# SYNOPSIS

| NAME OF SPONSOR/COMPANY: | INDIVIDUAL STUDY TABLE REFERRING TO PART OF THE DOSSIER | (FOR NATIONAL AUTHORITY USE ONLY) |
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| Centocor Ortho Biotech Services LLC., Medical Affairs<br><br>NAME OF FINISHED PRODUCT:<br><br>PROCRIT<br><br>NAME OF ACTIVE INGREDIENT(S):<br><br>epoetin alfa | Volume:<br><br>Page: | |

**Protocol No.: EPOCAN3005; CR010540**

**Title of Study: A Pilot Study to Evaluate the Safety and Efficacy of PROCRIT® (epoetin alfa) 80,000 Units Once Every 4 Weeks (q4w) vs. 40,000 Units Once Every 2 Weeks (q2w) in Cancer Subjects With Non-Chemotherapy Anemia (NCA)**

**Principal Investigator:** Daniel Shasha, M.D., Beth Israel Medical Center, New York, NY; USA

**Publication:** Blood. 2007;110:abstract 3775

| **Study Initiation/Completion Dates:** 18 April 2006 to 15 May 2007 | **Phase of development:** 2b |
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**Objectives:** The primary objectives of this study were to investigate the safety and efficacy of PROCRIT 80,000 Units (U) q4w and 40,000 U q2w subcutaneously (s.c.) in anemic subjects with cancer not receiving chemotherapy or radiation therapy.

The secondary objectives of the study were to assess the effect of these dosing regimens on time to hematopoietic response and transfusion requirements.

**Methods:** This was a prospective, randomized, open-label, multicenter pilot study. Sixty subjects with an active histologically confirmed nonmyeloid malignancy, a baseline Hb ≤11 g/dL, and not receiving or anticipated to receive chemotherapy or radiation therapy during the course of the study were enrolled into this study.

Enrolled subjects were randomized to 1 of 2 treatment groups receiving PROCRIT s.c. The starting dose was either 80,000 U q4w with a maximum of 4 doses up to Week 13 or 40,000 U q2w with a maximum of 8 doses up to Week 15. A follow-up visit for both treatment arms occurred on Week 17.

After randomization, the treatment period started at the Day 1, Week 1 visit. The entire study period was up to 19 weeks, with the screening period lasting up to 2 weeks, treatment period for a maximum of 15 weeks, and safety follow-up at Week 17.

All subjects were evaluated weekly for Hb and blood pressure (BP) measurements through Week 15 and at the follow-up visit or, if withdrawn early, followed for 2 weeks after the last dose of study drug. Additional safety follow-up for serious adverse events (SAEs) and ongoing adverse events (AEs) continued for 4 weeks beyond the study treatment period. To be considered as completing the study, subjects must have participated in the study through Week 13 (80,000 U q4w dosage group) and Week 15 (40,000 U q2w dosage group). Safety, tolerability, efficacy, and quality of life (ECOG [Eastern Cooperative Oncology Group] assessment) evaluations were performed at specified intervals during the study.

Iron: During the study, subjects received ferrous sulfate 325 mg by mouth (p.o.) once a day (q.d.) or an equivalent formulation as tolerated.

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**Dose Adjustments:** For subjects receiving either regimen, if the dosing visit Hb level increased to >12 g/dL, regardless of the Hb rate of rise, the PROCRIT dose was withheld until Hb decreased to <11 g/dL at a subsequent dosing visit and then resumed at a decreased dose. If the dosing visit Hb level increased to ≥11 g/dL, regardless of Hb rate of rise, the PROCRIT dose was decreased immediately but not withheld.

If Hb rate of rise was >1 g/dL in any 2-week period and the dosing visit Hb level was ≤12 g/dL, the PROCRIT dose was decreased immediately but not withheld. The dose continued to be decreased at each dosing visit until Hb was <11 g/dL and Hb rate of rise was ≤1 g/dL in any 2-week period.

If Hb rate of rise was >1 g/dL in any 2-week period and the dosing visit Hb level was >12 g/dL, the PROCRIT dose was withheld until Hb rate of rise was ≤1 g/dL in any 2-week period and dosing visit Hb decreased to <11 g/dL. The PROCRIT dose was then resumed at a decreased dose.

For subjects randomized to receive 80,000 U q4w, after a scheduled dose had been withheld, the study drug was resumed at any time when Hb was <11 g/dL. The dosing interval continued to be q4w. For example, if the Week 5 dose was withheld and Hb decreased to <11 g/dL at Week 7, the dose resumed at Week 7 and the subsequent dose was administered at Week 11.

Because of the short duration of the treatment period, if hematopoietic response was not observed, doses were not increased during the study.

**Number of Subjects (Planned and Analyzed):** One hundred subjects (50 subjects in each treatment arm) were planned, and 60 were enrolled and included in the safety (N=60) and efficacy (N=59) analyses. The study was terminated as it would not address important survival concerns raised in other recently conducted clinical trials in anemic subjects with cancer not receiving chemotherapy or radiation therapy.

