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: NA Page: NA	(FOR NATIONAL AUTHORITY USE ONLY) NA
Protocol No.: EPOCKD2001 CR003397		
Title of Study: An Open-Label, Randomized, Multicenter Study of the Initiation of Four Dosing Regimens of Procrit® (Epoetin Alfa) for the Treatment of Anemia of Chronic Kidney Disease (CKD)		
Coordinating Principal Investigator: Multi-center study		
Publication (Reference: reporting results of interim analysis): Spinowitz B, Germain M, Benz R, Wolfson M, McGowan T for the Epoetin Alfa Extended Dosing Study Group. Extended dosing regimens for initiation of epoetin alfa for treatment of anemia of chronic kidney disease. *Am J Kid Dis*. April 2007. Vol. 49, Issue 4, Page B84. Abstract 238. Poster presented at the National Kidney Foundation 2007 Spring Clinical Meetings, April 10-14, 2007, Orlando, FL.		
Study Period: 20 Sep 2005 to 11 Oct 2006		**Phase of Development:** 2
Objectives: The primary objective of this study was to compare change in hemoglobin (Hb) from Baseline to the end of the study between the Q2W (every 2 weeks) and the Q4W (every 4 weeks) dosing regimens in subjects with anemia of CKD initiated on PROCRIT. The hypothesis tested was that the Q4W dosing regimens were not inferior to the Q2W dosing regimen in mean change in Hb between Baseline and the average of the last 4 weeks of the study. The secondary objectives of this study were to evaluate the Hb response, time to Hb response, packed red blood cell (pRBC) transfusions, and PROCRIT dose.		
Methodology: This was an open-label randomized, multi-center study in pre-dialysis subjects with anemia of CKD. Subjects (N=259) were randomized in a 1:2:2:2 ratio to one of four treatment initiation regimens **Group 1**: PROCRIT 10,000 IU every week (QW) (N=37) **Group 2**: PROCRIT 20,000 IU every 2 weeks (Q2W) (N=74) **Group 3**: PROCRIT 20,000 IU every 4 weeks (Q4W) (N=74) **Group 4**: PROCRIT 40,000 IU every 4 weeks (N=74). The Hb target range was 11.0 to 12.0 g/dL. PROCRIT was administered subcutaneously (SC) at extended dosing intervals of up to 4 weeks. Hemoglobin was measured weekly using HemoCue201+ Analyzer®. HemoCue results were used for PROCRIT dose adjustments and to verify entrance criteria. In addition, Hb was evaluated weekly by a central laboratory, the results of which were used for efficacy analysis. Hematology, serum chemistry, and iron status was assessed at intervals throughout the study by a central laboratory. Clinical laboratory results, vital signs, and the incidence and severity of adverse events (AEs) were monitored during the study.		
Number of Subjects (planned and analyzed): Two hundred fifty-nine (259) subjects with CKD were planned for study participation. Two hundred sixty-two (262) subjects were randomized; 259 subjects were included in the modified intent-to-treat (mITT) and safety populations, and 229 subjects were included in the per-protocol population.		
Diagnosis and Main Criteria for Inclusion: Subjects with CKD, GFR 15-90 mL/min/1.73m^2, who had not received erythropoietic agents within 8 weeks of screening and had an entry Hb level of <11.0 g/dL were planned for study participation.		
Test Product, Dose and Mode of Administration, Batch No.: PROCRIT 10,000 IU/mL, subcutaneous administration, Batch No: R13569, R13841 PROCRIT 20,000 IU/mL, subcutaneous administration, Batch No: R13570, R13609, R13842, R13843 PROCRIT 40,000 IU/mL, subcutaneous administration, Batch No: R13571, R13844, R14002		
Reference Therapy, Dose and Mode of Administration, Batch No.: Not applicable		

Name of Sponsor/Company: Ortho Biotech Clinical Affairs, LLC	INDIVIDUAL STUDY TABLE REFERRING TO PART OF THE DOSSIER	(FOR NATIONAL AUTHORITY USE ONLY) NA
Name of Finished Product: PROCRIT	Volume: NA	
Name of Active Ingredient(s): epoetin alfa	Page: NA	

Duration of Treatment: Screening Phase of approximately one week, a Treatment Phase of 16 weeks and a Post-treatment Phase of 1 week.

