## SYNOPSIS

NAME OF SPONSOR/COMPANY:

Ortho Biotech Products, L.P.

NAME OF FINISHED PRODUCT:

PROCRIT® (Epoetin alfa)

NAME OF ACTIVE INGREDIENT(S):

Recombinant Human Erythropoietin

**Protocol No.:** CR002365

**Title of Study:** A double-blind, randomized, placebo-controlled study of the efficacy and safety of epoetin alfa administered weekly in patients with gastric or rectal cancers undergoing preoperative chemoradiation followed by surgery

**Coordinating Investigator:** Saraj Vadhan Raj, MD.

The University of Texas, MD Anderson Cancer Center; 1515 Holcombe Blvd.; Houston, Texas 77030

**Study Center(s):** This was a multicenter study conducted at 15 study sites located in the United States

**Publication (Reference):** none

**Studied Period (years):** October 29, 2001 – December 12, 2003

**Phase of development:** 3

**Objectives:** To demonstrate the effectiveness of epoetin alfa in reducing red blood cell transfusions in patients with gastric and rectal cancer undergoing preoperative chemoradiation therapy followed by surgery. Secondary objectives included the following: (1) to evaluate the efficacy of epoetin alfa in maintaining hemoglobin (Hb) levels during preoperative chemoradiation, (2) to evaluate the effect of epoetin alfa on quality of life (QoL) as measured by patient self-reported Linear Analog Scale Assessment (LASA), Functional Assessment of Cancer Therapy–Anemia (FACT-An), and the Brief Fatigue Inventory (BFI) and (3) to evaluate tumor response. The safety of epoetin alfa treatment was also to be assessed.

On the basis of the recommendations of the Data and Safety Monitoring Board, the study was terminated early due to a possible increased risk of developing deep vein thrombosis in epoetin alfa patients. Previously planned statistical analyses of the efficacy parameters were not done because the study was terminated early and the focus shifted primarily to safety. Descriptive statistics of all parameters, efficacy and safety, were provided.

**Methodology:** This study was a randomized, double-blind, placebo-controlled multicenter trial. A total of 60 adult patients were enrolled at 9 sites and were followed over 4 follow-up periods (Weeks 3, 6, 10, and 15) for a total of 16 weeks. Patients were evaluated for entry into the study and were randomly assigned to receive placebo or epoetin alfa (40,000 IU/dose). Randomization was stratified by the type of primary disease (gastric cancer: n=6; or rectal cancer: n=53) and by the presence of anemia (Hb $\leq$ 13 g/dL; n=25) or absence of anemia (Hb > 13 g/dL; n=35), and by study site. Study drug was administered by weekly (q.w.) subcutaneous (s.c.) injections starting 1 week before chemoradiation, for a total of 16 weeks or up to 4 weeks after surgery, whichever occurred first.

**Number of Patients (planned and analyzed):** The plan was to enroll 184 patients. At the time the study was stopped early, only 59 of 60 patients randomized were analyzed for safety (One patient did not receive any study drug).

**Diagnosis and Main Criteria for Inclusion:** Male or female patients, 18 years or older, who had a histologically confirmed diagnosis of gastric cancer or rectal cancer for whom the treatment plan was preoperative chemoradiation followed by surgery, had a baseline Hb value of $\geq$ 10 g/dL and <15 g/dL, and had adequate hematologic function defined as ANC $\geq$ 1.5/ x $10^9$/L and a platelet count $\geq$ 100 x $10^9$/L. Patients with reproductive potential were required to use an adequate contraceptive method (eg, abstinence, intrauterine device, oral contraceptives, barrier device with spermicide or surgical sterilization) during treatment and for 3 months after completing treatment. If a patient met the entry requirements within 7 days of admission the patient was to be enrolled in the study. The study was explained to the patient (and family, if applicable) and an informed consent form was signed.

