SYNOPSIS

NAME OF SPONSOR/COMPANY: Ortho Biotech Clinical Affairs, LLC NAME OF FINISHED PRODUCT: PROCRIT®; Epoetin alfa NAME OF ACTIVE INGREDIENT(S): Recombinant human erythropoietin	INDIVIDUAL STUDY TABLE REFERRING TO PART OF THE DOSSIER Volume: Page:	(FOR NATIONAL AUTHORITY USE ONLY)

Protocol No.: PR02-27-013

Title of Study: A Pilot Study to Evaluate the Hematologic Response Rate of PROCRIT® (Epoetin alfa) at 80,000 Units Once Weekly in Anemic Cancer Patients Receiving Chemotherapy

Publication (References): (1) Tarabay G, et al. Treatment of anemia with epoetin alfa 80,000 U QW in cancer patients receiving chemotherapy. Proc Amer Soc Clin Oncol 2004;22:780s. Abstract 8205. (2) Waltzman RJ, Braly P, Williams D. Safety and efficacy of epoetin alfa initiated at 80,000 U once weekly in anemic cancer patients receiving chemotherapy. Blood 2004;104(11):143b. Abstract 4228.

Principal Investigator: Roger Waltzman, MD, St. Vincents Comprehensive Cancer Center, New York, New York; United States

Study Initiation/Completion Dates: 20 Jun 2003 to 27 May 2004 | **Phase of development:** 3b

Objectives: To evaluate the hematologic response, safety, and clinical outcomes of PROCRIT at 80,000 units once weekly in anemic cancer patients receiving chemotherapy. To evaluate the incidence of anti-erythropoietin antibodies at baseline and at end of study/early withdrawal in study patients who received a minimum of 2 or more doses of PROCRIT over at least a 1-month period.

Methodology: Open-label, non-randomized pilot study

Number of Patients Planned: 60; Enrolled: 69; Completed: 47

Diagnosis and Main Criteria for Inclusion: Cancer patients with non-myeloid malignancies with a hemoglobin (Hb) $\leq$11.0 g/dL who were planning to receive at least 12 weeks of chemotherapy

Test Product, Dose and Mode of Administration, Lot No.: The starting dose of PROCRIT was 80,000 units subcutaneously once weekly. If, at any time the Hb rose to >13.0 g/dL, PROCRIT therapy was held until the Hb reached $\leq$12.0 g/dL, then resumed at 60,000 units weekly. The dose was also reduced if a very rapid Hb response occurred (a rise of >1.3.0 g/dL in a 2-week period.). Study drug lot numbers were D02LH0949 and D03LA1006.

Duration of Treatment: 12 weeks

Criteria for Evaluation:

Efficacy: The primary efficacy variable was major hematologic response, independent of transfusion within 28 days, in terms of Hb change and transfusion requirements from baseline to end of study. The primary efficacy endpoint was major response, defined as $\geq$2.0 g/dL Hb increase or Hb $\geq$12.0 g/dL (independent of transfusion within 28 days). Secondary efficacy assessments were minor hematologic response and incidence of transfusion. Minor hematologic response was defined as $\geq$1.0 g/dL Hb increase, up to a 1.9 g/dL increase, independent of transfusion within 28 days. Incidence of transfusion was measured by the number of units transfused per person and the proportion of patients who received transfusions.

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

SYNOPSIS (CONTINUED)

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Statistical Methods: During the course of writing the clinical study report (CSR), it was recognized that the intent-to treat (ITT) population as defined within the CSR and statistical analysis plan (SAP) should have been defined as the modified intent-to-treat (MITT) population. Therefore, any reference to the ITT population within the tables, listings, and figures should be considered the MITT population. From this point forward, all references within the CSR to this population will be the MITT population (except in the tables, listings, and figures).
The primary endpoint analyses were conducted on the modified MITT and per-protocol (PP) populations. Major and minor responses and the corresponding 95% confidence intervals (CIs) were calculated. Time to first major or minor response was summarized using descriptive statistics. The week that major or minor response occurred was summarized using counts and percents. Mean Hb and mean change in Hb from baseline to each scheduled visit, as well as to the last scheduled Hb value available, independent of transfusion within 28 days, were summarized. Units transfused for each patient were also summarized. The proportion of patients who received transfusions and the corresponding 95% CI for the proportion were calculated for the 3-month period prior to baseline and the period after baseline.

AEs were summarized by National Cancer Institute Common Toxicity Criteria (NCI CTC; Version 2.0) 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 that occurred during the study (AE start date on or before the last dose date) and AEs that occurred during the 30-day follow-up period (AE start date after the date of the last dose) were summarized separately. The change from baseline in anti-erythropoietin antibodies was summarized with descriptive statistics and 95% CIs. Physical examination findings, vital signs, and clinical laboratory results were summarized.

