PR03-32-026 SYNOPSIS

NAME OF SPONSOR/COMPANY: Ortho Biotech Clinical Affairs, LLC 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.: PR03-32-026

Title of Study: A Randomized, Double-blind, Placebo-controlled, Study to Assess Changes in Physical Function in Elderly Patients with Anemia of Chronic Disease (ACD) Receiving PROCRIT® (Epoetin alfa)

Principal Investigator: Not applicable

Publications (References): Yang M, Cox MA, Riordan DE, Fu M, Moyo V, Woodman RC. Iron Deficiency Is Common In Anemic Elderly Patients: Results With sTfr Index. [abstract] Proceedings of The American Society of Hematology (ASH) 47th Annual Meeting and Exposition. December 10-13, 2005; Atlanta, Georgia

Study Initiation/Clinical Cutoff Dates: 07-Sep-2004 to 16-Sep-2005 | **Phase of development:** 2

Objectives: The primary objective of this study was to assess changes in physical function in elderly patients (≥65 years of age) with chronic anemia (hemoglobin [Hb] ≤11.0 g/dL) due to anemia of chronic disease (ACD) receiving weekly subcutaneous (sc) doses of PROCRIT versus placebo.

The secondary objectives of this study were:

- To assess the effectiveness of weekly sc PROCRIT versus placebo dosing in achieving a target Hb range of 12.5-12.9 g/dL in elderly patients with anemia due to ACD
- To assess the change from baseline in the Functional Assessment of Cancer Therapy - Anemia (FACT-An) anemia subscale score in patients receiving PROCRIT versus placebo
- To assess the safety of weekly sc PROCRIT versus placebo dosing
- To assess the cognitive/executive function in patients receiving weekly sc PROCRIT versus placebo dosing
- To assess falls (the number, type, and associated injuries) in patients receiving weekly sc PROCRIT versus placebo dosing

Methodology: This was a randomized, double-blind, placebo-controlled, multicenter study. Assessments of physical disability, cognitive function, laboratory results, and safety information were obtained during the study.

Eligible patients with an Hb level ≤11.0 g/dL were enrolled and commenced weekly sc dosing with PROCRIT® or matching placebo at a starting dose of 10,000 units (U). Study drug dose was increased every 4 weeks until the target Hb range of 12.5-12.9 g/dL was achieved. Because PROCRIT dose adjustments could have resulted in a change of volume and had the potential to break the study blind, pre-determined random dose holds were provided on the randomization log for subjects who received placebo.

The maximum weekly dose of study drug allowed was 30,000 U. To avoid iron depletion and to adequately support erythropoiesis stimulated by PROCRIT, patients received appropriate iron supplementation to maintain the serum transferrin receptor (sTfr) index <1.5 (sTfr Index = $sTfr/ferritin^{log}$).

The total duration of this study was 21 to 22 weeks, including a 1- to 2-week screening phase, 16-week double-blind treatment phase, and 4-week post-treatment follow-up phase.

Number of Patients (planned and analyzed): This study was planned for an enrollment of approximately 80 patients. Twelve patients were enrolled and randomized. No statistical analyses were performed.

Diagnosis and Main Criteria for Inclusion: Community-dwelling patients ≥65 years of age with chronic anemia (present for at least 3 months), an Hb level ≤11.0 g/dL, and moderate disability (Short Physical Performance Battery [SPPB] score 4-10) were to be enrolled.

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Test Product, Dose and Mode of Administration, Batch Number: PROCRIT (Epoetin alfa) was formulated as a sterile, colorless, buffered solution containing 2.5 mg/mL human serum albumin. Each vial of PROCRIT contained approximately 1.1 mL of study drug in water for injection. Two formulations of PROCRIT were utilized:

10,000 U/mL Preservative-Free Vial: 1mL

20,000 U/mL Preserved Vial (containing 1% benzyl alcohol as the preservative)

Batch Numbers: PROCRIT 10,000 U/mL vials Lot P028155; PROCRIT 20,000 U/mL vials Lot P0008401.

