SYNOPSIS

NAME OF SPONSOR/COMPANY: Ortho Biotech Clinical Affairs, L.L.C. NAME OF FINISHED PRODUCT: epoetin alfa 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.: PR02-27-016

Title of Study: AN OPEN-LABEL PILOT STUDY TO EVALUATE THE EFFECTS OF HIGH DOSE PROCRIT® (EPOETIN ALFA) IN MAINTAINING HEMOGLOBIN LEVELS IN ANEMIC CANCER PATIENTS RECEIVING CHEMOTHERAPY ON AN EVERY 3 WEEK REGIMEN

Principal Investigator: Vernon Montoya, M.D. - Alachua, FL

Publications (References): ASH 2003: Langer CJ, Williams D. Anemia correction and hemoglobin maintenance with epoetin alfa 60,000 U QW followed by 80,000 U Q3W in anemic patients with cancer receiving chemotherapy. Blood 2003;102(11):166b (abstract 4374).

ASCO 2004: Grosbach A, Langer CJ, Montoya V, Williams D. Epoetin alfa 60,000 U QW followed by 80,000 U Q3W maintenance in patients with anemia and cancer receiving chemotherapy. J Clin Oncol, 2004 ASCO Annual Meeting Proceedings (Post-Meeting Edition). Vol 22, No 14S (July 15 Supplement), 2004: abstract 8215.

ASH 2004: Montoya V, Williams D. Every-three-week (Q3W) maintenance dosing of epoetin alfa in anemic cancer patients receiving chemotherapy: 60,000 U SC QW to target Hb 12 g/dL, followed by 80,000 U SC Q3W. Blood 2004;104(11):142b (abstract 4227).

ASH 2005: Montoya VP, Xie J, Woodman RC. Maintenance dosing with epoetin alfa every three weeks (Q3W) in anemic patients with cancer receiving chemotherapy every three weeks: final results. Blood 2005;106(11) abstract 3555.

Study Initiation/Completion Dates: 06 March 2003/24 January 2005	**Phase of development:** 2

Objectives: The primary objective was to determine the efficacy and safety of PROCRIT (epoetin alfa) at a starting dose of 60,000 Units (U) administered subcutaneously (sc) once per week (qw) to a target hemoglobin (Hb) of 12 g/dL in the Initiation Phase (IP), followed by a maintenance dose of 80,000 U once every 3 weeks (q3w) in the Maintenance Phase (MP) to maintain Hb range 11.5 to 12.5 g/dL in anemic cancer patients receiving chemotherapy.

The secondary objective of the study was to determine the incidence of anti-erythropoietin antibodies (anti-EPO Ab) at baseline and at end of study/early withdrawal in patients who received a minimum of 2 or more doses of epoetin alfa over at least a 1-month period.

Safety and tolerance of the dosing regimen was also assessed throughout the study.

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Methodology: This was an open-label, single-arm, multicenter pilot study All patients were assigned the same dosing regimen. The treatment period was divided into 2 phases, IP and MP. During the IP, patients received PROCRIT at a starting dose of 60,000 U administered sc qw until the target Hb of 12 g/dL was achieved (within 12 weeks). Patients who did not achieve the target Hb of 12 g/dL within the 12 weeks were not eligible to proceed to the MP of the study. Once the target Hb of 12 g/dL was achieved, patients proceeded to the MP. In the MP, patients received PROCRIT at 80,000 U sc q3w to maintain Hb range 11.5 to 12.5 g/dL. 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 of 20,000 U (i.e., from 60,000 U to 40,000 U in the IP and from 80,000 U to 60,000 U in the MP). A similar dose reduction was made if an Hb increase of more than 1.3 g/dL occurred in a 2-week period. Patients whose Hb fell below 11 g/dL during the MP dosing had a confirmatory Hb measurement performed within 24 hours. If the confirmatory Hb measurement remained below 11 g/dL, the patient was withdrawn from the study. There was a 90-day follow-up period after study completion or withdrawal. **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.

Number of Patients (planned and analyzed): One hundred thirty (130) patients were planned and 115 were treated and included in the safety and efficacy analyses.

Diagnosis and Main Criteria for Inclusion: Patients who were receiving chemotherapy once every 3 weeks for histologically-confirmed non-myeloid malignancy and who had a baseline Hb ≤11 g/dL.

