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.: PR02-27-011

Title of Study: A Pilot Study to Evaluate the Response Rate of PROCRIT® (Epoetin Alfa) at 40,000 Units Once Weekly in Anemic Cancer Patients 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, Williams D. Epoetin alfa 40,000 u once weekly (qw) increases hemoglobin (Hb) and improves quality of life (QOL) in anemic patients with cancer not receiving chemotherapy (CT) or radiation therapy (RT). Blood 2003;102:11. Abstract 4375. (2) Shasha D. Epoetin alfa 40,000 u qw increases Hb and is safe in anemic patients with cancer not receiving chemotherapy or radiation therapy. Blood 2004; 104:11. Abstract 4223.

Study Initiation/Completion Dates: 18 Nov 2002 to 26 Mar 2004	**Phase of development:** 2

Objectives: To evaluate the effectiveness, safety, and clinical outcomes of PROCRIT at 40,000 units once weekly in anemic patients with cancer not receiving chemotherapy or radiation therapy

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

Number of Patients (planned and analyzed): Planned: 100; Enrolled: 98; Completed Week 17: 65. The study was suspended on 29 September 2003 to amend the protocol; 96 patients were enrolled and 37 patients were completed through Week 13 at the time of suspension.

In September 2003, Ortho Biotech received preliminary data from 4 investigational, randomized, controlled oncology studies, directly sponsored or supported by Ortho Biotech, enrolling patients with cancer receiving chemotherapy and/or radiation therapy. Patients were treated with epoetin alfa to hemoglobin (Hb) concentrations higher than those specified in current labeling under the premise that this more-intensive treatment approach might enhance the anticancer efficacy of radiation and/or chemotherapy. At the time of the suspension, preliminary analyses of data from 3 suspended studies (PR00-03-006, PR01-04-005/GOG 191, and EPO-CAN-15) had indicated that a greater number of epoetin alfa-treated patients developed thrombotic vascular events (TVEs) compared with patients receiving placebo or standard of care. Patients who developed a TVE were enrolled with Hb concentrations greater than 13 g/dL or commonly had Hb concentrations greater than 13 g/dL in the 28-day period immediately prior to the event.

Following receipt of these preliminary data, Ortho Biotech took immediate action to ensure the protection of patients in investigational studies. Three of the investigational studies were suspended. Study PR02-27-011 was suspended in order to amend the protocol to avoid treatment of patients to Hb concentrations higher than those specified in current labeling.

The plan was to enroll 100 patients, but the study was stopped at 98 patients due to poor accrual after the suspension. The modified intent-to-treat (MITT) population included 91 patients, the safety population included 95 patients, the pre-suspension completer population included 37 patients, and the suspension completer population included 33 patients. The following diagram displays the breakdown of the patient populations.

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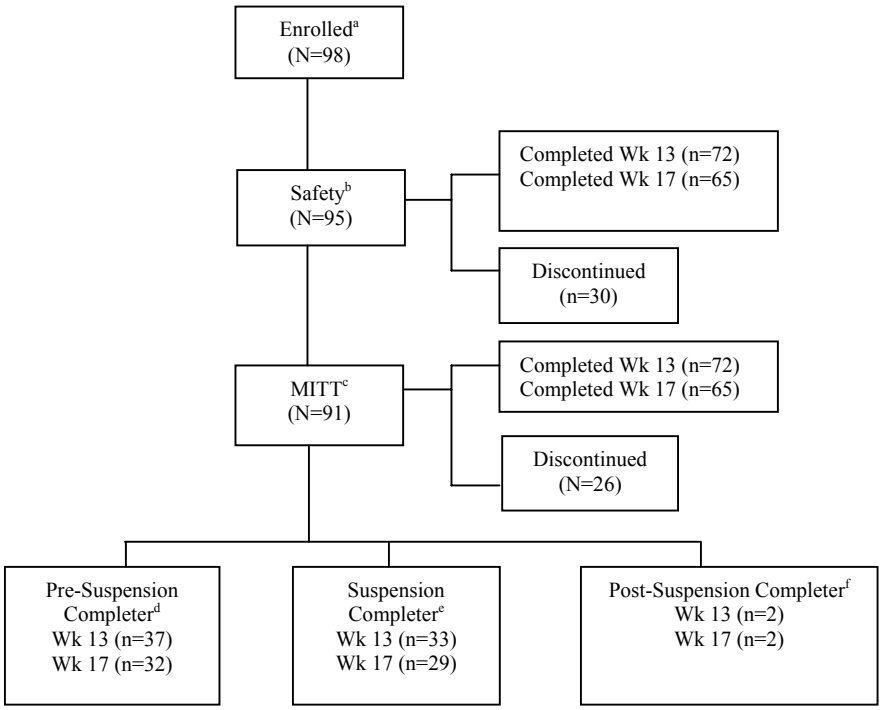

