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.: PR03-06-001

Title of Study: An Open-Label, Clinical Evaluation of the Initiation of Every 2 Week PROCRIT (epoetin alfa) in the Treatment of Subjects with the Anemia of Chronic Kidney Disease

Coordinating Principal Investigators: NA

Publication (Reference: reporting results of interim analysis): Benz R, Schmidt R, Bhaduri S, et al. Use of epoetin alfa once every two weeks for the initiation of treatment of anemia of chronic kidney disease. *J Am Soc Nephrol*. 2005;16:548A. Abstract F-PO971. Poster presented at The American Society of Nephrology (ASN); November 8- 13, 2005; Philadelphia, PA.

Study Initiation/Completion Dates: 14 Jun 2004 to 27 Oct 2005 | **Phase of development:** 2

Objectives:

The primary objective was to evaluate the hemoglobin (Hgb) response in subjects with anemia of chronic kidney disease (CKD) after initiation of PROCRIT using an every 2-week dosing regimen. A Hgb response was defined as achieving the target Hgb range of 11.0 to 12.0 g/dL for at least 2 consecutive weeks by Study Week 28.

The secondary objectives were to evaluate the time to Hgb response, transfusion requirements, PROCRIT dose, change in quality of life, and to explore factors that might influence the time to response..

Methodology:

This was a single arm study in which CKD subjects who had not received erythropoietic agents within the past 6 weeks initiated PROCRIT treatment with 20,000 International Units (IU) every 2 weeks. The Hgb target range was 11.0 to 12.0 g/dL. PROCRIT was administered subcutaneously (SC) every 2 weeks for 28 weeks.

Number of Subjects (planned and analyzed):

Sixty subjects with CKD, an entry Hgb of < 11.0 g/dL and an estimated glomerular filtration rate (GFR) between 10-60 ml/min/1.73m^2 were planned for enrollment at multiple centers in the United States; 67 subjects were enrolled; all subjects were included in the modified intent to treat (mITT) population and the safety population, and 65 subjects were included in the per protocol (PP) population.

Diagnosis and Main Criteria for Inclusion:

To be eligible for this trial, subjects had to be men or women at least 18 years of age with CKD. They were required to have a GFR within 10 to 60 ml/min/1.73m^2 as estimated from the Modification of Diet for Renal Disease (MDRD) equation[1], stable creatinine over the prior 6 months, and no expected need for dialysis during the study. Subjects had to have a Hgb < 11.0 g/dL and could not have received erythropoietic agents within 6 weeks before study entry.. Female subjects with reproductive potential were to use an adequate contraceptive method during treatment and to have a negative pregnancy test within 7 days of the first dose of study drug.

Test Product, Dose, and Mode of Administration, Batch No.: PROCRIT; initial study dose: 20,000 IU, SC, every 2 weeks (dosing algorithm allowed dose titration down to zero and up to 40,000 IU); batches: R12403, R12402, R12768, R12901, R12902, and R13095; 2 vial types provided (multidose, preserved vial containing 1 mL [20,000 IU/mL] and a single-dose, preservative-free vial containing 1 mL [40,000 IU/mL]).

Reference Therapy, Dose, and Mode of Administration, Batch No.: NA

Duration of Treatment: PROCRIT was administered every 2 weeks for 28 weeks

Criteria for Evaluation: Hgb was measured weekly by a central laboratory.

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Efficacy:

Primary:

The primary efficacy analysis was to evaluate the proportion of subjects with anemia of CKD experiencing a Hgb response after initiation of PROCRIT using a q2w dosing regimen. The Hgb response was defined as achieving the target Hgb range of 11.0 to 12.0 g/dL for at least 2 consecutive weeks by Study Week 28.

Secondary:

Secondary efficacy analysis included: time to Hgb response and duration of Hgb response, proportion of subjects who had a 1.0 and 2.0 g/dL-rise in Hgb from baseline, time to the first 1.0 and 2.0 g/dL-rise in Hgb from baseline, changes in Hgb over time, transfusion requirements, change in health related quality of life measurements (LASA: 3 domains and SF-36v1: 8 domains, physical composite score (PCS) and mental composite score (MCS) scales, cumulative PROCRIT dose up to time of Hgb response, proportion of subjects who achieved the target Hgb range by Week 14 (mid-study) and sustained a Hgb response in Weeks 15-28, correlation between changes in Hgb and changes in HRQoL (LASA: 3 domains and SF-36: 8 domains, PCS and MSC), proportion of subjects who had study dose held due to Hgb rise above 12.0 g/dL, or a cumulative Hgb increase of > 1.0 g/dL over any 1 or 2 week period, and time to the first study dose hold due to Hgb rise above 12.0 g/dL, or a cumulative Hgb increase of > 1.0 g/dL over any 1 or 2 week period.

