, Williams D. Early results suggest that epoetin alfa 60,000 U every 2 weeks improves hemoglobin in patients with cancer not receiving chemotherapy or radiotherapy. Blood. 2004;104(11 Part 2 of 2):141b. Abstract 4222.

Study Initiation/Completion Dates: 2 Mar 2004 to 15 Feb 2005 | **Phase of development:** 2

Objectives: The primary objective of the study was to evaluate the efficacy of PROCRIT® on hematopoietic response at 60,000 units administered subcutaneously every 2 weeks in anemic patients with cancer who were not receiving chemotherapy or radiation therapy. The secondary objectives of the study were to assess the time to a hematopoietic response in this dosing regimen and to assess the effect of the dosing regimen on measures of quality of life (QOL) using the Linear Analog Scale Assessment (LASA) and Functional Assessment of Cancer Therapy-Anemia (FACT-An) scale, on transfusion requirements, and on safety and tolerance.

Methodology: Open-label, non-randomized, multicenter pilot study

Number of Subjects (planned and analyzed): Planned: 50; Enrolled: 57; Completed: 42. Patients who completed the study through Week 13 were considered completers in terms of the efficacy analyses. A total of 45 patients completed the Week 13 visit; 50 completed the Week 17 visit, of which 8 were early withdrawals.

Diagnosis and Main Criteria for Inclusion: Male or female patients at least 18 years of age who had cancer with non-myeloid malignancies, had hemoglobin (Hb) ≤ 11 g/dL, and were not receiving chemotherapy or radiation therapy

Test Product, Dose and Mode of Administration, Batch No.: The starting dosage of PROCRIT was 60,000 units subcutaneously every 2 weeks. If, after 4 weeks of treatment with PROCRIT, the patient's Hb level did not increase by ≥1g/dL, the dose of study drug was increased to 80,000 units subcutaneously every 2 weeks. If the patient's Hb level was > 13g/dL on the day study drug was to be administered, PROCRIT was withheld until the Hb fell to ≤ 12 g/dL, then restarted at a dose reduction of approximately 25% (i.e., from 60,000 units subcutaneously every 2 weeks to 40,000 units subcutaneously every 2 weeks and from 40,000 units subcutaneously every 2 weeks to 30,000 units subcutaneously every 2 weeks). If the Hb level was > 12 g/dL on the day study drug was to be administered, the dose was not withheld but was reduced in the same manner. A similar dose reduction was made if a rapid Hb response occurred (e.g., an increase > 1.0 g/dL in a 2-week period). The protocol recommended that a confirmatory Hb measurement be performed within 24 hours prior to withholding the PROCRIT dose. Study drug lot numbers were R12332 and R12556.

Duration of Treatment: Treatment with study drug was for a maximum of 12 weeks followed by a 4-week observation period after the last dose of study drug.

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 over the course of the study. Secondary efficacy endpoints were the effects of PROCRIT on mean time to hematopoietic response, transfusion requirements, and change in QOL scores as measured by the LASA and FACT-An scales.

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NAME OF ACTIVE INGREDIENT(S): Epoetin alfa	Page:	

Safety: Safety evaluations were clinical laboratory tests (Hb and hematocrit [Hct]), vital signs measurements (blood pressure) and incidence and severity of adverse events (AEs).

Statistical Methods: The efficacy analysis was based on the modified intent-to-treat (MITT) approach. All patients who had at least 1 post-baseline efficacy observation (Hb or transfusion) were included in the MITT population. The primary efficacy endpoint, hematopoietic response, was calculated as the percent of patients with a Hb increase ≥ 2 g/dL and/or Hb ≥ 12 g/dL during the course of the treatment period. All hematopoietic responses were independent of transfusion within 28 days. The secondary efficacy endpoints were transfusion requirements, change in LASA and FACT-An scores, mean time to hematopoietic response, and mean time to ≥ 1g/dL change in Hb from baseline. Secondary endpoints were summarized using descriptive statistics. All proportions as secondary endpoints were estimated and 95% confidence intervals (CIs) were calculated.

AEs were summarized by National Cancer Institute Common Toxicity Criteria (NCI CTC) grade, system organ class, preferred term, and possible relationship to PROCRIT. AEs leading to discontinuation or death were also summarized. Thrombotic vascular events (TVEs) were summarized as the number and percent of patients experiencing at least 1 TVE and the relationship of the TVE to study drug. AEs and TVEs that occurred on study (start date on or before the last dose date) and AEs and TVEs that occurred during the 30-day follow-up period (start date after the date of the last dose) were summarized separately. Physical examination findings, vital signs, and clinical laboratory results were summarized.