Test Product, Dose and Mode of Administration, Lot No.: Epoetin alfa 40,000 IU solution was provided in commercially available, single-use vials and administered sc. Lot numbers included 05C08839 and R12493. The starting dose was 60,000 U in the IP and 80,000 U in the MP. Dose reductions of 20,000 U were made when Hb levels rose to >13 g/dL or when Hb increased more than 1.3 g/dL in a 2-week period.

Duration of Treatment: The IP lasted up to 12 weeks. The maximum duration of the study (IP and MP) was 24 weeks.

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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 eligible to be considered). The **primary efficacy endpoint** was the proportion of patients with a major response during IP (up to 12 weeks post-first dose). The definitions of responses for IP (qw dosing) were:

Major response in IP: ≥2 g/dL Hb increase from baseline or Hb ≥12 g/dL

Minor response in IP: ≥1 g/dL Hb increase from baseline (i.e., up to 1.9 g/dL)

The **secondary efficacy endpoints** were the proportions of patients with a minor response during the IP, a major response during the MP and a minor response during the MP. The definitions of responses for MP (q3w dosing) were:

Major response in MP: maintenance of Hb level 11.5 to 12.5 g/dL

Minor response in MP: maintenance of Hb level >11 g/dL (up to 11.4 g/dL)

MP responses were calculated in two ways:

At all weeks within phase – If every week's Hb value was between 11.5 to 12.5 g/dL ($11.5 \leq Hb \leq 12.5$), the patient was categorized as having a major response. If every week's Hb value was greater than 11 g/dL but at least one was less then 11.5 g/dL, the patient was categorized as having a minor response.

Average within phase – If the MP average Hb was between 11.5 to 12.5 g/dL ($11.5 \leq Hb \leq 12.5$), the patient was categorized as having a major response. If the MP average Hb was greater than 11 g/dL and up to 11.4 g/dL, the patient was categorized as having a minor response.

Safety: All safety analyses were performed on the Safety, IP Only (IP Only), and MP populations.

Safety evaluations included clinical laboratory tests (Hb and hematocrit), vital sign measurements (blood pressure), and incidence and severity of adverse events (AEs). In addition, the incidence of anti-EPO Ab at baseline and study completion/early withdrawal was evaluated in patients who received multiple doses of PROCRIT.

Statistical Methods: The Intent-to-Treat (ITT) population was defined as all patients enrolled and treated with at least 1 dose of study medication. All analyses were performed using the ITT population and using the following subgroup populations: **IP Only Population,** defined as patients receiving at least 1 dose during IP and not proceeding to the MP, and **MP Population**, defined as patients receiving at least 1 dose during MP. The Safety population was defined the same as the ITT population.

All efficacy endpoints and the corresponding 95% confidence intervals (CI) were calculated for the ITT population. For continuous variables, the CI was based on a t-distribution. For categorical variables, the CI was based on a binomial distribution. All statistical tests were 2-sided.

The median time and 95% CI to first major response in IP were summarized using Kaplan-Meier estimates; patients who did not have a major response in the IP were considered censored based on their last Hb assessment date.

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 received at least one dose of study drug and who had at least one post-dose Hb measurement. During study conduct, dose titrations for Hb RoR were based on the labeled recommendations in place at that time (i.e., >1.3 g/dL rise in a 2-week period). Subsequent post hoc TVE analyses were based on the currently accepted and labeled recommendations of >1 g/dL rise within a 2-week period.

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SUMMARY - CONCLUSIONS

BASELINE ASSESSMENTS: The ITT population included 115 patients, with 39 (33.9%) of those being men. The mean age of patients was 62.2 years. Seventy-four (64.3%) patients were Caucasian, and 25 (21.7%) patients were black. Most patients were rated as ECOG performance status of 0 (28.9%) or 1 (58.8%) at baseline. Mean Hb at baseline was 10.2 g/dL. Of the 112 patients who received at least 1 chemotherapy administration on or after Study Day 1, 50 (44.6%) patients were receiving platinum-based chemotherapy regimens. Most patients had solid tumor types (99 [86.1%]), with breast and lung being the most common primary sites (27 patients each [23.5%]). The next most common sites were gastrointestinal and gynecologic (12 patients [10.3%] each). Eighteen patients (15.7%) had therapy targeted toward a non-myeloid hematologic malignancy.