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**Test Product, Dose, and Mode of Administration:** Epoetin alfa (PROCRIT® 40,000 U/mL) was formulated as a sterile, colorless, preserved, buffered solution that contained 2.5 mg/mL human serum albumin. Each vial contained approximately 1.1 mL of study drug. Each mL of study drug contained 40,000 IU of epoetin alfa. Study drug (40,000 IU/dose epoetin alfa or placebo) was administered by s.c. injection beginning 1 week before chemoradiation treatment and was continued on a s.c. q.w. dosing regimen for up to 16 weeks or 4 weeks post-surgery, whichever occurred first. If the Hb level decreased by ≥ 1 g/dL and/or was ≤ 13 g/dL after 4 weeks of treatment, the dose of study drug was increased to 60,000 IU s.c. q.w., starting from Week 4 of chemoradiation. The dose of study drug was withheld if Hb levels increased to ≥ 15 g/dL. Study drug was resumed if Hb decreased to < 14.0 g/dL at a dose of 20,000 IU/wk less than the previous dose. Patients who missed more than one dose of study drug were to be removed from the study (does not include patients in which study drug was withheld, if indicated, until Hb decreased).

Bulk Lot Nos.: D00LM0566 (package lot nos.: R11437, R11619), and D02LH0949 (package lot nos.:R11999, R11950, R11948, R12029, R12034, R12032, R12046, R12057, and R12059) for the 40,000 IU (1 mL vials).

**Reference Therapy, Dose, and Mode of Administration, Batch No.:** Placebo was an inactive substance identical in appearance to epoetin alfa and for the purpose of calculating exposure to dose, was expressed as equivalent units of epoetin alfa. Placebo was formulated as a sterile, colorless, preserved, buffered solution containing 2.5 mg/mL human serum albumin without epoetin alfa.

Bulk Lot No. for placebo was D01LD0672 (package lot nos.: R11438, R11620, R12000, R11951, R11949, R12030, R12035, R12033, R12047, R12058, and R12060) for the 40,000 IU (1 mL vials).

**Criteria for Evaluation:**

Efficacy: After the study was terminated early, efficacy analyses (including inferential comparison of the treatment groups with respect to the primary and secondary efficacy outcomes) were not performed; however, descriptive data of these assessments were provided. Assessment of the safety parameters became the primary focus. No subgroup analyses were performed.

Safety: Safety evaluations included assessments of the incidence and severity of adverse events (AEs) and serious adverse events (SAEs), clinical laboratory tests (hematology, iron profile, and serum chemistry), physical examinations, and vital sign measurements. In addition to the safety assessment for all patients, separate evaluations of safety parameters were conducted with the data from the patients who developed a thrombotic vascular event (TVE).

**Statistical Methods:** Continuous variables were summarized using descriptive statistics (sample size [N], mean, standard deviation, median, minimum, maximum, and range). Patients with missing data at a given time point for an individual continuous variable were not included in descriptive calculations for that variable at that time point. Categorical variables were summarized utilizing frequency statistics (frequency and percent). Patients with missing data at a given time point for an individual categorical variable were not included in calculations of percentages for that variable at that time point; however, these patients were included in a 'missing' category in the tabulations where appropriate.

For certain variables, 2-sided 95% confidence intervals were calculated. Methods for calculating these intervals assumed large samples (ie, both treatment groups included more than 25 patients, and thus the normal distribution was assumed). Intervals for categorical variables assume the normal approximation to the binomial distribution.

All tabulations were performed by treatment group unless otherwise indicated. Select tabulations were performed by disease stratum (gastric or rectal cancer). Data listings were provided for all data in the database. The randomization strata (anemia status, ie, ≤ 13 g/dL versus Hb > 13 g/dL and cancer status, ie, gastric or rectal) as well as treatment group assignment were included in the data listings as appropriate.

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**Summary:**

Demographic and Baseline Characteristics: Thirty-five patients were randomized with baseline Hb > 13 g/dL (18 placebo; 17 epoetin alfa) and 25 patients (13 placebo; 12 epoetin alfa) were randomized with baseline Hb ≤ 13 g/dL. More patients with rectal cancer were enrolled in the study than patients with gastric cancer and tumors were in stage II or III for most patients. Forty-two (70%) of the patients completed the study, while 18 (30%) withdrew from the study early (5 [16%] placebo; 13 [45%] epoetin alfa). The average age of patients was 56 years, 64% of patients were male, and 80% of patients were Caucasian.