**Diagnosis and Main Criteria for Inclusion:** Cancer patients, aged ≥18 years, with an active histologically confirmed non-myeloid malignancy, a baseline Hb ≤11 g/dL, and not receiving or anticipated to receive chemotherapy or radiation therapy during the course of the study were enrolled into this study.

**Test Product, Dose and Mode of Administration, Lot No.:** PROCRIT (epoetin alfa) 40,000 U/mL was formulated as a sterile, preservative-free, buffered solution in a single-dose vial. Each 1 mL of solution contained 40,000 U of epoetin alfa, 2.5 mg albumin (human), 1.2 mg sodium phosphate monobasic monohydrate, 1.8 mg sodium phosphate dibasic anhydrate, 0.7 mg sodium citrate, 5.8 mg sodium chloride, and 6.8 mcg citric acid in water for injection, USP (pH 6.9±0.3). Lot numbers included P031508 (Expiration Date: March 2007), and P052069 (Expiration Date: May 2008). Study drug was drawn into a plastic syringe and administered s.c. according to standard sterile techniques.

**Duration of Treatment:** The entire study period was up to 19 weeks, with the screening period lasting up to 2 weeks, treatment period for a maximum of 15 weeks, and safety follow-up at Week 17. The 80,000 U q4w starting dose had a maximum treatment period of 13 weeks, and the 40,000 U q2w starting dose had a maximum treatment period of 15 weeks. A follow-up visit for both treatment arms occurred at Week 17.

**Criteria for Evaluation**:

**Efficacy:** All efficacy analyses were independent of blood transfusions within 28 days (i.e., Hb values collected within 28 days after a transfusion were excluded from the primary and secondary analyses). The **primary efficacy end point** was the hematopoietic response, defined as ≥1 g/dL rise in Hb from baseline.

Secondary analyses included the time to hematopoietic response, weekly Hb values and change from baseline in Hb values, the proportion of subjects with at least 1 packed red blood cell (PRBC) transfusion.

**Safety:**

Safety evaluations included clinical laboratory tests, vital sign measurements (blood pressure), physical examinations, and incidence and severity of adverse events.

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**Statistical Methods:** The **per-protocol population** included all enrolled subjects who completed the study without major protocol violations. The **modified intent-to-treat (m-ITT) population** was defined as all enrolled subjects who received at least 1 dose of study drug and had at least 1 post-baseline Hb value. The analysis of the primary efficacy end point was performed on both the m-ITT population and the per-protocol population, and all secondary efficacy analyses were performed on the m-ITT population. For the summary of Hb levels, the last-observation-carried-forward (LOCF) method was used to estimate missing values. The **safety population** was defined as all enrolled subjects who received at least a partial dose of study drug. The safety analyses were performed on the safety population.

There were no statistical comparisons performed between treatment groups in this study.

In general, descriptive statistics were used to summarize the efficacy variables along with 2-sided 95% confidence intervals (CI). Continuous variables were summarized by mean, median, standard deviation, and the range. Categorical variables were summarized utilizing frequency statistics such as frequency and percentages. The Kaplan-Meier method was used to estimate time to event end points. Hemoglobin values and change from baseline in Hb values were summarized by week for each treatment group. A paired t-test was used to test for the change from baseline equal to 0 for each treatment group.

Safety data were summarized descriptively; statistical tests were not performed.

Interim analysis, as planned in the protocol, was not performed due to study termination.

**Results**

**Baseline Assessments:** The safety population included 60 subjects with 36 (60.0%) of those being women. The mean age of subjects was 71.7 years. Thirty-five subjects (58.3%) were white, and 18 subjects (30.0%) were black. Most subjects were rated as an ECOG performance status of 0 (21.7%) or 1 (68.3%) at baseline. Mean Hb at baseline was 10.25 g/dL for the 80,000 U q4w treatment group and 9.93 g/dL for the 40,000 U q2w treatment group. Most subjects had solid tumor types (49 [81.7%]), with prostate and breast being the most common primary site (16 subjects [26.7%] and 15 subjects [25.0%], respectively). No other site was represented in ≥10% of subjects. Nine subjects (15.0%) had a diagnosis of a nonmyeloid hematologic malignancy (chronic lymphocytic leukemia [CLL], Hodgkin's disease, non-Hodgkin's lymphoma, and multiple myeloma).

**Extent of Exposure and Dose Adjustments:** All 60 subjects (100%) enrolled in the study received at least 1 dose of PROCRIT during the study. The mean cumulative dose over the course of the study was 216,210 U in the 80,000 U q4w treatment group and 191,940 U in the 40,000 U q2w treatment group, with a range across groups of 80,000 U to 320,000 U. The mean weekly dose was 17,967 U in the 80,000 U q4w treatment group and 15,538 U in the 40,000 U q2w treatment group. The mean duration of exposure over the course of the study ranged from 59 days in the 80,000 U q4w treatment group to 77 days in the 40,000 U q2w treatment group, with a range across groups of 1 to 101 days. In the 80,000 U q4w treatment group, 20 of 29 subjects (69.0%) had at least 1 dose reduction or dose withheld, and in the 40,000 U q2w treatment group, 27 of 31 subjects (87.1%) had at least 1 dose reduction or dose withheld.