Safety:

Safety endpoints included the incidence and severity of adverse events and any significant change from baseline in laboratory values or vital signs.

Statistical Methods:

Analysis populations included:

Modified Intent to Treat (mITT): all enrolled subjects who received at least 1 dose of study drug during the study. The mITT population was used for all efficacy analyses.

Per Protocol (PP): all enrolled subjects who received at least 1 dose of study medication and had at least 1 post-baseline Hgb measurement with no major protocol violations and no RBC transfusion during the study. The PP population was used for the sensitivity analysis of the primary efficacy endpoint.

Safety: included the same subjects as the mITT population; this population was used for all safety analyses.

Baseline and demographic characteristics of enrolled subjects are presented using summary statistics.

In the primary efficacy analysis the proportion of subjects who achieved a Hgb response was reported, and the 95% confidence interval (CI) of the response was computed. A Hgb response was defined as achieving the target Hgb range of 11.0 to 12.0 g/dL for at least 2 consecutive weeks by Study Week 28.

The change in Hgb over time from baseline was summarized using descriptive statistics. In addition, the 95% CI for mean changes at weekly time-points were calculated. The time to reach target Hgb and the cumulative PROCRIT dose up to time of response were summarized using descriptive statistics. The Kaplan-Meier estimate was used to estimate median time to Hgb response.

Descriptive statistics were provided for all additional secondary efficacy endpoints. Kaplan-Meier estimates were used to summarize time to Hgb response and time to the first 1.0 g/dL and first 2.0 g/dL-rise in Hgb. The 95% CI were calculated for the proportion of subjects with a 1.0 g/dL-rise in Hgb, change in Hgb over time, and for the proportion of subjects who achieved the target Hgb range by Week 14 and sustained the response in Weeks 15-28. Transfusion requirements, changes in HRQoL responses, and cumulative PROCRIT dose to Hgb response were summarized with descriptive statistics only. The correlation between changes in Hgb and changes in HRQoL was explored using a Pearson correlation coefficient at each time point. Logistic regression analysis was conducted to evaluate the impact of these demographic and clinical variables on Hgb response status (responder vs. non-responder) and to select variables that were significant predictors of Hgb response status.

Descriptive statistics were used to analyze demographic, safety, and efficacy data and are provided in summary tables. For continuous variables, this included number of observations, mean, standard deviation, median, range, and 95% CI where appropriate. Categorical variables were summarized using frequency and percentage.

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Summary - Conclusions

Efficacy Results:

Of the 67 subjects that enrolled, 50 (74.6%) completed the study, and 17 (25.4%) withdrew from the study. No subject withdrew due to adverse events, related or unrelated to PROCRIT, and no subjects withdrew due to treatment failure.

Primary:

Hemoglobin response: 59 subjects (88.1%; 95%CI: 77.82, 94.70) of the mITT population (67 subjects) had a Hgb response.

Secondary:

Time to Hgb response: The mean time to a Hgb response was 7.1 weeks for the 59 responders. The median time to response was 5.14 weeks (Kaplan-Meier estimate).

Proportion of subjects with a 1.0 and 2.0 g/dL-rise in Hgb: Sixty-one subjects (91.0%) had a 1.0 g/dL-rise in Hgb by Week 28. Forty-two subjects (62.7%) had achieved a 1.0 g/dL-increase by Week 5, and 57 subjects (85.1%) had achieved a 1.0 g/dL-increase by Week 9. Fifty-two subjects (77.6%) had a 2.0 g/dL rise in Hgb by Week 28. Fifteen subjects (22.4%) had achieved a 2.0 g/dL-increase by Week 5, and 37 subjects (55.2%) had achieved this increase by Week 9.

Time to first 1.0 or 2.0 g/dL rise in Hgb from baseline: The mean time for a 1.0 g/dL rise increase was 4.2 weeks, and the mean time for a 2.0 g/dL-increase was 7.7 weeks for the 59 responders.

Impact of major factors on response of 1.0 g/dL or 2.0g/dL-rise in Hgb: Baseline albumin (odds ratio [OR]: 25.822, p value: 0.0116) and baseline reticulocyte count (OR: 0.242, p value: 0.0163) were found to be significant predictors of subjects having at least a 1.0 g/dL-increase from baseline. Baseline Hgb (OR: 0.486, p value: 0.0671) and baseline reticulocytes (OR: 0.265, p value: 0.0109) were found to be significant predictors of subjects having at least a 2.0 g/dL-increase from baseline.