Efficacy Results: The number and percent of patients who received red blood cell transfusions was 10 (32%) in the placebo patients and 4 (14%) in the epoetin alfa patients. The two treatment groups had similar changes from baseline in QoL to last value (final) observed; however, no inferential testing was performed to assess statistical significance of these findings.

Safety Results: The safety population included all randomized patients who were treated with at least one dose of study drug (total=59). For those patients who were included in the safety population, the mean cumulative dose of study drug in the placebo group was twice that observed in the epoetin alfa group (770,323 units in placebo; 385,714 units in epoetin alfa).

All patients in the study reported experiencing at least one AE. The most frequently reported AEs by preferred terms were nausea (85%), fatigue (81%), diarrhea (80%), tenesmus (70%), and abdominal pain (64%). The investigator assessed most of the AEs as NCI Grade 1 or 2 (Common Toxicity Criteria, Version 2.0) (90% in placebo; 86% epoetin alfa) and almost all AEs as not related or doubtfully related to study drug. One patient died (randomized to the placebo group) of progression of gastric cancer, 3 months after the last dose of study drug. SAEs were reported in 9 (29%) of placebo patients and in 13 (46%) of epoetin alfa patients.

The most frequently reported SAE was a vascular disorder, thrombophlebitis deep (the preferred term by the WHO-ART system; the verbatim term used in this report is deep vein thrombosis or DVT, also referred to as thrombotic vascular event or TVE) (1 placebo; 6 epoetin alfa). Other frequently reported SAEs included dehydration, diarrhea, and intestinal obstruction. TVEs were reported in 2 (6%) placebo patients and 6 (21%) epoetin alfa patients. (These were the same SAEs included in the first sentence of this paragraph with the addition of one nonserious TVE reported in 1 placebo patient.) No patterns were seen in age (from 41 to 77 yrs), sex (4 females; 4 males), or in the timing from the first dose of study drug to the occurrence of the TVE. Seven (20%) patients with at least 1 baseline Hb > 13 g/dL experienced at least 1 TVE, compared with 1 (4%) patient with a baseline Hb ≤ 13 g/dL. Six of 8 patients with a TVE had at least one Hb > 13 g/dL within the 28 days before the TVE. No epoetin alfa patient with a TVE had a Hb increase of more than 2 g/dL in the 4-week period before the TVE and only two epoetin alfa patients with a TVE had a Hb increase of more than 1 g/dL in any 2-week period before the TVE. Two patients in the epoetin alfa group were discontinued from the study drug due to AEs of DVT.

Changes from baseline in clinical laboratory results and vital signs in both epoetin alfa and placebo patients were small and not clinically significant.

Recognizing the limited data available for the shift analysis of TNM staging from baseline to post-operative time points, there was no evidence that treatment with epoetin alfa was associated with a reduced response to combined chemotherapy and radiation therapy or with increased tumor progression.

Compared with placebo patients, epoetin alfa patients had higher levels of functional performance assessed by the Karnofsky Performance Status at the last study assessment.

**Conclusion**: Due to the small number of patients in the study and the number of patients who experienced a TVE, clear evidence of a drug effect was not proven in these patients with cancer. The ability to assess relationships between Hb levels > 13 g/dL and TVEs was limited due to the small number of patients and events in the study. Nonetheless, this study raised a concern that treatment of patients with Hb levels higher than those specified in the approved label (hematocrit > 40%; Hb > 13 g/dL) might be associated with an increased incidence of TVEs. Recognizing the limited data available for the shift analysis of TNM staging from baseline to post-operative time points, there was no evidence that treatment with epoetin alfa was associated with a reduced response to combined chemotherapy and radiation or with increased tumor progression.

**Disclaimer**

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