SYNOPSIS

Issue Date: 17 June 2009

Name of Sponsor/Company	Centocor Ortho Biotech Services, LLC
Name of Finished Product	PROCRIT®
Name of Active Ingredient(s)	Epoetin alfa

Protocol No.: PR04-15-001

Title of Study: A Randomized, Double-Blind, Placebo-Controlled Study to Assess the Effect of Recombinant Human Erythropoietin (Epoetin alfa; PROCRIT®) on Functional Outcomes in Anemic, Critically Ill, Trauma Subjects

Coordinating Investigator: Not applicable

Publication (Reference): None

Study Period: First Patient/First Visit: 13 September 2005; Date of Study Completion/Early Termination: 26 June 2008. Database lock was on 19 September 2008.

Phase of Development: Phase 2

Objectives: The primary objective of this trial was to evaluate the physical function outcomes in anemic, critically ill, trauma subjects treated with epoetin alfa (PROCRIT®) compared with placebo.

The secondary objectives were to assess the effectiveness of weekly epoetin alfa administration on the following:

- Functional Independence Measure (FIM) (motor subscore).

- Health-Related Quality of Life (HRQL) and fatigue evaluations (Medical Outcome Short Form [SF-36], Functional Assessment of Chronic Illness Therapy – Anemia subscale [FACIT–An], Functional Assessment of Chronic Illness Therapy – Fatigue subscale [FACIT – F]).

- Time to hemoglobin (Hb) response.

- Hb change over time.

- Evaluation of return to usual activities (RTUA).

- Neurocognitive function (COG).

- Time on mechanical ventilation.

Methods: This was a phase 2, prospective, randomized, double-blind, placebo-controlled, multi-center trial. Subjects were anemic, critically ill, blunt trauma subjects with major orthopedic injuries. Planned enrollment was 204 subjects, with 102 randomized in a 1:1 ratio to receive either epoetin alfa (PROCRIT®) or matching placebo. Actual enrollment was 192 subjects: 97 in the epoetin alfa (PROCRIT®) group and 95 in the placebo group.

A computer-generated randomization schedule was prepared by the sponsor before the study.

There were 4 consecutive phases: screening (Critical Care Area Day 1 up to 6 days [144 hours] prior to study entry [Baseline/Study Day 1]); In-Hospital Treatment (first day of study drug treatment through hospital discharge); Post-Hospital Discharge Treatment (from hospital discharge [Week 0] through the last day of Week 12 after hospital discharge); and Non-Treatment Follow-Up (from the first day of Week 13 after hospital discharge through the last day of Week 24 after hospital discharge).

All clinicians, caregivers, subjects, and the sponsor were blinded to study drug throughout the trial. However, in order to optimize acute care of the injured subject, during the In-Hospital Treatment phase only, study personnel were not blinded to complete blood count (CBC) or other laboratory results.

Study drug was administered weekly via the subcutaneous (SC) route both in the hospital and for a maximum of 12 weeks after hospital discharge or until the subject's hemoglobin (Hb) level was >12.0 g/dL, whichever occurred first. If the Hb was >12.0 g/dL, no further dosing occurred until the Hb was <11.0 g/dL. Study drug was to be administered within a window of ±3 days.

Hemoglobin was monitored weekly for study drug dose adjustments. Assessments of HRQL and fatigue were obtained periodically during the study. An optional pharmacogenomics component was also included in the study.

Subjects' laboratory results were checked for levels of iron, ferritin, transferrin saturation, zinc protoporphyrin, and serum transferrin receptor. Oral iron supplementation while the patient was hospitalized was at the discretion of the clinician. Parenteral iron supplementation was not permitted at any time during the study, unless specifically allowed after consultation with the medical monitor.

An independent Data Safety Monitoring Board (DSMB) assessed safety in this trial. It conducted periodic reviews when approximately 20% and 50% of subjects had completed 12 weeks of treatment (Post-Hospital Discharge phase). Safety analyses were specified in the DSMB charter. DSMB reviews recommended continuation of the trial.

No interim analysis was conducted during this study.

Number of Subjects (planned and analyzed): The disposition of subjects is presented in the following table need table numbers

Diagnosis and Main Criteria for Inclusion: Male or female critically ill, blunt trauma subjects, between 18 and 55 years of age, inclusive, with major orthopedic injuries, who required intensive care or intensive monitoring, and hemoglobin ≤12.0 g/dL.