SUMMARY – CONCLUSIONS

EFFICACY RESULTS: Efficacy analyses were performed on the MITT population (N=56). Overall, 43 (76.8%) patients achieved hematopoietic response through the Week 13 visit. By Week 5, 30 (53.6%) patients had achieved response; by Week 9, 41 (73.2%) patients had achieved response. Hb levels increased steadily over the first 12 weeks of the study period from 10.2 g/dL at baseline to 12.2 g/dL at Week 13 for a mean increase of 2.0 g/dL. Mean change from baseline in Hb levels was statistically significant at each study week. At Weeks 5, 9, 13, and 17/Early Withdrawal (WD), the mean increase from baseline was 1.5 g/dL ($p<0.0001$), 1.8 g/dL ($p<0.0001$), 2.0 g/dL ($p<0.0001$), and 1.3 g/dL ($p<0.0001$), respectively. At Week 13, after PROCRIT administration was stopped, Hb levels began to decrease to a mean decrease of -0.8 g/dL from Week 13 to Week 17/WD.

At baseline, 4 (7.1%) patients had received a transfusion within the last 6 months. From the date of the first dose through the Week 13 visit and through the end of the study, 3 (5.4%) patients had received a transfusion. From Day 29 to Week 17/WD, 5.4% of patients received transfusions, and from Day 29 through Week 13, 3.6% of patients received transfusions. The mean units of PRBC transfused from Dose 1 through Week 13 was 2.0 units. The mean number of units per patient transfused from Dose 1 through Week 13 was 4.0.

LASA scores increased from baseline in all categories (energy level, daily activities, overall QOL), and changes from baseline were statistically significant at all timepoints. At Week 17/WD, scores were still increased from baseline, despite study drug discontinuation for 4 weeks. The correlation analysis between changes in Hb and LASA scores revealed that Hb levels and LASA scores were statistically significant at Week 5 for daily activities ($p=0.04$); at Week 9 for energy level ($p=0.05$), daily activities ($p=0.02$), and quality of life ($p=0.01$); and at Week 13 for daily activities ($p=0.02$) and quality of life ($p=0.03$). No statistically significant associations between changes in Hb and LASA scores were seen in the Week 13 through Week 17/WD analysis.

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FACT-An scores decreased from baseline in the anemia subscale, fatigue subscale, non-fatigue subscale, and overall scores at all timepoints. These decreases from baseline were statistically significant for the anemia subscale at Weeks 5, 9, 13, and 17 (p=0.0233, 0.0056, 0.0077, and 0.0020, respectively); fatigue subscale at Weeks 5, 9, 13, and 17 (p=0.0038, 0.0001, 0.0017, and 0.0006, respectively); and for the overall scores at Week 9 (p=0.0028) and Week 13 (p=0.0046). The correlation analysis between changes in Hb and FACT-An scores revealed that Hb levels and FACT-An scores were statistically significant at Week 9 for the anemia subscale (p=0.02). No statistically significant associations between changes in Hb and FACT-An scores were seen in the Week 13 through Week 17/WD analysis.

The mean number of weeks to first hematopoietic response was 4.91 (median of 4.00 weeks). Overall, 51 (91.1%) patients had a mean change from baseline in Hb $\geq$ 1 g/dL through the Week 13 visit. At Week 5, 45 (80.4%) patients had a mean change $\geq$ 1 g/dL; at Week 9, 49 (87.5%) patients had a mean change $\geq$ 1 g/dL. The mean number of weeks to Hb $\geq$ 1 g/dL was 3.82.

SAFETY RESULTS: All safety analyses were performed on the safety population (N=57). PROCRIT at doses of 40,000 to 80,000 units subcutaneously once every 2 weeks was generally well tolerated. A total of 44 (77.2%) patients had at least 1 AE on study (i.e., between the first study-related procedure and the last dose of study drug). Peripheral edema and dizziness were the most frequently reported AEs, with each reported by 9 (15.8%) patients, followed by nausea and asthenia (7 [12.3%] patients each). Most AEs were assessed by the investigator as unrelated to study drug. Only 1 patient had an AE (asthenia) that was considered possibly related to study drug; none of the patients had an AE that was assessed by the investigator as probably or very likely related. Four (7.0%) patients had at least 1 AE that was assessed by the investigator as having a doubtful relationship to study drug. Most AEs that occurred on study were rated as Grade 1 (mild) or Grade 2 (moderate). No Grade 5 AEs were reported. A total of 11 (19.3%) patients experienced at least 1 Grade 3 or Grade 4 AE. Grade 4 AEs consisted of congestive cardiac failure, pneumonia, and throat cancer, each reported for 1 (1.8%) patient. The most frequent Grade 3 AE was fatigue, reported for 2 (3.5%) patients. No patients died on study. No patients had AEs on study that led to discontinuation.

