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

Protocol No.: CR002305

Title of Study: A Phase III Clinical Trial of Procrit® (Epoetin alfa) versus Placebo in Women Undergoing Adjuvant Chemotherapy for Stage, I, II, or III Breast Cancer

Coordinating Investigator: Joyce O'Shaughnessy, MD
Sammons Cancer Center
3535 Worth Street, Collins Building
Dallas, TX 75246

Study Center(s): This was a multicenter study conducted at 21 study sites located in the United States

Publication (Reference): none

Studied Period (years): December 2002 to June 2004 (1 year 10 months)	**Phase of development:** 3

Objectives: To evaluate the effect of Procrit on chemotherapy-related impairment of cognitive and executive function during chemotherapy and 6 months after completing chemotherapy in patients with breast cancer receiving adjuvant anthracycline-based chemotherapy with or without a taxane (measured by the Customized Research Tool [CRT] [HeadMinder™] and EXIT-25).

The secondary objectives were to evaluate the effect of Procrit treatment on asthenia as measured by Functional Assessment of Cancer Therapy-Anemia (FACT-An); quality of life (QoL) as measured by patient self-reported Linear Analog Scale Assessment (LASA); the effect of Procrit treatment on mood as measured by Profile of Mood States (POMS).

Methodology: This study was a randomized, double-blind, placebo-controlled multicenter trial. A total of 37 adult patients were enrolled at 21 sites and were followed over a 12- to 24-week-treatment period and a 6-month follow-up period. Patients were evaluated for entry into the study and were randomly assigned to receive placebo or epoetin alfa (40,000 IU/dose). Study medication was administered by weekly (QW) subcutaneous (SC) injections starting the first week of chemotherapy for a total of 12-24 weeks depending on chemotherapy regimen (anthracycline-based ± taxane).

Number of Patients (planned and analyzed): Planned: 300; Enrolled: 37.

In September 2003, Ortho Biotech received preliminary safety data regarding thrombotic vascular events (TVEs) from investigational, randomized, controlled studies, directly sponsored or supported by Ortho Biotech, enrolling subjects with cancer receiving chemotherapy and/or radiation therapy. Subjects were treated with epoetin alfa to hemoglobin (Hb) concentrations higher than those specified in current labeling. The preliminary analyses of data from these studies indicated that a greater number of epoetin alfa-treated subjects developed thrombotic vascular events (TVEs) compared with subjects receiving placebo or standard of care.

Study CR002305 was subsequently suspended for enrollment in order to amend the protocol to avoid treatment of enrolled subjects to Hb concentrations higher than those specified in current labeling. In the course of evaluating the protocol for amendment, it was noted that Hb levels for the intended patient population, patients with breast cancer receiving adjuvant anthracycline-based chemotherapy with or without a taxane, are often higher than 12 g/dL when starting chemotherapy (mean entry Hb 12.7 g/dL in this study). Dosing these patients would have elevated their Hb levels above the new upper limit guidelines of 13 g/dL established as a result of the safety analyses performed as described above. Therefore, since new patient enrollment and treatment would be severely limited by Hb restrictions it was determined that enrollment of new patients should be halted. Ongoing patients continued through 6-month follow-up only with new treatment guidelines as per the amendment to address safety concerns.

Descriptive and limited inferential statistics of all parameters, effecacy and safety, were provided.

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Diagnosis and Main Criteria for Inclusion: Female patients, 18 years or older, who had a histologically confirmed diagnosis of Stage I, II, or III breast cancer for whom the treatment plan was adjuvant anthracycline-based chemotherapy with or without a taxane, who had a baseline hemoglobin (Hb) value of ≥ 9 g/dL and ≤14 g/dL, and had adequate hematologic function defined as absolute granulocyte count (AGC) ≥ 1.5/ x 10^9/L and a platelet count ≥ 100 x 10^9/L. Patients were to have a ≥ 5 year life expectancy and be chemotherapy naïve for breast cancer. Patients with reproductive potential were required to use an adequate contraceptive method (eg, abstinence, intrauterine device, oral or barrier device) during chemotherapy and for 3 months after completing therapy. 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 IU/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 medication. Each mL of study medication contained 40,000 IU of epoetin alfa. Study medication (40,000 IU/dose epoetin alfa or placebo) was administered by SC injection beginning at cycle 1 of chemotherapy treatment and was continued on a SC QW dosing regimen for up to 24 weeks depending on chemotherapy regimen. For patients with Baseline Hb ≥ 9 and < 12, if the Hb level did not increase by ≥ 1 g/dL from the baseline level after 4 weeks of treatment, the dose of study medication was increased to 60,000 IU SC QW, starting with the fifth weekly dose. For those patients with a baseline hemoglobin ≥12 g/dL and ≤14 g/dL, if after 4 weeks of study medication the Hb had decreased by ≥2 g/dL from baseline, the dose of study medication was increased to 60,000 IU SC QW, starting with the fifth weekly dose or at subsequent study weeks, following the same criteria if not done at week 5. A dose escalation may have occurred at subsequent study weeks, following the same criteria as above if not done at week 5. In the original protocol (prior to safety related dosing amendment) the dose of study medication was withheld if Hb levels increased to > 15 g/dL. Study medication was resumed if Hb decreased to 13 g/dL and then resumed at 75% of the previous dose. A dose reduction should also have been considered it there was an increase of Hb > 1.3 g/dL in a 2 week period independent of transfusion.

Dosing adjustment were changed as follows following the safety related dosing amendment: At any time during study drug treatment, if a patient's Hb level measured > 13 g/dL, study drug was withheld until the Hb level decreased to ≤12.0 g/dL, at which time study drug administration was reduced from 40,000 IU to 30,000 IU or 60,000 IU to 40,000 IU. If a patient's rate of Hb increase exceeded 1 g/dL within any consecutive 2-week period, independent of transfusion, her dose of study drug was immediately reduced from 40,000 units to 30,000 units or from 60,000 units to 40,000 units.

