SYNOPSIS

NAME OF SPONSOR/COMPANY: Ortho Biotech Clinical Affairs, L.L.C. NAME OF FINISHED PRODUCT: PROCRIT 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.: CR003196

Title of Study: ASSESSMENT OF EARLY AND STANDARD INTERVENTION WITH PROCRIT® (EPOETIN ALFA) 120,000 UNITS ONCE EVERY THREE WEEKS (Q3W) IN PATIENTS WITH CANCER RECEIVING CHEMOTHERAPY

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Study Initiation/Completion Dates: 30 June 2005 to 30 August 2006 | **Phase of development:** 2

Objectives: The primary objective of this study was to obtain efficacy and safety data regarding PROCRIT (Epoetin alfa) administered at 120,000 Units (U) subcutaneously (sc) q3w in 2 groups of patients with cancer who were receiving chemotherapy: Early Intervention Group: PROCRIT treatment started at patient Hb ≥11.0 g/dL to ≤12.0 g/dL and Standard Intervention Group: PROCRIT treatment started once patient Hb dropped to <11 g/dL.

Safety and tolerance of the dosing regimen were assessed throughout the study.

Methodology: This was a randomized, open-label, multicenter study. Patients who were receiving myelosuppressive chemotherapy and had a baseline Hb of ≥11.0 g/dL and ≤12.0 g/dL were enrolled and randomized (1:1) to one of two groups:

- Early Intervention Group: Patients received PROCRIT 120,000 U sc q3w immediately.
- Standard Intervention Group: Patients received their first dose of PROCRIT 120,000 U sc q3w once their Hb level dropped to <11.0 g/dL.

To include additional patients that otherwise would have been excluded unnecessarily, the protocol was amended so that patients who met all inclusion/exclusion criteria but who had an Hb value of <11.0 g/dL at the Screening Visit could enter the Standard Intervention group (non-randomized) directly and begin therapy immediately. This group of patients is referred to as the Standard Intervention non-randomized group.

After randomization or group assignment, the Treatment Phase began at the Day 1, Week 1 visit. Treatment with PROCRIT was for a maximum of 5 doses for up to 16 weeks during chemotherapy administration. The last dose of PROCRIT was not administered after Week 15. PROCRIT was not administered once chemotherapy was stopped. All patients were evaluated weekly for Hb, hematocrit (Hct), and blood pressure (bp) measurements until 3 weeks after the last dose of PROCRIT or up to a maximum of 16 weeks on study whichever came first. Additional safety follow-up for Serious Adverse Events (SAEs) and ongoing Adverse Events (AEs) continued for 4 weeks beyond the study treatment phase.

Dose Adjustments: If the Hb level had risen to >12 g/dL at the time of the next dose or increased by more than 1.5 g/dL in a 3-week period, the PROCRIT dose was reduced initially from 120,000 U q3w to 80,000 U q3w. If subsequent dose reductions were required, the PROCRIT dose was reduced by 20,000 U q3w. If, at any time during the study, the Hb level rose to >13 g/dL, PROCRIT therapy was held until the Hb fell to ≤12 g/dL, then resumed at a dose reduction. If at any scheduled dosing visit the Hb level was <10.0 g/dL in any group once PROCRIT had been administered for at least 1 dose, that patient was considered to have failed q3w PROCRIT therapy (i.e., a "q3w non-responder") and was treated with PROCRIT 40,000 U qw starting at that visit. These "weekly" patients were analyzed separately, primarily to determine whether qw therapy can "rescue" q3w treatment failures. If after 4 weeks at the 40,000 U qw dose the Hb did not increase by ≥1 g/dL, the dose was increased to 60,000 U qw. If after 4 weeks at 60,000 U qw dose, the Hb had not increased at least 1 g/dL from baseline, the patient was considered to have failed qw PROCRIT therapy. **Iron:** Patients received supplemental iron, ferrous sulfate 325 mg orally every day or an equivalent iron preparation, as tolerated and if not contraindicated. Patients who were not able to tolerate the oral iron preparation received an intravenous formulation of iron as prescribed by their physicians and at their physicians' discretion.

