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 Number: PR03-33-055

Title of Study: A Randomized, Double-blind, Placebo-controlled Study to Assess Fatigue in Patients with Anemia of Chronic Disease (ACD) Due to Rheumatoid Arthritis Receiving PROCRIT® (Epoetin alfa)

Principal Investigator: Not applicable

Publications (References): Yang M, Cox MA, Fu M, Woodman RC. Iron Deficiency is Common in Anemic Patients with Rheumatoid Arthritis (RA): Results with sTfr Index. [poster] Proceedings of the American College of Rheumatology (ACR) Annual Scientific Meeting. November 13-17, 2005; San Diego, California

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/Completion Dates: 17 September 2004 to 17 January 2006	**Phase of Development:** 2

Objectives:

Primary Objective:

To assess changes in fatigue in patients at least 18 years old with chronic rheumatoid arthritis (RA) and chronic anemia (hemoglobin [Hb] ≤11.0 g/dL) due to anemia of chronic disease (ACD) receiving weekly (qw) subcutaneous (sc) doses of PROCRIT versus placebo.

Secondary Objectives:

• To assess Hb response in chronic RA patients with anemia due to ACD receiving qw sc doses of PROCRIT versus placebo

• To assess changes in anemia-associated health concerns in chronic RA patients with anemia due to ACD receiving qw sc doses of PROCRIT versus placebo

• To assess changes in vitality (VT) in chronic RA patients with anemia due to ACD receiving qw sc doses of PROCRIT versus placebo

• To assess changes in arthritis-related function in chronic RA patients with anemia due to ACD receiving qw sc doses of PROCRIT versus placebo

Exploratory Objectives:

• To assess the change in score of the other domains of the Medical Outcomes Study Short Form-36 (SF-36) Health Survey: Physical functioning, Role-physical, Bodily pain, General health, Social functioning, Role-emotional, and Mental health.

• To assess the change in global work productivity

• To assess the change in disease activity as measured by the American College of Rheumatology (ACR) 20/50/70 assessment criteria

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)

Methodology: This was a prospective, randomized, double-blind, placebo-controlled, multicenter study. The total study duration for each patient was approximately 25 to 26 weeks, including a 1- to 2-week screening phase, a 20-week double-blind treatment phase, and a 4-week post-treatment follow-up phase. Patients were randomly assigned in a 1:1 ratio to receive qw sc treatment with either PROCRIT or placebo. At the end of the double-blind study period, eligible patients could have been considered for enrollment into a 35-week open-label extension study.

Assessments of fatigue, anemia-associated health concerns, health-related quality of life, arthritis-related function, disease activity, global work productivity, and laboratory results were performed during the study. Assessments of fatigue were measured using the Functional Assessment of Chronic Illness Therapy questionnaire with the fatigue subscale (FACIT-F). Assessments of anemia-associated health concerns were measured using the Functional Assessment of Chronic Illness Therapy questionnaire with the anemia subscale (FACIT-An). The FACIT-F is composed of 13 of the 20 FACIT-An questions and can be scored separately. Vitality and other health-related quality of life (HRQL) issues (physical functioning, role-physical, bodily pain, general health, social functioning, role-emotional, and mental health) were assessed using the SF-36. Assessment of disease activity was performed using the ACR 20/50/70 assessment criteria. Arthritis-related function was assessed using the Health Assessment Questionnaire (HAQ) and global work productivity was assessed using a single question with a visual analog scale (VAS). The FACIT-F/FACIT-An was administered at Screening, Baseline, and every 2 weeks thereafter. All self-reported assessments of health outcomes were completed by the patient prior to any study-related assessments for that visit. Patients, investigators, study staff, and study monitors were blinded to treatment assignments, results of Hb and hematocrit measurements, red blood cell and reticulocyte counts, and dose adjustments during the course of the study. An independent third party, not otherwise involved in the care of the patients, was identified at each site to act as the unblinded Hb monitor for all patients at that site and to manage study drug dosing per protocol. The unblinded Hb monitor did not participate in any other study-related assessments or procedures.