Test Product, Dose and Mode of Administration, Batch No.: Epoetin alfa (PROCRIT®) 40,000 IU/mL, 1-mL vials. Bulk Lot: D06LC1831. Manufacturer lot: Amgen – P057913. Package lot: R14607; Bulk Lot: D06LL2030. Manufacturer lot: Amgen – P082229. Package lot: R1461.

Reference Therapy, Dose and Mode of Administration, Batch No.: Labeled placebo to match epoetin alfa (PROCRIT®) 40,000 IU/mL, 1-mL vials. Manufacturing lot: A039132. Package lot: R14608.

Duration of Treatment: Study drug was administered weekly via the SC route both in the hospital and for a maximum of 12 weeks after hospital discharge or until the subject's Hb level was >12.0 g/dL, whichever occurred first. If the Hb was >12.0 g/dL, no further dosing occurred until the Hb was <11.0 g/dL. Study drug was to be administered within a window of ±3 days.

Criteria for Evaluation: The primary efficacy evaluation, the SF-36, was completed at baseline; Week 0 (hospital discharge); Weeks 4, 8, 12, 16, 20, and 24 post-hospital discharge; and at early withdrawal. The primary efficacy endpoint for each subject was the average of all SF-36 Physical Function (PF) scores obtained between hospital discharge (Week 0) and the end of Week 24 after hospital discharge. Secondary efficacy evaluations were Functional Assessment of Chronic Illness Therapy – Anemia subscale (FACIT-An), Functional Independence Measure (FIM), Functional Assessment of Chronic Illness Therapy – Fatigue subscale (FACIT-F), Hb, and Cognitive Function Scale (COG), all of which were completed at baseline, Week 0 (hospital discharge), Weeks 4, 8, 12, 16, 20, and 24 post-hospital discharge, and at early withdrawal. Secondary efficacy endpoints were:

- The average FIM motor subscore and each motor subscore element obtained between hospital discharge (Week 0) and the end of Week 12 after hospital discharge.

- The average FACIT-An score obtained between hospital discharge (Week 0) and the end of Week 24/or early withdrawal.

- The average FACIT-F score obtained between hospital discharge (Week 0) and the end of Week 24/or early withdrawal. The FACIT-F comprised a subset of questions within the FACIT-An.

- The scheduled hemoglobin values measured between Baseline/Study Day 1 and the end of Week 24 after hospital discharge/or early withdrawal.

- The correlation between Hb and SF-36 PF at each time point.

- The change from baseline to hospital discharge (Week 0) in the FIM total, composite and item scores.

- The change from baseline to hospital discharge (Week 0) in the SF-36 composite and item scores.

- Time of Maximal Change in SF-36 PF score from hospital discharge through Week 24.

- The average Vitality, Bodily Pain, and Role-Physical domain scores of SF-36 from baseline through Week 24 after hospital discharge.

- Return to usual activities (RTUA), defined as a cumulative percentage of subjects returning to their usual activities by Weeks 12 and 24 after hospital discharge. The RTUA was assessed by comparing function prior to the current traumatic event (pretrauma SF-36) to the SF-36 at Week 24 after hospital discharge.

- Mechanical ventilation time (MVT), defined as total number of days during which subject was receiving mechanical ventilation support.

Safety evaluations included adverse events, clinical laboratory tests, vital signs, and a physical examination that was performed at baseline only. Clinical laboratory tests were completed at baseline; in-hospital Days 1, 8, 15, 22; at in-hospital additional weekly visits; in-hospital early withdrawal; at Week 0 (hospital discharge); Weeks 4, 8, 12, 16, 20, and 24 post-hospital discharge; and at early withdrawal. Adverse events, concomitant medications, surgical procedures, and red blood cell (RBC) transfusions were recorded as they occurred.

Statistical Methods:

This study was powered to detect a mean difference of 10 points between the epoetin alfa (PROCRIT®) and placebo group in the primary endpoint (SF-36 PF). Assuming an overall 37% attrition rate, it was estimated that an enrollment of 204 subjects (102 per arm) would be required to achieve the targeted number of 128 evaluable subjects.

There were 4 analysis populations in this study. The intent-to-treat (ITT) population included all subjects who were randomized. The efficacy evaluable (per protocol) population included all subjects who met the inclusion/exclusion criteria, received at least 1 dose of study drug, had a baseline and at least 3 Post-Hospital Discharge SF-36 PF measurements, received commercial recombinant human erythropoietin, and were randomized to receive 1 treatment but received the other. The efficacy evaluation with compliance population included all efficacy evaluable subjects who received at least 80% of the study drug for the duration of treatment. The safety population included all randomized subjects who received at least 1 dose of study drug.