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Number of Patients (planned and analyzed): One hundred eighty (180) patients were planned and 186 were enrolled and included in the safety and efficacy analyses.

Diagnosis and Main Criteria for Inclusion: Patients, age ≥18 years, who were receiving chemotherapy for a minimum of 9 weeks for a histologically-confirmed non-myeloid malignancy and who had a baseline Hb of either ≥11.0 g/dL and ≤12.0 g/dL or <11.0 g/dL.

Test Product, Dose and Mode of Administration, Lot No.: Epoetin alfa 40,000 U solution was provided in single-use vials and administered sc. Lot numbers were R13009, R13524, and R13954. One patient received 1 dose of commercial PROCRIT, Lot number P057905. The starting dose was 120,000 U. Dose reductions of 40,000 U or 20,000 U were made when Hb levels rose to >12 g/dL or when Hb increased more than 1.5 g/dL in a 3-week period.

Duration of Treatment: The entire study period was up to 22 weeks, with the screening phase lasting up to 2 weeks, treatment for up to 16 weeks, and safety follow-up for 4 weeks. Treatment with study drug was for a maximum of 5 doses of PROCRIT (up to 16 weeks) during chemotherapy administration through the final cycle. The last dose of PROCRIT was not to be administered after Week 15.

Criteria for Evaluation:

Efficacy: All efficacy analyses were independent of RBC/Whole Blood transfusions within 4 weeks (i.e., Hb values occurring within 28 days after a transfusion were not considered in the analyses). The **primary efficacy endpoint** was the mean proportion of weekly hemoglobin levels that were ≥11.0 g/dL and ≤13.0 g/dL. This included the time during which the standard intervention group was not receiving PROCRIT. This is referred to as the Percent Values in Range (PVR).

A s**econdary efficacy endpoint** was the complete success rate (CSR) defined as the proportion of randomized patients for whom all Hb values during PROCRIT treatment were ≥11.0 g/dL and ≤13.0 g/dL for the Early Intervention group and were ≥11.0 g/dL and ≤13.0 g/dL once Hb was ≥11.0 g/dL for the patients assigned to the randomized Standard Intervention group.

Additional secondary endpoints for the Early Intervention and randomized Standard Intervention group were: the mean proportion of weekly Hb levels for patients during PROCRIT treatment that were ≥11.0 g/dL and ≤13.0 g/dL (for the randomized Standard Intervention group once patients achieved an Hb value of ≥11.0 g/dL); the proportion of patients with Hb <10.0 g/dL during treatment; the number of patients who received at least 1 transfusion while on study; weekly and overall mean Hb values and mean change from baseline in Hb values; and change in Quality of Life (QoL) scores.

Additional secondary endpoints for the Standard Intervention group only (randomized and non-randomized patients) were the proportion of patients and time to achieving a ≥2 g/dL Hb increase or Hb of ≥12 g/dL from the first dose date; the proportion of patients and time to achieving an Hb of ≥11 g/dL from first dose date, the proportion of patients and the time to achieving a ≥1 g/dL Hb increase from first dose date, the time to Hb <11 g/dL, and the proportion of patients not requiring PROCRIT therapy.

Safety:

Safety evaluations included clinical laboratory tests, vital sign measurements (blood pressure), and incidence and severity of AEs.

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Statistical Methods: The **Modified Intent-to-Treat (MITT) population** was defined as all enrolled patients assigned to a treatment group who had at least 1 post baseline Hb value. All efficacy analyses were performed using the MITT population. Hemoglobin values occurring within 28 days after a transfusion were set to missing and the last-observation-carried-forward (LOCF) method was used to estimate missing values for transfused patients. The observations from patients who switched from treatment given q3w to qw were not included in the efficacy analysis, but were included in a separate sensitivity analysis. The **Safety population** was defined as all enrolled patients assigned to a treatment group.

