SYNOPSIS

NAME OF SPONSOR/COMPANY: Ortho Biotech Clinical Affairs, L.L.C.	INDIVIDUAL STUDY TABLE REFERRING TO PART OF THE DOSSIER	(FOR NATIONAL AUTHORITY USE ONLY)
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Protocol No.: PR97-19-002

Title of Study: An Open-Label, Randomized, Parallel Group Study to Confirm the Safety and Efficacy of PROCRIT® (Epoetin alfa) Administered Perioperatively Versus the Standard of Care in Blood Conservation in Subjects Undergoing Major Elective Spinal Surgery

Principal Investigator: Multicenter study (see Appendix 1.4.1)

Publication (Reference): none

Study Initiation/Completion Dates: 23 April 1998 to 24 May 2006 (First Subject Randomized to Last Subject Last Visit)

Phase of development: IV

Objective: The primary objective of the study was to demonstrate that there was no clinically important additional risk for deep vein thrombosis (DVT) in adult spine surgery using a perisurgical regimen of PROCRIT (Epoetin alfa) versus the standard of care (SOC) for blood conservation. A secondary objective was to evaluate the efficacy of PROCRIT in protecting subjects from receiving allogeneic red cell transfusions across spinal procedures.

Methodology: This was an open-label, randomized, parallel group multicenter study conducted in the United States (US) to evaluate the incidence of DVT in subjects receiving a perisurgical regimen of PROCRIT as compared to subjects receiving the SOC for blood conservation management. The study consisted of four periods: Screening, Preoperative, Surgery, and Postoperative.

Subjects who provided written informed consent and met study eligibility criteria were randomly assigned to one of two treatment groups (Group 1: PROCRIT treatment, or Group 2: SOC) using a central interactive voice response system (IVRS). Randomization occurred at least three weeks prior to the scheduled surgery date. Subjects assigned to Group 1 received four doses of PROCRIT 600 U/kg administered SC weekly on days -21, -14, and -7 prior to the surgery and on the day of surgery. Subjects in Group 2 were treated with the hospital/institution's policy for blood conservation but did not receive PROCRIT or any other erythropoietic agent. Subjects assigned to PROCRIT could donate blood only prior to the first dose of study medication. All subjects received oral iron therapy beginning no later than day -21 and continued until the day of surgery. After surgery, subjects stayed in the study for four days (or until hospital discharge). Transfusions were given at the discretion of the investigator; however, every effort was made to avoid transfusion postoperatively unless warranted by clinical symptoms. The use of mechanical DVT prophylaxis was allowed for all subjects.

Safety and efficacy evaluations were performed at specified intervals throughout the study and consisted of laboratory tests (complete blood count [CBC], hemoglobin and hematocrit, serum chemistry, serum ferritin), blood pressure measurements, and the occurrence and severity of adverse events. Serious adverse events were to be reported through 30 days after the last dose of study medication or through 30 days after the day of surgery, whichever was later. Subjects were screened for DVT by Color Flow Doppler Imaging (CFDI) four days after surgery or within 24 hours of discharge, whichever was earlier. Color Flow Doppler Imaging was also obtained at any time during the study for confirmation testing of suspected DVT.

A Data Safety Monitoring Board (DSMB) was constituted with a preapproved charter. It was responsible for monitoring safety data including the incidence of all thrombotic/vascular events (TVEs) and for recommending termination of the study if there was evidence of a significant difference between the two treatment groups.

Number of Subjects (planned and analyzed): Approximately 674 subjects were planned to be enrolled to obtain 572 evaluable subjects (i.e., at least 286 subjects per treatment group). The required sample size was 674 subjects to provide a power of 80% (assuming a 15% dropout rate) for demonstrating noninferiority of DVT incidence for the PROCRIT group relative to the SOC group. A total of 681 subjects (341 subjects in the PROCRIT group and 340 subjects in the SOC group) were randomized. One subject was randomized twice and was excluded from the ITT population.

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Diagnosis and Main Criteria for Inclusion: To be eligible to enroll in this study subjects must have been adults, 18 years of age or older, who were scheduled for elective spinal surgery (with a minimum of three weeks lead time) with anticipated perioperative blood loss of two to four units. The selection of subjects was limited to those who had a pretreatment hemoglobin (Hb) of >10 to ≤13 g/dL. No perioperative anticoagulation therapy was to be administered during the study. Subjects were excluded for clinically significant systemic disease or laboratory chemistry abnormalities, any primary hematologic disease, history of DVT or pulmonary embolism (PE), history of seizure disorder (uncontrolled by medication), uncontrolled hypertension (e.g., diastolic blood pressure of 90 mmHg or greater), recent gastrointestinal or intracranial bleeding, any condition that would compromise the ability to respond to erythropoietin therapy, or use of any erythropoietin product, experimental drug or device within 30 days prior to admission.