Eight (14.0%) patients had an SAE on study, none of which were assessed by the investigators as related to study drug. Three of the SAEs (congestive cardiac failure, sepsis syndrome, throat cancer) were assessed by the investigators as Grade 4. Five (8.8%) patients had at least 1 TVE on study: chest pain (1 [1.8%] patient), chest wall pain (2 [3.5%] patients), cerebrovascular accident (1 [1.8%] patient), and DVT (1 [1.8%] patient). All TVEs were assessed by the investigators as having no relationship to study drug.

During the 30-day follow-up period, 10 (17.5%) patients had at least 1 AE, all of which were assessed by the investigators as having no relationship to study drug. No AEs occurred in more than 1 patient. The system organ class with the most AEs was gastrointestinal disorders. One patient (201002) died from exacerbation of rectal cancer during the follow-up period. The event was assessed by the investigator as not related to study drug. No other SAEs, TVEs, or other significant AEs were reported during the follow-up period.

The number of AEs and SAEs experienced on study and during the 30-day follow-up period was consistent with the underlying disease state of the patients and the established safety profile of PROCRIT.

Vital signs remained near baseline levels throughout the study, and there were no changes of clinical concern in physical examination findings or ECOG scores.

CONCLUSION: PROCRIT at 60,000 units once every 2 weeks elevated Hb, decreased the need for transfusions, and improved quality of life in anemic cancer patients who were not receiving chemotherapy or radiation therapy. PROCRIT at this dose level was generally safe and well tolerated.

Date of the report: Final CSR 07 Sep 2005

Table 1: Schedule of Events

(Study PR03-27-002)

Test/Observation	Screening[a]	D1/ W1	W2	W3	W4	W5	W6	W7	W8	W9	W10	W11	W12	W13	W14	W15	W16	W17/Early Withdrawal
Informed consent	X																	
Inclusion/exclusion criteria	X																	
Demographic information	X																	
Medical history/current therapy	X[b]																	
Transfusion history	X[c]																	
PROCRIT administration[d]		X		X		X		X		X		X						
Iron supplementation	X	Patients received supplemental iron, ferrous sulfate 325 mg orally once a day, or equivalent in iron preparation, as tolerated and if not contraindicated																
Physical exam/weight/height[e]	X																	X
ECOG performance status	X					X				X				X				X
Blood pressure[d]	X	X[f]	X	X	X	X	X	X	X	X	X	X	X	X	X[g]	X[g]	X[g]	X
LASA		X[f]				X				X				X				X
FACT-An		X[f]				X				X				X				X
Concomitant transfusions[h]	Recorded as necessary throughout study participation																	
Concomitant chemotherapy, radiotherapy	Recorded as necessary throughout study participation																	
Concomitant medications	Recorded as necessary throughout study participation																	
Serum pregnancy test[i]	X																	
CBC with differential	X	X[f]	X	X	X	X	X	X	X	X	X	X	X	X	X[g]	X[g]	X[g]	X
Serum chemistry panel	X																	X
Serum iron, ferritin, TIBC	X																	
Serum folate, vitamin B_{12}	X																	
Adverse events[j]	Evaluated throughout study participation using National Cancer Institute Common Toxicity Criteria																	

[a]Within the 14-day period immediately preceding the first dose of PROCRIT, except for the serum pregnancy test, which was performed within 7 days prior to the first dose, and LASA, Hb, Hct, and blood pressure, which were completed within 3 days of the first dose.

[b]All prior therapies, including chemotherapy and radiation therapy.

[c]Transfusion history (including pre-transfusion Hb) within prior 6 months.

[d]Hb, Hct, and blood pressure were measured weekly. CBC results were to be available before PROCRIT administration.

[e]Height measured during screening only.

[f]Baseline measurement.

[g]Patient visit not required but was performed at the discretion of the physician.

[h]Date and type of transfusion, Hb prior to transfusion (obtained at the time of type/cross match), Hb after transfusion, and the number of units transfused were recorded.

[i]Performed on female patients of childbearing potential.

[j]Began monitoring after the first study related procedure was performed (i.e., after the informed consent form was signed). Monitoring of adverse events occurred throughout study.

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