Eligible patients were given a starting dose of 20,000 units (U) of PROCRIT sc or placebo at the Week 1/Baseline visit. Subsequent dosing with PROCRIT was determined by using both the Hb level from the previous visit and the rate of increase in Hb levels over the prior 2-week interval as indices. The Hb levels were monitored weekly through Week 21 by a designated unblinded Hb monitor at each study site. The PROCRIT dose was confirmed with a central Hb monitor at the CRO prior to administration. Safety dose evaluations were made at each visit by comparing the Hb level from the previous visit with that obtained 2 weeks prior. If the rate of rise in Hb level was >1.0 g/dL over the previous 2 weeks or the Hb level was ≥13.0 g/dL, the PROCRIT dose or the equivalent volume of matching placebo was withheld for 2 consecutive weeks and the Hb level was monitored weekly. Dosing was resumed with a decrease in the PROCRIT dose by 10,000 U when the rate of rise in Hb level was ≤1.0 g/dL over the previous 2 weeks and the Hb level was ≤12.9 g/dL. After resumption of PROCRIT at the decreased dose, the patient was not eligible for any increase in dose until the next dose adjustment evaluation visit (Week 6, 12, or 16).

Dose increases were made only at Weeks 6, 12, and 16 until the target Hb level of 12.5 g/dL to 12.9 g/dL (inclusive) was achieved. Once the target Hb level was achieved, the PROCRIT dose was maintained for the duration of the treatment period provided the target Hb level was maintained and the rate of rise was within defined safety parameters. Dose adjustments were made based on the criteria shown below.

DOSE INCREASE EVALUATION
(Weeks 6, 12, 16)

Target Hb (Current week compared to last Dose Increase Evaluation Visit)	
Hb Level	**≤ 1.0 g/dL**
≥ 13.0	**HOLD** for at least 2 wks & monitor Hb weekly
12.5 - 12.9	**Maintain** current dose
< 12.5	**Increase 10,000 units**

SAFETY DOSE EVALUATION
(Assessed Weekly)

Hb Rate of Rise (over 2 weeks)	
Hb Level	**≤ 1.0 g/dL**
≥ 13.0	**HOLD** for at least 2 wks & monitor Hb weekly
≤ 12.9	**Maintain** current dose

DOSE RESTART EVALUATION
(After Dose Hold of a minimum two weeks)

Hb Rate of Rise (over 2 weeks)	
Hb Level	**≤ 1.0 g/dL**
≥ 13.0	**Continue HOLD**
≤ 12.9	**RESUME with decrease of 10,000 units**

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)

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 was 40,000 U of PROCRIT or an equal volume of placebo. To avoid iron depletion and to adequately support erythropoiesis stimulated by PROCRIT, patients with decreased iron stores (as indicated by the serum transferrin receptor [sTfr] index) were given iron supplementation 3 times per week to maintain the sTfr index at <1.5. The dose and formulation of iron supplementation was adjusted at the discretion of the treating physician and continued over the course of the study. The determination of serum ferritin, serum iron, total iron binding capacity, transferrin saturation, and sTfr levels were performed at Baseline and Weeks 5, 9, 13, 17, and 21 to assess iron levels.

Number of Patients (planned and analyzed): This study was planned for an enrollment of approximately 270 patients. Twenty-nine patients were randomized. Only descriptive summaries of selected demographics, baseline characteristics and selected efficacy assessments were performed.

Diagnosis and Main Criteria for Inclusion: Patients at least 18 years of age who had chronic RA with chronic anemia (Hb ≤11.0 g/dL twice over an extended period of time within one year prior to screening) due to ACD were eligible for enrollment. Patients were to have a diagnosis of ACD as defined by an sTfr index of <2.0 and a FACIT-F score of <36 at enrollment.

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:

- 20,000 U/mL Preserved Vial (containing 1% benzyl alcohol as the preservative)
- 40,000 U/mL, Preservative-Free Vial: 1mL

Batch Numbers: PROCRIT 20,000 U/mL vials B08028 (R12643, R12720); PROCRIT 40,000 U/mL vials B08030 (R12722); Re-Labeled PROCRIT 40,000 U/mL vials F18369 (R13502)

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

Batch Numbers: Placebo to match PROCRIT 20,000 U/mL vials B08029 (R12644, R12721); Placebo to match PROCRIT 40,000 U/mL B08031 (R12646, R12723)

Statistical Methods: This study was terminated prematurely due to slow enrollment despite four amendments to the protocol to modify the entrance criteria; therefore, only an abbreviated examination of the efficacy and safety objectives was undertaken. Apart from descriptive summaries of selected demographic and baseline characteristics and selected efficacy assessments, no summary analyses were performed for this study. Change from baseline by visit was assessed for selected efficacy variables and selected clinical laboratory evaluations. Adverse events were summarized. No formal statistical testing was undertaken.