Safety: All safety analyses were performed on the safety population, unless otherwise stated. No statistical inference between the treatment groups was performed on safety parameters.

Analysis of the primary endpoint was performed on the ITT, efficacy evaluable, and efficacy evaluable with compliance populations, using analysis of covariance (ANCOVA), with treatment as the fixed effect and baseline SF-36 PF as the covariate. Analysis of secondary endpoints was also performed on the ITT, efficacy evaluable, and efficacy evaluable with compliance populations, as follows:

- ANCOVA was performed on average FACIT-An and FACIT-F score through 24 weeks after hospital discharge, with treatment as the fixed factor and corresponding baseline measure as a covariate. A Minimal Important Difference (MID) of 3 was used for the FACIT-An and a MID of 3 for the FACIT-F.

- Hemoglobin was analyzed by time point through Week 24 after hospital discharge.

- The correlation coefficient between Hb and SF-36 PF was calculated at each time point.

- The Wilcoxon rank sum test was performed for the time (weeks) to the maximal positive change from baseline in SF-36 PF score.

- Analysis of variance (ANOVA) was used in assessing other continuous variables: RTUA, change from baseline to Week 0 after hospital discharge in FIM and SF-36 scores, average Vitality, Bodily Pain, and Role-Physical domain scores of SF-36 from baseline through Week 24 after hospital discharge, and MVT.

Results:

The disposition of all randomized subjects is presented in Table S-1. Approximately 50% of study subjects in both groups withdrew from the study prior to study completion. The most common reasons for early withdrawal were voluntary withdrawal and being lost to follow-up.

Table S-1: Subject Disposition

	PROCRIT® (N=97) n (%)	Placebo (N=95) n (%)	Total (N=192) n (%)
Completed	49 (50.5)	50 (52.6)	99 (51.6)
Withdrawn	48 (49.5)	45 (47.4)	93 (48.4)
Adverse Event	1 (1.0)	2 (2.1)	3 (1.6)
Protocol Violation	1 (1.0)	5 (5.3)	6 (3.1)
Lost to Follow-up	11 (11.3)	11 (11.6)	22 (11.5)
Death	1 (1.0)	0	1 (0.5)
Voluntarily Withdrew	29 (29.9)	20 (21.1)	49 (25.5)
Investigator Request	0	2 (2.1)	2 (1.0)
Sponsor Request	1 (1.0)	0	1 (0.5)
Other	4 (4.1)	5 (5.3)	9 (4.7)

Demographics for the safety population are summarized in Table S-2. The 2 groups were well balanced for demographic characteristics.

Table S-2: Demographic Characteristics

	PROCRIT® (N=96)	Placebo (N=92)
Sex, n (%)		
Male	64 (66.7)	57 (62.0)
Age, years		
Mean (SD)	32.2 (10.94)	33.5 (11.06)
Race		
Caucasian	63 (65.6)	55 (59.8)
African American	17 (17.7)	19 (20.7)
Hispanic	16 (16.7)	16 (17.4)

EFFICACY RESULTS:

The primary efficacy analysis is presented in Table S-3.

Table S-3: Primary Efficacy Endpoint – Average of All Post-Hospital Discharge SF-36 PF Score (Study PR04-15-001)

Analysis Population/Time Point Observed Cases	PROCRIT® (N=96)		Placebo (N=93)		p-value
	n	Mean ± SD[a]	n	Mean ± SD[a]	
ITT					
Baseline	89	34.38 ± 42.918	87	25.17 ± 39.821	
Average Post-Hospital Discharge	85	27.30 ± 23.668	81	30.88 ± 23.522	0.3807

[a] Average of the average of each individual's SF-36 Physical Functioning score.

ITT = intent-to-treat; SD = standard deviation; SF-36 PF = Medical Outcome Survey Short Form (Physical Function).

The analysis of the primary endpoint in the ITT population demonstrates no statistically significant difference in mean SF-36 PF scores between the treatment groups. The results for the efficacy evaluable and efficacy evaluable with compliance populations (both observed cases and LOCF) were consistent with those for the ITT population.

Both treatment groups showed improvements in mean FIM total and motor subscore values, FACIT-An, FACIT-F, and all 3 SF-36 domain scores between baseline and the average of Weeks 0 to 12. The cumulative percentage of subjects returning to usual activities increased in both treatment groups between PHDT Weeks 12 and 24. However, none of these secondary efficacy endpoints showed any statistically significant difference between the epoetin alfa (PROCRIT®) and placebo treatment groups. The results of analyses of the efficacy evaluable and efficacy evaluable with compliance populations (observed cases and LOCF) were consistent with those for the ITT population.