Patients who missed more than one dose of study medication were to be removed from the study (does not include patients in which study medication was withheld, if indicated, until Hb decreased).

Bulk Lot Nos. D00LJ0521, D02LL0992, D02LL0953, D03LB1027

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. D00LM0565, D02LH0953, D03LB10216, D02LH0953

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Criteria for Evaluation:

Efficacy: After enrollment was terminated early (see the Number of Patients section of the Synopsis), efficacy analyses (including inferential comparison of the treatment groups with respect to the primary and secondary efficacy outcomes) were not performed with the exception of limited inferential analysis conducted on CRT data. However, descriptive data of these assessments were provided.

Safety: Safety evaluations included assessments of the incidence and severity of adverse events (AEs) and serious adverse events (SAEs), clinical laboratory tests (hematology panel, iron profile, EPO antibodies and serum chemistry), physical examinations, and vital sign measurements.

Statistical Methods: Summaries and analyses of all safety variables were performed using data from all patients who were randomized and received at least one dose of study medication (safety population). Continuous variables were summarized using descriptive statistics (sample size [N], mean, standard deviation, median, minimum, maximum, and range). Categorical variables were summarized utilizing frequency statistics (frequency and percent). Patients with missing data at a given time point for an individual variable were not included in descriptive calculations for that variable at that time point. 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 to be calculated.

Baseline characteristics were tabulated, as was exposure to study medication. Adverse events were coded using the MedDRA coding dictionary, Version 6.0, and were tabulated by their system organ class (SOC) and preferred term. Treatment phase laboratory and vital sign data values and their change from baseline values at weekly time points were tabulated. Transfusion incidence was tabulated. Cognitive function and quality of life indices, including FACT-AN, LASA, POMS, CRT, and the EXIT-25 values and their change from baseline values were tabulated at specified time points. All tabulations were performed by treatment group unless otherwise indicated. Due to the early termination of enrollment and the subsequent reduction in sample size, inferential analyses were not performed for this study with the exception of limited inferential analyses performed on CRT data.

Summary:

Demographic and Baseline Characteristics: The 2 treatment groups had similar demographic and baseline characteristics. Breast cancer baseline characteristics were similar for both treatment groups – all patients had breast surgery with the majority in both groups having Stage I cancer with T1 as primary tumor site. Approximately 64% and 60% of patients in the placebo and Procrit groups, respectively, had 4 cycles of chemotherapy scheduled with the remaining patients having 6 cycles scheduled. The majority of patients in each treatment group were scheduled for chemotherapy with AC – 12 (75.0%) in the placebo group and 14 (66.7%) in the Procrit group. Baseline laboratory values were similar in both treatment groups with only small differences observed in some values. Mean Baseline Hb values were 12.6 g/dL and 12.7 g/dL for the placebo and Procrit groups, respectively.

Efficacy Results: Procrit-treated patients experienced statistically significantly greater improvement between baseline and pre-cycle 4 or pre-cycle 6 in the visuo-motor speed 3 CRT test and marginally statistically significantly greater improvement in the visuo-motor speed 1 CRT between baseline and pre-cycle 4 or pre-cycle 6 ($p = 0.02$ and 0.07, respectively). The placebo-treated patients did not show improvements in these tests between baseline and pre-cycle 4 or pre-cycle 6. The Hemoglobin Responder rates of Procrit-treated patients were 95.0% (19/23) at Week 9 and 100% (6/6) at Week 13 compared to 5.0% (1/11) at Week 9 and 0% (0/2) at Week 13 for placebo-treated patients. At the final visit, 85.7% (18/29) of Procrit-treated patients were Hemoglobin Responders compared to 14.3% (3/8) of placebo-treated patients.

Synopsis (Continued)

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Summary (cont.)

Safety Results: Overall, the most frequently reported AEs occurred in the following body systems: gastrointestinal, general conditions and administration site conditions, and skin and subcutaneous tissue. The most frequently reported AEs overall were nausea (89.2%), alopecia (81.1%), fatigue (59.5%), constipation (40.5%), and neutropenia (35.1%). The incidence of these AEs was similar in both treatment groups. The incidence of most AEs was similar in both treatment groups. The investigators assessed most of the AEs as NCI Grade 1 or 2 (92.5% in placebo vs. 86.8% Procrit) and almost all AEs as not related or doubtfully related to study medication.

One (6.3%) patient in the placebo group experienced at least one SAE, while 2 (9.5%) patients in the Procrit group experienced at least one SAE. SAEs were febrile neutropenia, leukopenia, and ulna fracture. The investigators assessed all SAEs as not related to study medication. Two patients in the Procrit group had deep vein thrombosis (DVT) that were considered nonserious. One was due to a line clot (Patient 1203) and was considered unrelated to study medication. Patient 1233 had a Grade 3 DVT that persisted through the end of the study. The patient was treated with Coumadin and Lovenox for 7 days for the DVT. No action was taken regarding study medication administration and the event was considered unrelated to the study medication. There were no deaths during the study.

Conclusion:

While no differences in tabularized efficacy assessments were observed between treatment groups, limited inferential analysis of CRT data revealed that Procrit-treated patients had significantly greater improvement in 2 visuo-motor speed tests between baseline and pre-cycle 4 or pre-cycle 6. At the final visit, 85.7% (18/29) of Procrit-treated patients were Hemoglobin Responders compared to 14.3% (3/8) of placebo-treated patients. Procrit was well tolerated during the study with the incidence and severity of AEs similar to those observed with the placebo group.

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