SUMMARY – CONCLUSIONS

Efficacy Results: Primary efficacy was measured by the number of patients achieving major response, which was defined as $\geq$2.0 g/dL Hb increase and/or Hb $\geq$12.0 g/dL (independent of transfusion within 28 days). A total of 49 (72.1%; 95% CI=59.85, 82.27) patients in the MITT population achieved major response. The mean number of weeks to first major response was 6.69. A total of 51 (75.0%; 95% CI=63.01, 84.71) patients in the MITT population were minor responders. Of these 51 patients, 38 (55.9%) went on to achieve a major response, and 13 (19.1%) patients achieved a minor response at best. The mean number of weeks to first minor response was 5.08.

Hemoglobin levels increased steadily over the first 12 weeks of the study period. At Week 5, the mean change in Hb from baseline was 1.2 g/dL (SD 1.39; 95% CI=0.77, 1.56). At Week 9, the mean change from baseline was 1.9 g/dL (SD 1.37; 95% CI=1.54, 2.35). At Week 13/early withdrawal, the mean change from baseline was 2.2 g/dL (SD 1.28; 95% CI=1.80, 2.51).

In the MITT population, 6 (8.8%; 95% CI=3.30, 18.22) patients received a PRBC transfusion from the date of the first dose through the end of the study. Four (5.9%; 95% CI=1.62, 14.38) patients received a PRBC transfusion between Day 1 and Day 28. Two (2.9%; 95% CI=0.35, 10.22) patients received a PRBC transfusion after Day 29. The mean units of PRBC transfused from Day 1 to Day 28 was 2.20 (SD 0.45; 95% CI=1.69, 2.71). The mean units of PRBC transfused from Day 29 to study end was 2.00 (SD 0.00; 95% CI=2.00, 2.00).

Similar efficacy results were seen in the PP population and in the last observation carried forward (LOCF) analyses of the MITT and PP populations.

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Safety Results: PROCRIT at doses of 40,000 to 80,000 units subcutaneously was generally well tolerated. A total of 65 (94.2%) patients in the safety population had at least 1 AE during the study. Nausea was the most frequently reported AE, reported by 15 (21.7%) patients. Eight AEs during the study were considered by the investigator to have a doubtful relationship to study drug; 3 AEs (edema peripheral, bone pain, pruritus) were considered by the investigator as possibly related to study drug; no AEs were considered by the investigator as probably or very likely related to study drug. During the follow-up period, 2 AEs were considered by the investigator to have a doubtful relationship to study drug; 2 AEs (bone pain, pruritus) were considered by the investigator as possibly related to study drug; no AEs were considered by the investigator as probably or very likely related to study drug.

Four patients died during the study. Causes of death included 1) massive pulmonary embolism; 2) Hodgkin's lymphoma and seizure disorder; 3) influenza, metastatic colon cancer, and cardiac arrest; and 4) dyspnea, fatigue, pancytopenia, and pneumonia. The events were considered by the investigator as not related to study drug. A total of 19 (27.5%) patients had at least 1 serious adverse event (SAE) during the study. The most common SAE was sepsis not otherwise specified (NOS), reported by 3 (4.3%) patients. All SAEs during the study were considered by the investigator as not related to study drug. A total of 6 (8.7%) patients, including the 4 patients who died, discontinued from the study because of an AE.

A total of 10 (14.5%) patients had a clinically relevant TVE during the study. The most frequently occurring clinically relevant TVEs were chest wall pain and deep vein thrombosis (DVT), each occurring in 3 (4.3%) patients. No TVEs were considered by the investigator as related to study drug.

During the 30 days following study completion or withdrawal, 16 (23.2%) patients had at least 1 AE. Arthralgia and myalgia were the most frequently reported AEs during this period, each reported by 2 (2.9%) patients. Two AEs were considered by the investigator to have a doubtful relationship to study drug; 2 AEs (bone pain, pruritus) were considered by the investigator as possibly related to study drug; no AEs were considered by the investigator as probably or very likely related to study drug. 1 patient died as a result of septic shock; the event was considered by the investigator as not related to study drug. No patients had a SAE or TVE during the follow-up period.

Conclusion: PROCRIT at 80,000 units once weekly elevated Hb and decreased the need for transfusions in anemic cancer patients receiving chemotherapy despite frequent dose reductions and holds. The proportion of patients achieving a major Hb response ($\geq$ 2.0 g/dL Hb increase or Hb $\geq$ 12.0 g/dL independent of transfusion within 28 days) was similar to that seen in historical trials of 40,000 to 60,000 units once weekly.[3] In addition, mean Hb levels were similar after 4 and 8 weeks of therapy compared to standard dosing. PROCRIT at 80,000 units once weekly is generally safe and well tolerated.

Date of the report: Final 24 Aug 2005

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