Q3w non-responders were patients in either treatment group (Early Intervention or Standard Intervention) whose dosing schedule changed from q3w dosing to qw dosing because their Hb value decreased to <10.0 g/dL once PROCRIT had been administered for at least 1 dose. These patients are also referred to as "switchers." These weekly observations collected after patients switched from q3w to qw dosing were not included in overall MITT efficacy analyses, but are included in a separate sensitivity analysis.

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 endpoints.

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

In addition to the planned analyses, post hoc analyses were performed in order to determine if an association existed between Hb level >13 g/dL or Hb rate of rise (RoR) ≥1 g/dL within a 2-week period and the occurrence of a thrombovascular event (TVE) or clinically relevant TVE (CRTVE). These analyses included patients who had at least one post-dose Hb measurement.

SUMMARY - CONCLUSIONS

Baseline Assessments: The Safety population included 186 patients with 59 (31.7%) of those being men. The mean age of patients was 61.2 years. One hundred forty-one (75.8%) patients were white, and 10 (5.4%) patients were black. Most patients were rated as having an ECOG performance status of 0 (36.0%) or 1 (56.5%) at baseline. Mean Hb at baseline was 11.47 g/dL for the Early Intervention group, 11.48 g/dL for the randomized Standard Intervention group, and 10.12 g/dL for the non-randomized group. Of the 186 patients who received concomitant chemotherapy administration, 96 (51.6%) were receiving a taxane drug, 76 (40.9%) received a platinum-based chemotherapy regimen, and 4 (2.2%) did not receive further chemotherapy following randomization. Most patients had solid tumor types (162 [87.1%]), with breast being the most common primary site (58 patients [31.2%]). The next most common sites were gastrointestinal (39 patients [21.0%]) and lung (25 patients [13.4%]). Twenty-four (12.9%) patients had a diagnosis of a non-myeloid hematologic malignancy.

Extent of Exposure and Dose Adjustments: One hundred sixty-nine (169) of the 186 (90.9%) patients enrolled in the study received at least 1 dose of PROCRIT during the study. The mean cumulative dose over the course of the study ranged from 415,686 U in the randomized Standard Intervention group to 442,000 U in the non-randomized group, with a range across groups of 120,000 U to 700,000 U. The mean for the average weekly dose of PROCRIT for the Early Intervention group was 34927 U, for the randomized Standard Intervention group was 38573 U, and for the non-randomized group was 39578 U. The mean duration of exposure over the course of the study ranged from 76 days in the randomized Standard Intervention group to 87 days in the Early Intervention group, with a range across groups of 21 to 119 days. Of the 169 patients who received study drug, 53 (31.4%) patients had at least 1 dose reduction during the study. In the Early Intervention group, 29 of 68 (42.6%) patients had a dose reduction, in the randomized Standard Intervention group, 13 of 51 (25.5%) patients had a dose reduction, and in the non-randomized group 11 of 50 (22.0%) patients had a dose reduction. Forty-six of 169 (27.2%) patients had at least 1 dose held during the study.

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EFFICACY RESULTS: The primary population for all analyses was the MITT population. All efficacy analyses were independent of RBC/Whole Blood transfusions within 4 weeks (i.e., Hb values occurring within 28 days after a transfusion were not eligible to be considered in calculating changes from baseline in Hb values or in the determination of response).

Primary endpoint (PVR): For the 68 patients in the Early Intervention group, 59.9% (CI: 52.7, 67.1) of the Hb values were in range (≥11.0 g/dL and ≤13.0 g/dL). For the 67 patients in randomized Standard Intervention group, 60.0% (CI: 52.8, 67.2) of the Hb values were in range (≥11.0 g/dL and ≤13.0 g/dL).

Secondary endpoints:

CSR: In the Early Intervention group, 4 of 68 patients (5.9%; 95% CI: 0.3, 11.5) had a complete success rate. Of the 41 randomized patients in the randomized Standard Intervention group who received PROCRIT treatment and achieved an Hb of ≥11.0 g/dL, 5 patients (12.2%; 95% CI: 2.2, 22.2) had a complete success rate.