[a] 96 patients enrolled prior to suspension; 1 patient enrolled on day of suspension; 1 patient enrolled after suspension started.

[b] All patients who received at least 1 dose of study drug.

[c] All patients who had at least 1 post-baseline efficacy observation (Hb or transfusion).

[d] All patients who completed through Week 13 or Week 17 prior to suspension.

[e] All patients who were enrolled prior to suspension, went through suspension, and completed through Week 13 or Week 17 after suspension was lifted.

[f] One patient enrolled on day of suspension; 1 patient enrolled after suspension started.

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Diagnosis and Main Criteria for Inclusion: Cancer patients with non-myeloid malignancies who had hemoglobin (Hb) ≤11.0 g/dL and who were not actively receiving chemotherapy or radiation therapy

Test Product, Dose and Mode of Administration, Batch No.: The starting dosage of PROCRIT was 40,000 units subcutaneously (SC) once weekly (QW). If after 4 weeks of treatment with PROCRIT, the patient's Hb level did not increase by ≥1.0 g/dL, the dose of study drug was to be increased to 60,000 units subcutaneously once weekly.

Prior to Amendment 1 in October 2003, if a patient's Hb level measured >15.0 g/dL, the dose was withheld until the Hb level decreased to <13.0 g/dL, and then restarted at a 25% reduction. A similar dose reduction was to be made if the patient's rate of Hb increase exceeded 1.3 g/dL over any consecutive 2-week period.

After Amendment 1, the dose of study drug was decreased as follows due to safety concerns associated with high-target Hb levels and too-rapid Hb response:

1. If a patient's Hb level measured >13.0 g/dL, study drug was withheld until the Hb level decreased to ≤12.0 g/dL, at which the time study drug dose was reduced from 40,000 units to 30,000 units SC QW or from 60,000 units to 40,000 units SC QW.
2. If a patient's rate of Hb increase exceeded 1.0 g/dL over any consecutive 2-week period, independent of transfusion, that patient's dose of study drug was reduced from 40,000 units to 30,000 units SC QW or from 60,000 units to 40,000 units SC QW.

Treatment with study drug was for a maximum of 12 weeks followed by a 4-week observation period after PROCRIT treatment had been stopped.

Duration of Treatment: 12 weeks plus 4 weeks of follow up

Criteria for Evaluation:

Efficacy: The primary efficacy variable was hematologic response. Response could be achieved at any time during the treatment period (baseline to Week 13). Major response was defined as ≥2.0 g/dL Hb increase from baseline. Minor response was defined as ≥1.0 g/dL Hb increase. Hb values within 28 days following a transfusion were excluded from the analyses. Secondary efficacy variables included the effects of PROCRIT on transfusion requirements and on quality of life (QOL) as measured by the Linear Analog Scale Assessment (LASA). A separate and independent analysis of cognitive functioning (attention, processing speed, reaction time, and executive functioning) was also performed.

Safety: Incidence and severity of adverse events (AEs), physical examinations, vital signs (blood pressure), clinical laboratory results, and incidence of erythropoietin antibodies were evaluated.

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Statistical Methods: Primary efficacy was calculated as the proportion of patients achieving major or minor response during the treatment period. Response could be achieved at any time during the treatment period (baseline to Week 13). Major response was defined as an increase in Hb of at least 2.0 g/dL; minor response was defined as an increase in Hb of at least 1.0 g/dL. Hb values within 28 days following a transfusion were excluded from the analyses. The count of minor responders included all major responders.