Change in Hgb over time: At baseline, the mean Hgb value was 9.75 g/dL. By Week 5 mean Hgb had risen to 10.93 g/dL, (mean increase: 1.18 g/dL; 95% CI: 0.964, 1.395) and at Week 9 mean Hgb was 11.57 g/dL, a mean increase of 1.73 g/dL (95%CI: 1.465, 1.992). Mean Hgb values were stable from Weeks 10-28.

Transfusion requirements: 1 subject (1.5%) required transfusion while on study.

Cumulative PROCRIT dose over the duration of the study: The mean cumulative PROCRIT dose per subject over the course of the study was 188,671 IU. The mean cumulative dose to the first Hgb response was 89,110 IU. The mean q2w dose for the entire study was 15,603 IU.

Proportion of subjects who had study dose held due to Hgb rise above 12.0 g/dL, or a cumulative Hgb increase of > 1.0 g/dL over any 1 or 2 week period. Fifty-two subjects (77.6%) had study medication withheld at least once at some time during the study for one of these reason.

Time to the first study dose hold due to Hgb rise above 12.0 g/dL, or a cumulative Hgb increase of > 1.0 g/dL over any 1 or 2 week period. The mean time to the first study drug hold was 10.1 weeks (range: 3.1 to 24.3 weeks, Kalplan Meier estimate: median 10.9 weeks) for the 52 subjects who met the specified criteria.

Sustainability of Hgb Response: Defined as maintaining at least 80% of non-missing Hgb values at ≥ 11.0 g/dL during study Weeks 14 - 28 after achieving a Hgb response by Week 14. Fifty subjects (74.6%) had achieved target Hgb by Week 14; 29 of those subjects (58%) sustained target Hgb levels in Weeks 14 to 28.

Change in HRQoL using LASA and SF-36 measurements: All domains evaluated in LASA showed improvement from baseline (daily activity, energy. and overall quality of life), and the SF-36 mean scores for physical functioning (PF), role physical (RP), vitality (VT), role emotional (RE), and social functioning (SF) showed increases. Parameters that showed an improvement in score were generally observed at Week 7, and the increases were retained through the end of the study.

Correlation of change in HRQoL (LASA and SF-36) and change in Hgb values: There were no significant ($p > 0.1$) correlations between changes in Hgb and changes in HRQoL.

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Safety Results:

Adverse events recorded during the study period were consistent with those expected in a study population of subjects with CKD. Fifty-four subjects (80.6%) of the safety population experienced at least 1 adverse event. Twelve subjects (17.9%) had an adverse event with a maximum severity of severe. The majority of events were considered not related to study mediation.

All of the adverse events of severe intensity occurred only once, with the exception of acute renal failure and chronic renal failure. Adverse events reported as moderate in severity by at least 2 subjects included hypertension, constipation, cough, nausea, edema, fatigue, arthralgia, headache, dyspnea, and peripheral edema.

Eight subjects experienced adverse events of worsening renal failure that led to a permanent discontinuation of PROCRIT administration. One subject died during the study. No event leading to permanent withdrawal was considered related to PROCRIT. One event, not leading to withdrawal, was considered very likely related (adverse reaction to study drug); the event was not serious. Three subjects experienced a total of 3 clinically relevant TVEs (2 incidences of angina pectoris and 1 incidence of catheter related subclavian vein thrombosis). No subject with a clinically relevant TVE had a Hgb > 12.0 g/dL or a Hgb rate of rise > 1.0 g/dL over a 1 or 2 week period at the time of or immediately prior to the TVE occurrence. No TVE was considered related to study medication. A total of 15 subjects (22.4%) reported 29 serious adverse events during the study. The most common were renal and urinary disorders and cardiac disorders. One serious adverse event was considered possibly related to PROCRIT (hypertension) and 2 subjects experienced serious adverse events that were considered doubtfully related to PROCRIT (hypertension aggravated, a urinary tract infection, acute on chronic renal failure, congestive cardiac failure).

Five subjects had interruptions in dosing of PROCRIT due to adverse events, and 7 subjects had a permanent stop of study drug administration (6 for need of chronic dialysis therapy and 1 due to sudden death).

Study procedures and treatments were well-tolerated by subjects; these safety results are expected based on previous clinical experience with these medications and the overall health status of the enrolled subjects.

Conclusions:

This study provides data to support the hypothesis that q2w epoetin alfa dosing is a feasible, effective, and safe strategy for treating anemia in subjects with CKD. Increasing dosing intervals beyond 3 times a week can increase convenience and optimize anemia management.

Date of the report: 20 June 2006

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