Reference Therapy, Dose and Mode of Administration, Batch Number: Matching placebo was formulated identically to PROCRIT, except the placebo vials did not contain the active ingredient (Epoetin alfa).

Batch Numbers: Placebo for PROCRIT 10,000 U/mL – 1 mL vials, 005A030945; Placebo for PROCRIT 20,000 U/mL – 1 mL vials, 05A017635

Criteria for Evaluation: The study was terminated early due to slow enrollment after 12 patients had been randomized. All patients who had received PROCRIT or matching placebo during the study were identified in the listings.

Efficacy: The primary efficacy outcome was to be the change in SPPB summary score from baseline to end of study. SPPB summary score, as well as the constituent variables of the SPPB (SPPB-Balance, SPPB-Gait, and SPPB-Chair Stand Test), were listed and summarized using descriptive statistics. Because the study was terminated early, analysis sets associated with efficacy were not used. Change from baseline, change from previous visit, and determination of minimally important difference (MID) (an improvement by 2 points in the SPPB summary score) attainment were not calculated.

The secondary efficacy outcomes were to have been measured by Hb results, FACT-An scores, 6-Minute Walk Test (6-MWT) scores, and Trail Making Test (TMT) scores. Individual results were listed for these assessments. Baseline Hb results were summarized using descriptive statistics. No other efficacy summaries were performed.

Safety: Adverse events (AEs) were classified according to the product-specific Medical Dictionary for Regulatory Activities (MedDRA) dictionary version 8.0. Adverse events (AEs), as well as serious adverse events (SAEs) and AEs that led to withdrawal from treatment, were listed individually. All available laboratory results were listed and compared to the normal range. Change from baseline for these laboratory assessments was not calculated. All vital sign results were listed; change from baseline for these assessments was not calculated. All physical examination results for each body system were listed, as was the existence of a change compared to baseline for each body system identified on the physical examination case report form page.

Statistical Methods: Due to the early termination of this study, an abbreviated examination of the efficacy and safety objectives was performed. All data were listed and reviewed. Descriptive statistics (n, mean, median, standard deviation, minimum, and maximum) were utilized for selected demographic and baseline characteristics and selected efficacy assessments. No other summaries or any formal statistical analyses were performed.

SUMMARY – CONCLUSIONS

EFFICACY RESULTS: The primary efficacy outcome was to be the change in SPPB summary score from baseline to end of study. SPPB summary score, as well as the constituent variables of the SPPB (SPPB-Balance, SPPB-Gait, and SPPB-Chair Stand Test), were listed and summarized using descriptive statistics. Because the study was terminated early, analysis sets associated with efficacy were not used. Change from baseline, change from previous visit, and determination of minimally important difference (MID) (an improvement by 2 points in the SPPB summary score) attainment were not calculated. Five of the 6 (83%) patients in the PROCRIT group reached the target Hb level of 12.5 to 12.9 g/dL during the study. No patients in the placebo group reached the target Hb level.

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SAFETY RESULTS: A total of 22 AEs were reported in 7 of 12 (58%) patients; 4 (67%) patients in the PROCRIT group and 3 (50%) patients in the placebo group. Fourteen AEs were assessed by the investigators as mild in intensity, 5 were moderate, and 3 were rated severe. No deaths occurred during the course of this study. Three SAEs in 1 (8%) patient (who received placebo) occurred during the course of this study; one of these events (deep vein thrombosis) was classified as a thrombotic vascular event (TVE), which was considered by the investigator to be possibly related to study drug. The other two SAEs experienced by this patient were atrial tachycardia and hip fracture. The patient was withdrawn from the study due to the SAEs. No other patients experienced an SAE or an AE leading to withdrawal from the study.

CONCLUSIONS:

- Due to the early termination of the study and the limited number of patients enrolled, no efficacy conclusions could be made. Five of 6 (83%) patients receiving PROCRIT and no patients receiving placebo achieved the target Hb level during the study.
- There were no significant safety findings; the incidence of AEs and abnormal laboratory results observed were expected for this population of elderly patients with anemia due to ACD. One patient receiving placebo experienced a TVE (deep vein thrombosis), which was considered by the investigator to be possibly related to study drug.

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