Hematologic responses were calculated as the percent of patients with an increase in Hb ≥1.0 g/dL (minor response) or ≥2.0 g/dL (major response) from baseline to the start of weeks 5, 9, 13, and 17. A 95% confidence interval (CI) was also calculated for the estimates. Hb was evaluated weekly from baseline to the end of treatment (start of Week 13/WD[early withdrawal]), and for an additional 4 weeks after study drug treatment cessation (to the start of Week 17/WD [early withdrawal]). Mean Hb levels were summarized for each evaluation period using descriptive statistics (i.e., number of patients, mean, median, standard deviation [SD]). A 95% CI around the mean was also calculated. Change in Hb from baseline through endpoint (Week 17/WD) was summarized using descriptive statistics, and a 95% CI around the mean was calculated. Change in Hb levels from baseline through the last value were analyzed using paired t-test or the nonparametric Wilcoxon Signed Rank test (if there was indication of departure from normality). Units transfused per person were quantified using descriptive statistics, and a 95% CI around the mean was calculated. The proportion of patients transfused was summarized, and a 95% CI was also calculated for the proportion. Change in mean LASA scores from baseline to the last value was analyzed using a paired t-test.

The study population used for most analyses of both the primary and secondary endpoints is all randomized patients who received at least one dose of study medication and had at least one post-baseline efficacy observation, previously referred to as the ITT population in the study protocol and SAP. Since this definition more correctly defines an MITT population by most conventions, MITT will be used instead of ITT in the remainder of this document. In addition, any reference to the ITT population within the tables, listings, and figures should be considered the MITT population.

The SAP was revised to reflect changes in the analyses due to the suspension of the study and to account for additional analyses that were planned for in the protocol but had been inadvertently omitted from the SAP. The original SAP, dated 11 Mar 2004, and the final SAP, dated 20 Sep 2004, are included in Appendix 2.

Adverse events (AEs) were summarized by National Cancer Institute (NCI) Common Toxicity Criteria (CTC) (Version 2.0) grade, system organ class, preferred term, and possible relationship to PROCRIT. AEs leading to discontinuation or death were also summarized. SAEs and deaths that occurred during the 90 days following study completion or withdrawal were summarized. TVEs were summarized as the number and percent of patients experiencing at least 1 TVE, the number and percent of patients experiencing at least 1 TVE by system organ class and preferred term, and the relationship to study drug. Physical examination findings, vital signs, and clinical laboratory results were summarized.

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SUMMARY - RESULTS

EFFICACY RESULTS: By Week 13, 70 (76.9%; 95% CI=66.9, 85.1) patients had achieved major response, and 82 (90.1%; 95% CI=82.1, 95.4) patients had achieved minor response. By Week 17/WD, 73 (80.2%) patients in the MITT population were major responders, and 86 (94.5%) patients were minor responders; 73 (84.9%) of these patients later achieved a major response. The mean number of weeks to first minor response was 4.1; the mean number of weeks to first major response was 5.8. Similar results were seen in the pre-suspension completer and suspension completer populations.

Hb levels increased steadily over the first 12 weeks of the study period from 10.4 (SD 0.7) g/dL at baseline to 13.3 (SD 1.5) g/dL at Week 13 for a mean increase of 2.9 (1.5) g/dL. At Week 13, after PROCRIT administration was stopped, Hb levels began to decrease to a mean decrease of -1.43 (SD 1.10) g/dL from Week 13 to Week 17/WD. Mean change from baseline in Hb level was statistically significant ($p<.0001$) at each study week starting with Week 2 to the end of the study in all of the efficacy populations. Mean decrease in Hb from Week 13 to Week 17/WD in the MITT and pre-suspension completer populations, including LOCF analyses, was statistically significant starting at Week 15 ($p<.005$).

For the MITT population at baseline, 6 (6.6%) patients had received a transfusion within the last 3 months. From the date of the first dose through the end of the study, 1 (1.1%) patient had received a transfusion. The mean units of packed red blood cells (PRBC) transfused from the date of the first dose through the end of the study was 1.6 units per transfusion.

In the MITT population at Week 9, LASA scores had increased from baseline in all categories (energy level, daily activities, overall QOL). At Week 17/WD, scores were still increased from baseline, despite study drug discontinuation for 4 weeks. Change from baseline in each category at both Week 9 and Week 17/WD was statistically significant ($p<0.0001$).