Criteria for Evaluation:

Efficacy:

The primary efficacy endpoint was the change in Hb from Baseline to the end of the study.

The secondary efficacy endpoints for this study included Hb response, defined as achieving an Hb increase of ≥1.0 g/dL from Baseline any time during the study; time to Hb response; proportion of subjects with an Hb >11.0 g/dL and an increase of ≥1.0 g/dL from Baseline any time during the study; change in Hb over time; proportion of subjects who failed treatment; number of units of pRBC transfused; proportion of subjects who received a pRBC transfusion; cumulative and adjusted weekly PROCRIT dose when Hb response was achieved; and cumulative and adjusted weekly PROCRIT dose.

Safety:

Safety was evaluated by assessing adverse events, clinical laboratory tests (hematology, serum chemistry, and urinalysis), vital sign measurements, and physical examinations.

Statistical Methods:

The primary endpoint of this study is the change in Hb from baseline to the end of the study. Assuming a difference in the mean change in Hb from baseline to end of study of –0.3g/dL between Group 2 and Group 4, a pooled standard deviation of 1.4g/dL, and a non-inferiority margin of -1g/dL, a sample size of approximately 65 for each of Groups 2, 3, and 4 will provide 80% power to demonstrate that Group 4 (and Group 3) is not inferior to Group 2 at an overall 2-sided 0.048 significance level. This significance level maintains an overall significance level of 0.05, adjusting for conducting an interim analysis on change in Hb. Adjusting a 12% drop-out rate, a sample size of 74 for each of Groups 2, 3, and 4 is reached.

The primary analyses for the primary endpoint were based on the per-protocol population.

An estimate of the difference in means (Group 4 minus Group 2 and Group 3 minus Group 2) was computed along with the 2-sided 95.2% confidence interval for the difference. The estimate of the difference and the CI was calculated using an analysis of covariance (ANCOVA), including baseline Hb as a covariate.

Time to achieving Hb response was estimated using Kaplan-Meier method. Descriptive statistics and the 2-sided 95% confidence intervals were used to summarize all other secondary endpoints. These analyses were conducted using the mITT and per-protocol populations.

SUMMARY – CONCLUSIONS:

Of the 262 subjects randomized into the treatment phase, (39 subjects in Group 1, 77 in Group 2, 73 in Groups 3 and 4), 259 (98.9%) received at least 1 dose of study drug. These 259 subjects represent the mITT/Safety population. Two hundred twenty-nine subjects were included in the per protocol population. A total of 230 (87.8%) subjects completed the study. Overall, demographic and baseline characteristics were similar across treatment groups. There were more females enrolled in the study (59%) compared with males (41%). Subjects ranged in age from 20 to 94 years, with a mean overall age of 67 years. The majority of subjects were Caucasian (54%), followed by Black (25%).

The primary causes of CKD for subjects enrolled in this study were diabetes (51%) and hypertension (36%). The mean GFR overall was 30.2 mL/min/1.73m^2 and the overall mean baseline Hb was 10.2 g/dL.

EFFICACY RESULTS:

Primary efficacy results:

Mean Baseline Hb was similar across treatment groups, ranging from 10.1 to 10.3 g/dL. Mean end-of-study Hb was also similar across treatment groups ranging from 11.2 to 11.5 g/dL. The average Hb change from baseline was 1.1g/dL for Group 1, 1.0 g/dL for Group 2, 1.1 g/dL for Group 3, and 1.2 g/dL for Group 4.