The primary efficacy variable was the change in FACIT-F score from baseline to end of study (Week 21/Early Withdrawal [EW]) and was to have been analyzed using the Analysis of Covariance (ANCOVA) model with baseline score as covariate.

The secondary efficacy variables were the change in VT domain (SF-36) score, FACIT-An score, and arthritis-related function (HAQ) score from baseline to end of study (Week 21/EW) and were to have been analyzed using the ANCOVA model with baseline score as covariate. Fisher's Exact test was to have been performed to compare the two treatment groups with respect to the proportion of patients who achieved a hematologic response defined as an increase in Hb from baseline of at least 2 g/dL or achievement of an Hb level of at least 12 g/dL at any time point in the study, the proportion of patients who had a minimally important difference (MID; 4-point increase from baseline) in FACIT-F score, and the proportion of patients who had a MID (5-point increase from baseline) in FACIT-An score. Kaplan-Meier estimates were to have been calculated and the corresponding survival functions were to have been compared using the log-rank test for the time to Hb change from baseline of 2 g/dL or achieving an Hb of 12 g/dL and the time to a 4-point increase from baseline in FACIT-F score.

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)

SUMMARY - CONCLUSIONS

EFFICACY RESULTS: Only descriptive statistics for selected parameters were performed. Eleven of 15 (73.3%) patients receiving PROCRIT achieved a hematologic response compared with 1 of 14 (7.1%) of patients receiving placebo. Unblinding occurred for 8 patients after the study was terminated and patients were given the option of remaining in the study on an open label basis. All 4 patients still on study receiving PROCRIT continued on study after their treatment was unblinded while the 4 patients receiving placebo all discontinued treatment.

SAFETY RESULTS: The incidence of adverse events (AEs), clinical laboratory tests, vital signs, and other safety assessments suggested no clinically meaningful changes and findings were consistent with expected findings in this population of anemic patients with RA. There were more treatment-emergent AEs in patients receiving PROCRIT (14 of 15 [93.3%] patients) compared with placebo (9 of 14 [64.3%]). The mean weeks of exposure to PROCRIT was slightly higher than that of placebo (17.9 weeks compared with 15.3 weeks) due to the continuing participation of 4 of the 15 patients receiving PROCRIT on an open-label basis after the study was unblinded. The most frequently reported AEs were infections, with 11 of 15 (73.3%) patients receiving PROCRIT experiencing treatment-emergent AEs in the infections and infestations body system compared to 4 of 14 (28.6%) patients receiving placebo. Of the 15 patients receiving PROCRIT, 4 (26.7%) experienced urinary tract infections. One of 14 (7.1%) patients receiving placebo had a treatment-emergent urinary tract infection. Due to the early termination of the study and the limited number of patients enrolled, it cannot be established if the higher incidence of infections in the PROCRIT group was a result of the study drug. Three PROCRIT patients had a total of five AEs considered by the investigator to be possibly drug related (nausea, non-cardiac chest pain, left face numb; redness on cheeks) compared with one placebo patient with two drug-related events (nausea and vomiting). There were no reports of loss of effect (LOE) or pure red cell aplasia (PRCA). One patient in the placebo group with a history of chronic renal failure died during the study due to acute renal failure.

CONCLUSION:

- Due to the early termination of the study because of the limited number of patients enrolled, no efficacy conclusions could be made about the primary objective, the potential effects of PROCRIT on fatigue in this population, or about the majority of secondary endpoints.
- Weekly doses of PROCRIT (5,000 U to 40,000 U) produced a hematologic response in this population compared with placebo. Eleven of 15 (73.3%) patients receiving PROCRIT achieved a hematologic response compared with 1 of 14 (7.1%) of patients receiving placebo.
- An examination of change over time in laboratory parameters associated with iron levels (ferritin, iron binding capacity, serum iron, and sTfr index) showed that iron stores decreased by a greater degree in the PROCRIT-treated group.
- An evaluation of the safety endpoints in this study yielded expected findings in this population and suggested no clinically meaningful changes with PROCRIT therapy compared with placebo. A higher rate of infections was observed in the PROCRIT group compared with placebo (73.3% vs. 28.6%, respectively) but the clinical significance is not clear due to the longer time on study for PROCRIT patients compared with placebo (mean of 17.9 weeks and 15.3 weeks, respectively) and the limited number of patients enrolled due to the early termination of the study.

Date of the Report: 17 August 2006

Disclaimer

Information in this posting shall not be considered to be a claim for any marketed product. Some information in this posting may differ from, or not be included in, the approved labeling for the product. Please refer to the full prescribing information for indications and proper use of the product.