**EFFICACY RESULTS:** The primary efficacy analysis was performed on both the m-ITT population and the per-protocol population. All Hb response criteria were independent of blood transfusions within 28 days. That is, Hb values collected within 28 days after a transfusion were excluded from the primary and secondary analyses.

**Primary End Point (Hematopoietic Response):** In the m-ITT population, 89.3% (25/28) of the subjects in 80,000 U q4w treatment group and 90.3% (28/31) of the subjects in the 40,000 U q2w treatment group achieved a Hb increase of ≥1 g/dL during the study. In the per-protocol population, 94.1% (16/17) of the subjects in 80,000 U q4w treatment group and 88.2% (15/17) of the subjects in the 40,000 U q2w treatment group achieved a Hb increase of ≥1 g/dL during the study.

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**EFFICACY RESULTS cont.:**

**Secondary End Points**:

**Time to Hematopoietic Response:** Based on a Kaplan-Meier analysis, the median time from the first dose of PROCRIT to a hematopoietic response was 14.0 days for the 80,000 U q4w treatment group (n=25) and 20.0 days for the 40,000 U q2w treatment group (n=28).

**Weekly Hb Values (Observed Case):** Based on a paired t-test of the mean change in Hb value, mean Hb values increased significantly beginning at Week 2 for both the 80,000 U q4w and the 40,000 U q2w treatment groups and remained significantly increased through the end of the study. The target Hb range for the study was 10 to 12 g/dL. For both treatment regimens (80,000 U q4w and 40,000 U q2w), mean Hb values were within the target range except at Week 11 for the 80,000 U q4w treatment group (Hb mean: 12.20; n=22) and at the Week 17 follow-up visit for the 40,000 q2w treatment group (Hb mean: 12.01; n=22).

**On-study PRBC Transfusion:** During the study, 6 subjects (10.2%) received a PRBC transfusion, 4 subjects (14.3%) and 2 subjects (6.5%) in the 80,000 U q4w and the 40,000 U q2w treatment groups, respectively. Four subjects (6.8%) received a PRBC transfusion from Day 29 to the end of the study, 3 subjects (10.7%) and 1 subject (3.2%) in the 80,000 U q4w and the 40,000 U q2w treatment groups, respectively.

**SAFETY RESULTS:** PROCRIT was generally safe and well tolerated. Clinical laboratory tests, BP readings taken throughout the study, and other safety assessments suggested no clinically relevant changes from baseline.

The incidence of AEs is shown below. The most common AEs in the safety population (N=60) were anorexia (10.0%), arthralgia (10.0%), peripheral edema (8.3%), and hypotension (8.3%). There were 2 drug-related AEs (headache and hypoesthesia) in 2 subjects. The only SAEs reported by more than 1 subject were malignant lung neoplasm (2 subjects, 1 in each treatment group) and congestive cardiac failure (2 subjects, 1 in each treatment group).

Two subjects died due to progression of prostate cancer and progressive lung cancer, respectively. Neither subjects died of an SAE considered related to study drug.

**Incidence of Adverse Events During Study Treatment**
(Study EPOCAN3005: Safety Population, N=60)

| | **PROCRIT Dose** | | |
|---|---|---|---|
| | **80,000 U q4w N=29** | **40,000 U q2w N=31** | **Total N=60** |
| Subjects with any AE, n (%) | 19 (65.5) | 20 (64.5) | 39 (65.0) |
| Deaths | 0 | 2 (6.5) | 2 (3.3) |
| Subjects with any SAE | 4 (13.8) | 4 (12.9) | 8 (13.3) |
| Subjects with any AE leading to permanent discontinuation of study drug | 0 | 4 (12.9) | 4 (6.7) |

Note: Unique events for a subject are counted once within each MedDRA system organ class and preferred term.

Thrombotic vascular events (TVEs) were reported in 1 subject (1.7%) during the study. This subject in the 40,000 U q2w treatment group) experienced 2 TVEs (DVT and myocardial ischemia). Neither TVE was fatal. Both TVEs were clinically relevant TVEs and considered by the investigator to be not related to study drug.

**CONCLUSION:** PROCRIT (epoetin alfa) at doses of 80,000 U q4w and 40,000 U q2w administered s.c. to achieve a hematopoietic response, defined as ≥1 g/dL rise in Hb from baseline, was safe and well tolerated in anemic cancer subjects not currently receiving chemotherapy or radiation therapy. Efficacy data from this pilot study suggest that PROCRIT can be administered at 80,000 U q4w or 40,000 U q2w to achieve a hematopoietic response within 2 to 3 weeks.

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