Mean Hb in Range: The proportion of patients with mean Hb in range (≥11.0 g/dL and ≤13.0 g/dL), calculated by averaging all week values (including Weeks 1 through 16) within patient, was 72.1% (49/68 patients; 95% CI: 64.1, 82.7) for the Early Intervention group and 68.3% (28/41 patients; 95% CI: 54.0, 82.5) for the patients in the randomized Standard Intervention group.

Hb value <10 g/dL during treatment: In the Early Intervention group, 18 of 68 patients (26.5%; 95% CI: 16.0, 37.0) had at least 1 Hb value <10 g/dL during treatment. In the randomized Standard Intervention group, 23 of 67 patients (34.3%; 95% CI: 23.0, 45.7) had at least 1 Hb value <10 g/dL during treatment.

On-study pRBC transfusion: Nine of 68 (13.2%) patients in the Early Intervention group, 5 of 67 (7.5%) patients in the randomized Standard Intervention group, and 13 of 49 (26.5%) patients in the non-randomized group received a pRBC transfusion during the study.

Weekly Hb values (LOCF): Patients who had switched to weekly dosing were included in the data analysis, but the Hb values after the dosing change were excluded. Weekly mean values for the Early Intervention group (N=67) remained steady from baseline (11.47 g/dL; 95% CI: 11.4, 11.6) to a mean high at Week 5 (11.65 g/dL; 95% CI: 11.4, 11.9) and a mean low at Week 10 (11.26 g/dL; 95% CI: 10.9, 11.6). Weekly mean values for the randomized Standard Intervention group initially decreased from baseline (N=67; 11.48 g/dL; 95% CI: 11.4, 11.6) to a mean low at Week 2 (N=64; 11.04 g/dL; 95% CI: 10.9, 11.2) and then increased to a mean high at Week 14 (N=67; 11.41 g/dL; 95% CI: 11.1, 11.7). Weekly mean values for the non-randomized group increased from baseline (N=49; 10.12 g/dL; 95% CI: 9.9, 10.3) to a mean high at Week 16 (N=49; 10.54 g/dL; 95% CI: 10.0, 11.1).

Patients who were assigned to the randomized Standard Intervention group did not receive treatment with PROCRIT until their Hb value was <11.0 g/dL. The median time to an Hb value of <11 g/dL for the randomized Standard Intervention group was 15 days (95% CI: 10, 24) using Kaplan-Meier estimates. Patients who did not receive PROCRIT, as their Hb value never decreased to <11.0 g/dL, are included in the randomized Standard Intervention group. During the study period, 16 of 67 patients (24%, 95% CI: 13.7, 34.1) in the randomized Standard Intervention group did not receive PROCRIT therapy.

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SUMMARY – CONCLUSIONS (continued)

By Week 15, 53 of 100 patients (53%, 95% CI: 43.2, 62.8) in the Standard Intervention group (randomized and non-randomized), who received treatment with PROCRIT, had achieved a ≥2 g/dL increase in their Hb value or had achieved an Hb value ≥12 g/dL from the time of their first dose date.

By Week 15, 70 of 100 patients (70%, 95% CI: 61.0, 79.0) in the Standard Intervention group (randomized and non-randomized), who received treatment with PROCRIT, had achieved an Hb value ≥11 g/dL from the time of their first dose date.

By Week 15, 59 of 100 patients (59%, 95% CI: 49.4, 68.6) in the Standard Intervention group (randomized and non-randomized), who received treatment with PROCRIT, had achieved a ≥1 g/dL increase in their Hb value from the time of their first dose date.

QoL assessment: At the final assessment the mean change from baseline for the Early Intervention group was -1.65 (SD=13.8; 95% CI: -5.2, 1.9) and for the Standard Intervention group was 0.83 (SD=14.1; 95% CI: -2.2, 3.9).