Test Product, Dose, and Mode of Administration, Batch No.: Epoetin alfa (PROCRIT®) was supplied as a 1 mL vial containing 20,000 units of epoetin alfa and 2.5 mg human albumin. In the PROCRIT treatment group, the dose was 600 U/kg by SC injection for a total of four doses. Lot numbers for epoetin alfa were P001049, P001120, P001310, P002176, P003497, P005262, P006212, P008400, P008873, P008954, P009114, P009115, P009413, P009677, P010982, P010983, P011375, P011376, P024844, P0024894, P027186, P028154, P029325, P031221, P031222, and P032913 (NDC # 59676-320-01).

Duration of Treatment: The duration of treatment for subjects assigned to the PROCRIT group was 22 days. After surgery, subjects stayed in the study for four days (or until hospital discharge).

Criteria for Evaluation:

Safety: The primary endpoint was the proportion of subjects with DVT identified by either CFDI on postoperative day 4 or on the day of discharge, or by clinical symptoms at any time during the study. The secondary safety endpoint was the proportion of subjects with TVEs. Other safety evaluations included the incidence of deaths, adverse events (including serious adverse events) and changes from baseline in blood pressure. Serious adverse events, including symptomatic DVTs, were reported through 30 days after the last dose of study medication or through 30 days after the day of surgery, whichever was later.

Efficacy: Secondary efficacy endpoints were the proportion of subjects who received transfusions (transfusion rate) during or after surgery and the change in Hb and hematocrit (Hct) levels from baseline to postoperative day 4 (or the day of discharge).

Statistical Methods: Statistical significance for all tests was interpreted using $p \leq 0.05$, unless otherwise specified.

Safety: The primary safety analysis for DVTs was based on the final CFDI Data Set augmented by DVTs which were not confirmed by CFDI for the ITT population. A one-sided 97.5% (1.0 – 0.025) upper confidence limit was calculated for the DVT incidence difference between the PROCRIT and SOC groups. If the upper limit of the confidence limit was less than or equal to the 4% prespecified margin, then the conclusion was that there was no additional risk for DVT in adult spinal surgery attributable to the use of PROCRIT. In addition to the ITT population, the primary safety analysis was also performed on the evaluable population, consisting of all randomized subjects who had surgery and underwent postoperative CFDI for evaluation of symptomatic and asymptomatic DVT, and the per protocol population, which included the evaluable population with no major protocol deviations and with interpretable CFDI. Additionally, subjects assigned to the PROCRIT group were to have received at least one of the four doses of study medication to be included in the per protocol population.

The secondary safety analysis (i.e., proportion of subjects who had TVEs at any time during the study) was performed on the ITT, evaluable and per protocol populations. Adverse experiences were classified as TVEs and clinically relevant TVEs using the TVE dictionary. The number of TVEs, as well as the proportion of subjects who developed clinically relevant TVEs, were summarized by treatment group.

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Statistical Methods (Continued)

Efficacy: The secondary efficacy analyses included the incidence of transfusion and the change in Hb and Hct levels. The transfusion endpoint was analyzed for the ITT and the completer population which consisted of all subjects who were randomly assigned to treatment, had surgery and no major protocol deviations. Subjects assigned to PROCRIT were to have received at least three of the four doses of study medication. The change in Hb and Hct levels was analyzed for the ITT, evaluable, and completer populations.

The number of subjects receiving allogeneic, autologous, or any red cell transfusion was listed by treatment group. In addition, the number of subjects in each treatment group receiving transfusions during the perioperative (Operating and Recovery Room), postoperative and total study (perioperative and postoperative) was listed. The proportion of subjects in the two treatment groups receiving transfusions was compared using a Chi-square test. An analysis of covariance (ANCOVA) model with treatment as the fixed factor and baseline Hb or Hct as covariates was used to analyze the change from baseline in Hb and Hct to the end of the study (postoperative day 4 or the day of discharge).

Other Safety: Safety data were analyzed for the ITT population. Adverse events were summarized by body system, preferred term, and treatment group. Adverse events were also summarized by severity and relationship to treatment group. Summary statistics (mean, standard deviation, median, range, 25^{th} and 75^{th} percentile) and changes from baseline were provided by treatment group for blood pressure measurements.

All safety and efficacy analyses described in the protocol were performed. A DVT sensitivity analysis was conducted with the ITT population and included subjects who had a finding of a possible DVT identified by either the local or core laboratory; however, the finding was not confirmed by the adjudicator (i.e., Final CFDI Assessment was normal).

Additional exploratory analyses were performed, including the influence of risk factors for DVT/TVE on the primary outcome and examining the relationship between baseline Hb and Hb change from baseline to surgery with the DVT/TVE outcome. Finally, a logistic multivariate regression analysis was performed to explore the relationship between risk factors and occurrence of DVT or TVE (including DVT).