The epoetin alfa (PROCRIT®) and placebo groups showed a statistically significant positive correlation between Hb level and SF-36 PF score at late time points only.

The Acute Physiology and Chronic Health Evaluation (APACHE) II Total Score, Sequential Organ Failure Assessment (SOFA) Total Score, and Cognitive Function Scale (COG) showed no statistically significant differences between treatment groups at any of the post-baseline time points.

Transfusion requirements were similar between the epoetin alfa (PROCRIT®) group compared with the placebo group.

SAFETY RESULTS:

The overall incidence of adverse events was 88.5% in the epoetin alfa (PROCRIT®) group and 89.1% in the placebo group. The incidence of treatment-emergent adverse events was 88.5% in the epoetin alfa (PROCRIT®) group and 88.0% in the placebo group.

No clear patterns of difference between treatment groups were evident in the incidences of specific treatment-emergent adverse events, and the incidences of most of the reported adverse events were low in both treatment groups.

Most of the adverse events in both treatment groups were mild to moderate in intensity. No clear differences between treatment groups were evident in the occurrence of mild, moderate, or severe adverse events as categorized by system organ class.

Most treatment-emergent adverse events in both treatment groups were considered not related to study treatment. The incidence of events considered related to study treatment was 10.4% in the epoetin alfa (PROCRIT®) group and 4.3% in the placebo group. The only system organ class for which the incidence of treatment-related events exceeded 1% in the epoetin alfa (PROCRIT®) group was vascular disorders (5.2% in the epoetin alfa (PROCRIT®) group and 1.1% in the placebo group).

One subject in the epoetin alfa (PROCRIT®) group had an adverse event of peritoneal hemorrhage that resulted in death. This event was not considered related to study medication.

Serious adverse events occurring in more than 1 subject in any treatment group are summarized in Table S-4.

Table S-4: Summary of Serious Adverse Events Occurring in More Than One Subject in
Any Treatment Group
(Study PR04-15-001: [Safety Population])

| System Organ Class/Preferred Term | Number of subjects/events, n (%)[a,b] | |
	PROCRIT® (N=96)	Placebo (N=92)
Number of Subjects with at Least 1 Event	17 (17.7)	20 (21.6)
Number of Events	25	45
Gastrointestinal Disorders	1 (1.0)	3 (3.3)
Infections and Infestations	7 (7.3)	10 (10.9)
Injury, Poisoning and Procedural Complications	3 (3.1)	6 (6.5)
Post-Procedural Hemorrhage	0	2 (2.2)
Musculoskeletal System Disorders	1 (1.0)	3 (3.3)
Nervous System Disorders	0	2 (2.2)
Respiratory, Thoracic and Mediastinal Disorders	3 (3.1)	5 (5.4)
Respiratory Failure	2 (2.1)	2 (2.2)
Pulmonary Embolism	1 (1.0)	2 (2.2)
Vascular Disorders	4 (4.2)	4 (4.3)
Deep Vein Thrombosis	4 (4.2)	4 (4.3)

[a] Percentages are based on the number of subjects in each treatment group.
[b] Subjects were counted once within each preferred term.

The incidence of serious adverse events was similar in the 2 treatment groups (17.7% in the epoetin alfa (PROCRIT®) group and 21.7% in the placebo group). The only specific serious adverse events occurring in more than 1 subject in either treatment group were deep vein thrombosis, respiratory failure, and pulmonary embolism. The incidence of each of these events was less than 5% in both treatment groups.

Most of the serious adverse events in both treatment groups were considered not related to study treatment, and in most cases the subject recovered without sequelae. In most cases, the serious adverse event did not result in a change in study medication; in 1 case of vomiting in the epoetin alfa (PROCRIT®) group and 1 case of severe thrombocytopenia and 1 case of ileus (both in the placebo group), the event led to a permanent stop of study medication.

Three subjects (1 in the epoetin alfa (PROCRIT®) group and 2 in the placebo group) had adverse events that led to discontinuation from the study. Vomiting in 1 subject in the epoetin alfa (PROCRIT®) group was considered possibly related to study treatment. Thrombocytopenia and ileus in 1 subject each in the placebo group were considered not related to study treatment.

CONCLUSION:

Efficacy: There were no significant differences in physical function outcomes in anemic, critically ill, trauma subjects treated with epoetin alfa (PROCRIT®) compared with placebo in this study.

Safety: Safety assessments, including AEs, clinical laboratory test results, vital signs, and physical examination findings, showed epoetin alfa (PROCRIT®) group to be similar to placebo group in the study population of trauma patients.