SAFETY RESULTS: PROCRIT was generally safe and well tolerated. Clinical laboratory tests, blood pressure readings taken throughout the study, or other safety assessments suggested no clinically relevant mean changes from baseline. No cases of pure red cell aplasia or suspected loss of effect were reported by the investigators.

The incidence of AEs is shown below. There were 30 drug-related adverse events; the most frequently reported drug-related AE was deep vein thrombosis reported in 3 patients. Thrombotic vascular events were reported in 19 (10.2%) patients during the study. The incidence and types of TVEs and CRTVEs are shown below.

Incidence of Adverse Events during Study Treatment
(Study PR04-27-018: Safety Population, N=186)

	Early Intervention N=68	Standard Intervention N=68	Non-randomized N=50
Patients with any AE, n (%)	66 (97.1)	64 (94.1)	49 (98.0)
Deaths	2 (2.9)	2 (2.9)	5 (10.0)
Patients with any SAE	15 (22.1)	18 (26.5)	15 (30.0)
Patients with any AE leading to withdrawal from study[b]	3 (4.4)	4 (5.9)	4 (8.0)

a. Includes randomized and non-randomized patients.
b. Two additional patients (Early Intervention group and non-randomized group) had study drug discontinued due to an AE and were withdrawn from the study due to disease progression.
Note: Unique events for a patient are counted once within each MedDRA System Organ Class and Preferred Term.

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Incidence of TVEs and CRTVEs
(Study PR04-27-018: Safety Population, N=186)

	Early Intervention N=68	Standard Intervention N=68	Non-randomized N=50
Patients with at least one TVE	6 (8.8)	7 (10.3)	6 (12.0)
Patients with at least one CRTVE	6 (8.8)	6 (8.8)	6 (12.0)
Types of CRTVEs (preferred term)			
Myocardial infarction	0	0	2 (4.0)
Pulmonary artery thrombosis	1 (1.5)	0	0
Deep vein thrombosis	3 (4.4)	3 (4.4)	4 (8.0)
Pulmonary embolism	1 (1.5)	3 (4.4)	0
Thrombosis NOS	1 (1.5)	1 (1.5)	0
Jugular vein thrombosis	1 (1.5)	0	0

Grouped terms defined as a TVE and clinically relevant TVE were defined by the sponsor. The TVE that was not considered clinically relevant was phlebitis.

Incidence of CRTVEs Among Patients with a Rapid Hb Rate of Rise or an Elevated Hb (Safety Population)

	Early Intervention (N=68)	Standard Intervention (N=68)	Non-randomized (N=50)
Rapid Rate of Rise (≥1 g/dL in a 2-week period)			
Rate of Rise ≥1 g/dL	6/51 (12%)	2/46 (4%)	3/25 (12%)
Rate of Rise <1 g/dL	0/17	4/22 (18%)	3/25 (12%)
Elevated Hb >13 g/dL			
Hb >13 g/dL	1/28 (4%)	0/22	1/11 (9%)
Hb ≤13 g/dL	5/40 (13%)	6/46 (13%)	5/39 (13%)

* Note: Hb changes may have occurred either before or after the CRTVE. The CRTVE may have occurred up to 4 weeks after study completion/withdrawal.

The percentage of patients who had an Hb rate of rise ≥1 g/dL over a 2-week period during the study and also experienced a CRTVE ranged from 4% (randomized Standard Intervention group) to 12% (Early Intervention group and non-randomized group).

CONCLUSION: PROCRIT (epoetin alfa) at a dose of 120,000 U administered sc q3w to achieve and maintain a protocol-defined Hb level in the target range of 11.0 to 13.0 g/dL was safe and well tolerated in anemic cancer patients receiving chemotherapy. Efficacy data from this pilot study suggests that PROCRIT can be administered q3w and still maintain mean Hb levels within the target range. Both early intervention treatment and standard intervention treatment were effective in maintaining Hb levels in the target range. Additional studies are warranted to confirm benefits of early and standard intervention treatment with q3w PROCRIT.

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