An ancillary protocol, which included a cognitive screening tool (Headminder Cognitive Test), was conducted at 4 sites. Data for 12 patients completing two test instances were analyzed. Additional analyses were performed on 9 patients completing all three test instances. In the cognitive screening tool results, statistically significant improvements were seen between baseline and Week 9 in the domains of attention ($p=0.037$), executive functioning ($p=0.019$ [Visuo-Motor 2] and 0.047 [Visuo-Motor 3]), and processing speed ($p=0.050$). Statistically significant improvement was also seen between assessments at Week 9 and Week 17/WD in the domain of reaction time ($p=0.043$). Comparison of baseline and Week 17/WD measurements for patients completing all 3 test instances ($N=9$) revealed statistically significant improvement in the domains of reaction time ($p=0.013$) and executive functioning ($p=0.014$).

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SAFETY RESULTS: PROCRIT at doses of 30,000 to 60,000 units subcutaneously once weekly was generally well tolerated. Although 75 (78.9%) patients in the safety population had at least 1 AE, the majority of AEs were considered not related to study drug. No AEs were considered probably or very likely related to study drug. Fatigue was the most frequently reported AE, reported by 18 (18.9%) patients. The majority of AEs were classified as NCI Grade 1 (mild) or NCI Grade 2 (moderate). A total of 4 (4.2%) patients discontinued from the study because of an AE; all of these were considered not related to study drug.

One patient (4003) died during the study due to progression of prostate cancer and 7 patients died during the 90 days following study completion or withdrawal. A total of 24 (25.3%) patients had at least 1 SAE during the study. The most common SAE was dehydration, reported by 4 (4.2%) patients. One SAE (DVT) was considered possibly related, and the relationship to study drug was considered doubtful for 1 SAE (change in mental status). All other SAEs were considered not related to study drug.

A total of 7 (7.4%) patients had an event classified as a TVE for safety purposes. The most frequently occurring TVE was chest pain, occurring in 3 (3.2%) patients. Two (2.1%) patients had DVT; 1 (1.1%) patient had angina pectoris; and 1 (1.1%) patient had chest discomfort.(Chest discomfort alone does not imply TVE unless there is a definitive diagnosis. No TVEs were considered by the investigator to be probably or very likely related to study drug; 1 TVE (DVT) was considered possibly related to study drug; the other 6 TVEs were considered to have no relationship to study drug.

During the 90 days following study completion or withdrawal, 7 patients died. Four of the deaths were attributed to disease progression; none of the deaths were related to study drug. None of the events were considered related to study drug.

There were no significant deviations from expected mean values for hematology or chemistry at baseline or end of study. All vital signs remained near baseline levels throughout the study. The majority of patients did not have a change from baseline in physical examination findings at Week 17/WD. No serum erythropoietin antibody levels were detected during the study (26 patients had a sample taken at Visit 1 and at Visit 17/Early Withdrawal).

SUMMARY – CONCLUSIONS

CONCLUSION: This study evaluated the effectiveness, safety, and clinical outcomes of PROCRIT at 40,000 units once weekly in anemic cancer patients not receiving chemotherapy or radiation therapy. Despite a temporary suspension in the study and modifications to the protocol that could have potentially complicated the analysis and affected the results, PROCRIT at this dosage clearly elevated Hb and decreased the need for transfusions in these patients. By Week 13, 70 (76.9%) patients had achieved major response, i.e., had a Hb increase of at least 2.0 g/dL, and 82 (90.1%) patients had achieved minor response. A total of 80.2% of patients had a Hb increase of at least 2.0 g/dL (major response) by Week 17/WD, and 94.5% of patients had a minor response of Hb increase of at least 1.0 g/dL by Week 17/WD. Patients experienced statistically significant steadily increasing levels of Hb over the treatment period. During the 12 weeks of treatment, there was virtually no need for transfusions. These results were similar for all patients, whether or not they had been affected by the suspension.

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Quality of life also improved for patients in this study as evidenced by statistically significant increases from baseline in the LASA. Modest enhancements in cognitive performance for patients experiencing cancer-induced cognitive dysfunction were seen as evidenced by the results of the cognitive assessment tool. PROCRIT at doses of 30,000 to 60,000 units subcutaneously once weekly was generally well tolerated. The number and nature of AEs experienced during the study was consistent with the underlying disease state of the patients. No AEs were considered probably or very likely related to study drug. A total of 24 (25.3%) patients in the safety population had at least 1 SAE during the study. A total of 7 (7.4%) patients had a TVE. One TVE (DVT) was considered possibly related to study drug. Date of the report: May 6, 2005		

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