The primary efficacy analysis was conducted in a step-down manner to control for multiplicity. Groups 4 and 2 were compared first. Because the lower limit of the 95.2% confidence interval of the difference between Group 4 (40,000 IU Q4W) and Group 2 (20,000 IU Q2W) was -0.21 g/dL, which was greater than the pre-specified non-

Name of Sponsor/Company: Ortho Biotech Clinical Affairs, LLC	INDIVIDUAL STUDY TABLE REFERRING TO PART OF THE DOSSIER	(FOR NATIONAL AUTHORITY USE ONLY)
Name of Finished Product: PROCRIT	Volume: NA	NA
Name of Active Ingredient(s): epoetin alfa	Page: NA	

inferiority margin of -1 g/dL, the non-inferiority of Group 4 to Group 2 was established. Similarly, because the lower limit of the 95.2% confidence interval of the difference between Group 3 (20,000 IU Q4W) and Group 2 was -0.38 g/dL, also greater than the pre-specified non-inferiority margin of -1.0 g/dL, the non-inferiority of Group 3 to Group 2 was established.

The results of the sensitivity analysis of the primary endpoint, using the mITT population, were consistent with the results for the per-protocol (PP) population.

Secondary efficacy results (for mITT population):

Hemoglobin response was defined as achieving a Hb increase of ≥1.0 g/dL from Baseline any time during the study. Fewer subjects in Group 3 achieved a Hb response compared to Groups 1, 2, and 4. In addition, Group 3 subjects exhibited a longer time to Hb response than those in Groups 1, 2, and 4.

Median time to Hb response was 22, 29, 35, and 28 days for Groups 1, 2, 3, and 4 respectively.

Most subjects across all dosing groups achieved both a 1 g/dL rise in Hb as well as a Hb >11.0 g/dL during the study. However, a lower overall proportion of subjects in Group 3(69.4%) achieved this target as compared with 86.1%, 86.2%, and 79.4% for Groups 1, 2, and 4, respectively.

The Hb achieved was similar in all groups by the end of the study. All 4 treatment groups showed an increase in Hb values over time. The steepest rate of rise was observed in subjects who received 10,000 IU every week (QW) followed by subjects who received 20,000 IU Q2W. Similarly, a more brisk increase of Hb was observed in subjects who received 20,000 IU every other week compared with subjects who received the same dose at intervals of every 4 weeks.

Two subjects were considered treatment failures.

A total of 5 subjects (1.9%) received a pRBC transfusion during the study with an average of 1.7 units per subject per transfusion.

The mean adjusted weekly dose at the time when Hb response was achieved ranged from 9282 IU for Group 1 to 18356 IU for Group 4.

The mean adjusted weekly dose was 5943 IU, 7376 IU, 4522 IU and 8660 IU for Groups 1, 2, 3 and 4 respectively.

SAFETY RESULTS:

All dosing regimens were well tolerated. The incidence of adverse events was comparable in all 4 treatment groups and the overall safety profile was typical of this study population.

There were 4 deaths, 2 in Group 2 and 1 in Group 3, during the study and 1 in Group 4, 30 days after study completion. None of the deaths were considered by the investigator to be related to study drug.

A total of 43 subjects reported serious adverse events (SAEs) during the study; of these, 40 (15.4%) subjects experienced a treatment-emergent SAE during the study, the most common of which was congestive cardiac failure, experienced by 10 (3.9%) subjects. All SAEs were considered by the investigator to be unrelated to study drug, with the exception of 1 subject in Group 4, who was hospitalized on Day 5 for severe hypertension, considered by the investigator to be possibly related to study drug. Five subjects experienced an SAE that led to permanent withdrawal of study drug. No trends were noted in regard to SAE reporting and treatment group.

Two subjects (1 in each of Groups 3 and 4) experienced a clinically relevant thrombovascular event (TVE) of myocardial infarction. Both events resolved without sequelae.

CONCLUSION:

The results of this study support the hypothesis that initiation of PROCRIT with a dose of 40,000 IU every 4 weeks is not inferior to initiation with a dose of 20,000 IU every other week. All dosing regimens were well tolerated. In conclusion, the option for Q4W dosing of PROCRIT may provide added flexibility and convenience for anemic CKD patients and their health care providers.

Date of Report: 02July2007 (final)

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.