EXTENT OF EXPOSURE AND DOSE ADJUSTMENTS: The mean cumulative dose over the course of the study was 460,435 U, with a range of 60,000 U to 1,040,000 U. The mean duration of exposure over the course of the study was 66.0 days, with a range of 1 to 155. The mean duration in the IP was 6.5 weeks and mean duration in the MP was 6.5 weeks. Thirty-eight patients (33.0%) had at least 1 dose reduction during the study. In the IP, 30 (26.1%) patients had a dose reduction and, in the MP, 9 (7.8%) patients had a dose reduction. Forty-one patients (35.7%) had at least 1 dose held during the study. In the IP, 31 (27.0%) patients had a dose held and, in the MP, 16 (13.9%) patients had a dose held.

EFFICACY RESULTS: The primary population for all analyses was the ITT 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). The Last Value Carried Forward (LVCF) method was used to impute missing data for efficacy analysis of Hb values at the end of the study.

Primary endpoint: Eighty-four patients (76.4%; 95% CI: 68.4, 84.3) had a major response during the IP.

Secondary endpoints: Six patients (5.5%; 95% CI: 1.2, 9.7) had a minor response during the IP. During the MP (n=73), using the "average within phase" method, 44 patients (60.3%; 95% CI: 49.0, 71.5) had a major response and 10 patients (13.7%; 95% CI: 5.8, 21.6) had a minor response. During the MP (n=73), using the "data at all weeks within phase" method, 5 patients (6.8%; 95% CI: 1.1, 12.6) had a major response and 7 patients (9.6%; 95% CI: 2.8, 16.3) had a minor response

Seventeen patients of the 115 enrolled (14.8%) received 1 or more PRBC transfusions during the IP, and 2 of the 73 patients who proceeded to the MP received a PRBC transfusion during the MP.

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. Anti-EPO Ab results (n=26) were negative for all assessments. No cases of suspected loss of effect were reported by the investigators. The incidence of AEs is shown below. Thrombotic vascular events were reported in 17 (14.8%) patients during the study. The incidence and types of TVEs and CRTVEs are shown below. These data reflect TVEs occurring during treatment or within 90 days after study completion or withdrawal.

Incidence of Adverse Events during Study Treatment
(Study PR02-27-016: Safety Population, N=115)

Patients with any AE	112 (97.4%)
Patients with any drug-related AE	7 (6.1%)
Deaths	18 (15.7%)
Patients with any SAE	51 (44.3%)
Patients with any AE leading to permanent discontinuation from study	6 (5.2%)
Patients with any thrombotic vascular event (TVE)	17 (14.8%)

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 Occurring With Hb Change*

(Study PR02-27-016: Safety Population, N=115)

	n	
Patients with at least one TVE	17	
Patients with at least one CRTVE	11	
Types of CRTVEs (preferred term)		
Pulmonary Embolism	4	
Deep Vein Thrombosis	4	
Iliac Vein/Inferior Vena Cava Thrombosis	1	
Myocardial Infarction	1	
Cerebrovascular Accident	1	
Cerebral Artery Occlusion*	1	
Incidence of Hb rate of rise (RoR) >1 g/dL in a 2-week period	**Hb RoR**	**No Hb RoR**
Patients with TVEs in Patients with Incidence of Hb RoR	11/93 (11.8)	6/21 (28.6)
Patients with CRTVEs in Patients without Incidence of Hb RoR	6/93 (6.5)	5/21 (23.8)
Incidence of Hb >13 g/dL	**At least one Hb > 13 g/dL**	**All Hb values ≤ 13 g/dL**
Patients with TVEs	2/36 (5.6)	15/78 (19.2)
Patients with CRTVEs	1/36 (2.8)	10/78 (12.8)

* Note: Hb changes may have occurred either before or after the TVE/CRTVE. Grouped terms defined as a TVE and CRTVE were defined by the sponsor.

The incidence of a TVE or a CRTVE occurring during the treatment period or within 90 days of study completion or withdrawal was lower among subjects exhibiting a >1 g/dL rise in Hb over a 2-week period or an Hb rise to >13 g/dL at any time versus those who did not exhibit either Hb response. TVEs that were not considered clinically relevant were chest pain and chest discomfort.

CONCLUSION:

PROCRIT (epoetin alfa) at a starting dose of 60,000 U administered sc qw to achieve a target Hb of ≥12 g/dL in the IP, followed by a maintenance dose of 80,000 U q3w in the MP (to maintain Hb range 11.5 to 12.5 g/dL), was safe and well tolerated in anemic cancer patients receiving chemotherapy. Efficacy data from this open-label, pilot study suggest that maintenance therapy can be administered less frequently than weekly and still maintain average Hb levels within the target range.

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