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BASELINE ASSESSMENTS AND EXTENT OF EXPOSURE: A total of 681 subjects were randomized in the study (341 PROCRIT and 340 SOC). One subject was randomized twice and was excluded from the ITT population. Thus, 680 subjects (340 PROCRIT and 340 SOC) subjects were included in the ITT analyses. A total of 93 subjects were withdrawn from the study: 60 subjects in the PROCRIT group and 33 subjects from the SOC group. The major reason for withdrawal in both groups was surgery cancellations and insurance issues related to surgery (i.e., Other reasons). Demographic and baseline characteristics were similar between the two treatment groups. The ITT population consisted of subjects who were mainly Caucasian (85.1%), female (88.4%) and had a mean age of 59.8 years. The mean baseline Hb value was 12.2 g/dL in both the PROCRIT and SOC groups.

Among the 340 subjects randomized to the PROCRIT group, 9 (2.6%) subjects received 1 dose, 5 (1.5%) subjects received 2 doses, 33 (9.7%) subjects received 3 doses, and 268 (78.8%) subjects received 4 doses of study medication. A total of 25 subjects did not receive any dose. The mean dose in the PROCRIT group during the study was 46,743 Units on day –21 (N=314); 46,872 Units on day –14 (N=305); 46,907 Units on day –7 (N=300); and, 46,779 Units on the day of surgery (N=271).

SAFETY RESULTS:

Primary Safety Endpoint: The overall incidence of any DVT (ITT population) in the current study was 3.4% (23/680). The incidence in the PROCRIT group was 4.7% (16/340) as compared to 2.1% (7/340) in the SOC group. The one-sided 97.5% upper confidence limit of the difference in DVT incidence between the two treatment groups was 5.4%. Because the upper confidence limit was greater than the 4% pre-specified margin, an additional risk of DVT attributable to the use of PROCRIT could not be excluded. Similar results were seen with the evaluable and per protocol populations.

Secondary Safety Endpoint: In addition to the 23 subjects with DVTs included in the primary analysis, 19 (2.8%) subjects in the ITT population experienced thrombotic vascular events: 12 subjects in the PROCRIT group and 7 subjects in the SOC group. Eleven of the 19 subjects experienced a non-clinically relevant TVE (either chest pain or superficial thrombophlebitis). Of the 8 (2.4%) subjects with clinically relevant TVEs, 5 (1.5%) were randomized to PROCRIT and 3 (0.9%) to SOC.

Exploratory Analyses: Baseline Hb values of subjects receiving PROCRIT had no effect on the incidence of DVT. Subjects in the PROCRIT group entering the study with a baseline Hb of >12 to ≤13 g/dL had a 4.3% incidence of DVT compared to 4.7% in subjects with a baseline Hb of 10 to ≤12 g/dL (OR 0.91; 95% CI 0.31 – 2.69).

Hemoglobin change from baseline to surgery was also not related to the incidence of DVT in the PROCRIT group. Subjects in the PROCRIT group with >1.5 g/dL Hb increase had a 6% incidence of DVT compared to 4% incidence of DVT in subjects with Hb increase ≤ 1.5 g/dL (OR 1.53; 95% CI 0.56 – 4.23).

A logistic multivariate regression analysis indicated a significant association of age (OR 2.63, >65 versus <65) and gender (OR 0.42, females versus males) with the risk of developing DVT. In the presence of these factors, PROCRIT treatment effect remained similar to the primary analysis (OR 2.2, PROCRIT versus SOC).

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EFFICACY RESULTS:

Secondary Efficacy Endpoints:

A statistically significant smaller proportion of subjects in the PROCRIT group was transfused with allogeneic blood compared to the SOC group (PROCRIT 15.3%, SOC 25 %; p=0.002). The use of any transfusions (allogeneic and/or autologous) occurred in 29.7% of the subjects in the PROCRIT group compared to 55% in SOC group (p<0.001).

At baseline the mean Hb was 12.2 g/dL in both the PROCRIT and SOC groups. From baseline to the day of surgery, Hb increased to 13.5 g/dL in the PROCRIT group and decreased to 11.8 g/dL in the SOC group. At discharge the mean Hb value was 10.9 g/dL in the PROCRIT group and 10.0 g/dL in the SOC group. Similar results were seen with the evaluable and completer populations.

CONCLUSION: Based on the non-inferiority analysis, an additional risk of DVT attributable to the use of PROCRIT could not be excluded.

In addition to the 23 subjects with any DVTs included in the primary analysis, 19 (2.8%) subjects experienced thrombotic vascular events (12 PROCRIT; 7 SOC).

The overall incidence of adverse events (76.5% PROCRIT versus 73.2% SOC) and serious adverse events (12.9% PROCRIT versus 11.8% SOC) was similar.

In addition to treatment, age (>65 years) and gender (male) were also identified as risk factors for DVT (logistic multivariate regression analysis).

The efficacy of perioperative use of PROCRIT for increasing patients' hemoglobin concentrations and reducing exposure to allogeneic red blood cell transfusion was confirmed in this study.

Date of the report: 13 APRIL 2007

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